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Clinical Reasoning: A 48-Year-Old Man With Spasticity and Progressive Ataxia

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Abstract

We present the case of a 48-year-old man who was referred to the movement disorders clinic for 10 years of progressive slurred speech, spasticity, limb incoordination, and wide-based gait. Extensive neurological workup was inconclusive, including serum and CSF testing, neuroimaging, EMG/NCS, exome sequencing, and mitochondrial testing. An ataxia repeat expansion panel ultimately revealed the final diagnosis. In this report, we review the clinical characteristics of a rare, late-onset, autosomal recessive cerebellar ataxia and discuss the importance of pursuing targeted gene testing to avoid diagnostic delays, especially as new treatments for this and other genetic diseases become available.

Section 1

A 48-year-old White man with a history of concussion, hypertension, and attention deficit hyperactivity disorder was referred to the movement disorders clinic for 10 years of progressive slurred speech, spasticity, limb incoordination, and wide-based gait. At age 38, he first noticed leg stiffness and mild balance impairment. He could ambulate independently but had more trouble descending stairs. Over the next 2-3 years, his speech became more slurred and incoordination worsened in his lower extremities. Symptoms were constant without fluctuations. His childhood development was normal. He played both high school and college football without difficulty. There was no family history of neurological disorders or gait dysfunction. There was no tobacco or recreational drug use history, and he did not drink alcohol regularly. He took meloxicam intermittently for pain.

At age 42, he was seen by a neuromuscular specialist who noted scanning speech. Mental status, cranial nerve, and strength exams were normal. He had decreased tone and hyporeflexia in his upper extremities and increased tone and hyperreflexia in his lower extremities with bilateral Babinski signs. Pinprick, temperature, and vibration sensation were reduced in his hands and, to a lesser degree, in his feet. Proprioception and coordination were normal, and gait was mildly wide-based.

Where would you localize the lesion?

What is the differential diagnosis?

Section 2

His presentation was notable for cerebellar dysarthria, pyramidal tract dysfunction in his lower extremities (e.g., spasticity, hyperreflexia, bilateral Babinski signs), a non-length-dependent reduction to pinprick, temperature, and vibration sensation in his hands and feet, and an ataxic gait. Cerebellar dysarthria is characterized by irregular articulation, equal and excessive stress on syllables (i.e., scanning speech), and variations in pitch and intensity. A symmetrical, bilateral lower extremity pyramidal syndrome typically localizes to the corticospinal tracts in the cervical or thoracic spinal cord, or, less likely the bilateral medial precentral gyri or brainstem. However, when combined with sensory dysfunction involving the spinothalamic tracts (e.g., pinprick, temperature) and dorsal columns (e.g., vibration), a pyramidal syndrome more often localizes to the spinal cord. Finally, a non-length-dependent reduction to pinprick, temperature, and vibration sensation combined with segmental hyporeflexia should prompt the consideration of a sensory ganglionopathy or multifocal polyneuropathy. Thus, his symptoms suggest a multifocal process involving the cerebellum, spinal cord, and dorsal root ganglia or peripheral nerves.

The differential diagnosis for a slowly progressive adult-onset ataxia with neuropathy or neuronopathy favors a hereditary, toxic, iatrogenic, or neurodegenerative etiology (Table 1).¹⁻⁴ Although the absence of a family history makes an autosomal dominant condition less likely, an autosomal recessive condition or *de novo* autosomal dominant mutation is possible. There was no history of chronic alcohol abuse or medication exposure, arguing against a toxic or iatrogenic cause. Lastly, autoimmune and infectious etiologies were considered, but these conditions were thought less likely given his disease duration and lack of other systemic findings.

What investigations can help narrow the differential diagnosis?

Section 3

After his initial visit at age 43, MRI of the brain, cervical, thoracic, and lumbar spine were unremarkable, arguing against several conditions typically associated with cerebellar atrophy (Table 1). Nerve conduction studies showed reduced median, ulnar, and radial sensory amplitudes bilaterally with normal leg sensory responses; motor potentials were normal. Needle EMG was unremarkable. These findings support a sensory ganglionopathy or a non-length-dependent neuropathy. Given prominent lower extremity spasticity, his symptoms were initially attributed to hereditary spastic paraplegia (HSP), a heterogeneous group of disorders caused by degeneration of the lateral corticospinal tracts in the cervical and thoracic spinal cord. Persons with “pure” forms of HSP develop lower extremity spasticity and increased deep tendon reflexes with extensor plantar responses, while persons with “complex” forms of HSP can develop dysarthria, polyneuropathy, cerebellar ataxia, parkinsonism, and cognitive impairment, among other symptoms.⁴ He was referred for genetic testing.

HSP multi-gene panel was notable for a heterozygous 15q11.2 multi-gene deletion (i.e., *loss-of-function* mutation) involving the entire *NIPA1* gene. Because only missense variants in *NIPA1* resulting in pathologic *gain-of-function* mutations have been associated with autosomal dominant HSP,^{6,5} his variant was classified as one of uncertain significance as the disease risk and significance to function remain unclear. Subsequent exome sequencing (ES) with mitochondrial DNA analysis was negative. His genetic testing was considered non-diagnostic, and he was started on baclofen and diazepam with improvement in stiffness.

What additional investigations can help narrow the differential diagnosis?

Section 4

Around age 46, he was seen by a neuroimmunologist, and the following labs were unremarkable: vitamin B12, SPEP with immunofixation, TSH, ANA, and SSA/SSB. He had a mildly elevated hemoglobin A1c at 6.0 mg/d. He was evaluated for stiff-person syndrome (