



Clinical Reasoning: A 47-year-old man with progressive gait disturbance and stiffness in his legs

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SECTION 1

A 47-year-old man presented with a 5-year history of slowly progressive gait disorder with clumsiness and unsteadiness during walking, as well as stiffness and cramping pain in his legs. He also had erectile dysfunction and nocturia. He denied sensory deficits and other focal neurologic or systemic symptoms. He had a medical history of hypogonadism, diagnosed 1 year before the onset of the gait disorder, attributed to a bilateral orchiectomy due to a testicular tumor, performed elsewhere when he was 37. He was receiving IM testosterone injections every 3 weeks. His family medical history included pes cavus in his mother and siblings, otherwise unremarkable.

Neurologic examination revealed a wide-based spastic gait with positive Romberg sign. Cognition and cranial nerve examination were normal. Strength was 4/5 in both iliopsoas, and 4+/5 in the remaining muscles of the lower limbs, with increased muscle tone. Deep tendon reflexes (DTR) were very brisk, with bilateral Achilles clonus, and bilateral Babinski signs. Vibration sensation was decreased in lower limbs, and joint position sense was lost in the toes. The rest of the examination was normal.

Questions for consideration:

1. What is the syndromic diagnosis?
2. What is the differential diagnosis at this stage?

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SECTION 2

The pattern of weakness and gait disturbance is consistent with a chronic spastic paraparesis syndrome, beginning in the adulthood, and progressing steadily. The syndrome includes upper motor neuron signs (increased muscle tone, hyperactive DTR, and Babinski signs) and deep sensory disturbances (sensory ataxia) probably involving the dorsal ascending columns. The involvement of sensory peripheral nerves is unlikely because of the hyperactive DTR. Therefore, the signs and symptoms suggest a disease of the spinal cord. Although infrequent, bilateral damage of the frontoparietal cortex (e.g., parasagittal meningioma) may cause a slowly progressive spastic paraparesis syndrome with sensory symptoms and sphincter disturbances.

A syndrome of this type may be indicative of hereditary spinocerebellar degeneration (Friedrich ataxia) or

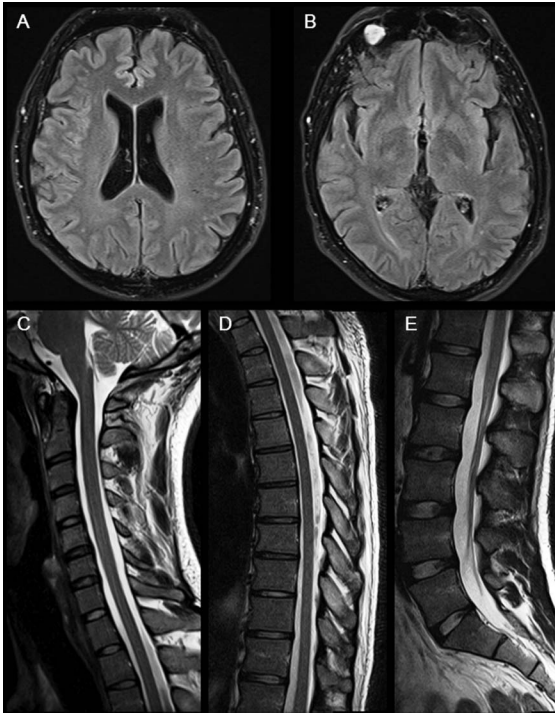
one of its variants.¹ In young adults, progressive multiple sclerosis (MS) is a common cause. In middle and late adult life, a slow compression of the spinal cord by spondylosis is a frequent cause of myelopathy. Subacute combined degeneration (vitamin B₁₂ or copper deficiency), spinal arachnoiditis, spinal arteriovenous shunts, and spinal tumors, particularly meningioma, are important diagnostic considerations. Infections, such as AIDS, tropical spastic paraparesis, syphilis, and Lyme disease, may also cause myelitis. Less common causes include hereditary spastic paraparesis (HSP), adrenomyeloneuropathy (AMN), and primary lateral sclerosis (PLS), although the sensory signs would be atypical for this condition.²

Question for consideration:

1. Which diagnostic studies should be performed?

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Figure 1 Brain MRI fluid-attenuated inversion recovery images



Images show no white matter lesions or other abnormalities (A), except for an incidental right frontal mucocele (B). Spinal T1-weighted sagittal MRI shows no atrophy or other abnormalities throughout the entire spinal cord (C–E). To check whether there existed any differences in terms of regional atrophy, a volumetric comparison with the supratentorial white matter volume of 10 healthy subjects with similar age (47.9 ± 8.3 years) with voxel-based quantitative analysis (using statistical parametrical mapping) was performed. There were no differences between the white matter volume of the controls (0.327; 95% confidence interval 0.308–0.347) and the patient (0.315).

SECTION 3

Brain and spinal MRI were normal (figure 1). Blood tests, including vitamin B₁₂, folic acid, copper, homocysteine, proteinogram, thyroid hormones, HIV, human T-cell lymphotropic virus (HTLV)-1, Venereal Disease Research Laboratory, and Lyme, were normal or negative. No mutations of *SPG4* (which comprises 40%–50% of all cases of autosomal dominant HSP³) or *frataxin* genes were found. EMG and nerve conduction studies were normal in the 4 limbs. Somatosensory evoked potentials revealed an increased latency in the central components of upper limb potentials, and altered potentials in lower limbs. Transcranial magnetic stimulation showed greater delay in the lower than the upper limbs.

Brain ¹⁸fluorodeoxyglucose PET (FDG-PET) showed bilateral hypometabolism in the paramedian frontal, anterior parietal, and temporal lobes (figure 2).

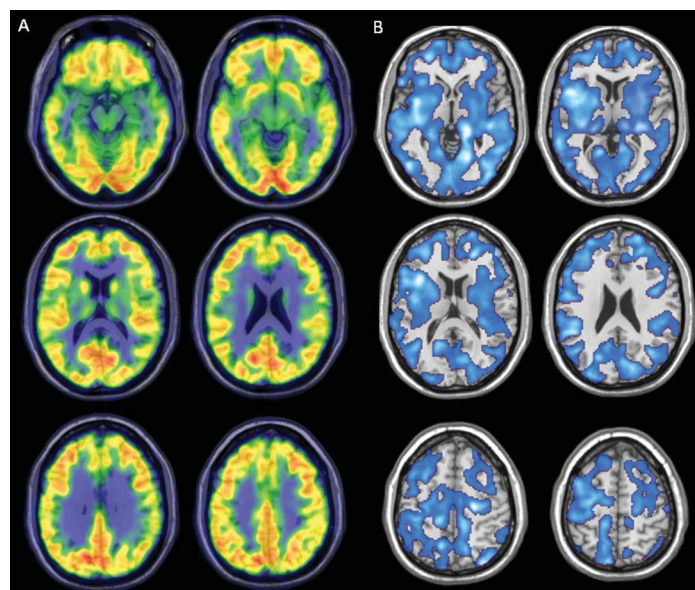
Empiric therapy with coenzyme Q (100 mg, 2 times a day) and symptomatic therapy with baclofen to reduce spasticity (10 mg, 3 times a day) and sildenafil citrate to treat erectile dysfunction were initiated.

Questions for consideration:

1. How do the results of the tests narrow the diagnosis?
2. What is the significance of the FDG-PET finding?

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Figure 2 Brain MRI FDG-PET image



Brain MRI-¹⁸fluorodeoxy-glucose PET fusion image, axial view (A), shows bilateral hypometabolism in the paramedian frontal, anterior parietal, and temporal lobes. (B) Comparative analysis, using statistical parametrical mapping, with the brain metabolism of 10 healthy subjects with similar age, shows a global hypometabolism, involving the cortex and the white matter ($p < 0.01$).

SECTION 4

Normal neuroimaging ruled out the possibilities of MS, spondylosis, brain and spinal tumors, and other spinal diseases such as arachnoiditis or arteriovenous shunts. In addition, blood tests ruled out B₁₂ and copper deficiency, AIDS, Lyme disease, syphilis, and HTLV-1 infection. Interestingly, B₁₂ deficiency can be present even with normal B₁₂ levels. However, the normal serum homocysteine levels and a normal mean corpuscular volume ruled out this possibility. Genetic tests ruled out Friedrich ataxia and HSP type 4. EMG and nerve conduction studies dismissed the occurrence of myopathy or polyneuropathy. Thus, other types of HSP, variants of Friedrich ataxia, PLS, and AMN remained as diagnostic possibilities.

Brain FDG-PET hypometabolism suggests diffuse brain damage, even in light of a negative MRI. This finding makes PLS (in which the typical finding is an isolated hypometabolism in the motor cortex) improbable. In patients with HSP, diffuse brain hypometabolism is not usually present.^{4,5} Although the absence of white matter lesions in brain or spinal MRI makes highly unlikely the diagnosis of AMN or other forms of adrenoleukodystrophy (ALD), several cases of MRI-negative ALD have been described.^{6,7}

At 6-month follow-up, the patient reported increasing walking difficulties and pain in his legs. He also complained of severe asthenia, dizziness with postural changes, and generalized skin hyperpigmentation. Blood tests revealed decreased cortisol basal level (3.8 µg/dL) and increased basal ACTH level (1,945 pg/mL) with negative anti-21-hydroxylase antibodies, consistent with nonautoimmune adrenal insufficiency (AI). Due to the concurrence of AI and spastic paraparesis, we suspected AMN, which was confirmed by high plasma levels of very long-chain fatty acids (VLCFA), and a mutation in the *ABCD1* gene (c.1415_1416delAG).

Question for consideration:

1. How does adrenomyeloneuropathy present and what are the main therapeutic options?

DISCUSSION ALD can be classified into 4 main categories: cerebral inflammatory, AMN, Addison-only, and asymptomatic.⁸

AMN, which is often misdiagnosed as MS, HSP, or PLS, presents in adults (second to fourth decade of life) as a slowly progressive spastic paraparesis syndrome, with sensory and sphincter disturbances, and impotence, such as the present case. AI is present in two-thirds of patients. Hypogonadism may be present as well. Although it was absent in our patient, peripheral nerve involvement is present in most cases.⁹

AMN is subdivided further into pure AMN (in which radiologic, clinical, and pathologic features are

limited to the spinal axonopathy) and AMN-cerebral (in which there is also cerebral involvement).⁸ MRI may show white matter abnormalities in brain and atrophy in the spinal cord.¹⁰ Interestingly, both findings were absent in this case. However, brain FDG-PET showing a metabolic brain dysfunction suggested an AMN-cerebral form.

Treatment includes supportive and symptomatic treatment for patient and family, with rehabilitation and social support. Adrenal hormone replacement therapy, which can be lifesaving, is mandatory in those patients with ALD and AI.⁸ We initiated treatment with hydrocortisone 30 mg/day and fludrocortisone 0.05 mg/48 hours with calcium carbonate and vitamin D to prevent osteopenia. Dietary therapy with 4:1 glyceryl trioleate–glyceryl trierucate (Lorenzo oil) was not recommended in our case because its benefit has been proven only in asymptomatic boys whose brain MRI is normal.¹¹ The utility of hematopoietic stem cell transplantation is limited in adulthood and it is not known whether it can benefit patients with AMN.⁸

This case argues for the inclusion of AMN in the differential for any progressive spastic paraparesis syndrome regardless of the brain or spinal MRI findings. Thus, we suggest that plasma levels of VLCFA be obtained in any patient with spastic paraparesis in which the initial workup for other common causes is negative, especially if endocrine disturbances such as AI coexist. Brain FDG-PET also may be helpful in the diagnosis, as it may be more sensitive than MRI for detecting metabolic brain dysfunction in ALD.

AUTHOR CONTRIBUTIONS

Drafting/revising the manuscript for content: A.F.-V., J.-A.P., P.d.C. Study concept or design: A.F.-V., J.-A.P. Analysis or interpretation of data: A.F.-V., J.-A.P., M.A.F.-S., M.A.P., P.d.C. Acquisition of data: A.F.-V., J.-A.P., M.A.F.-S., M.A.P. Study supervision: P.d.C.

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DISCLOSURE

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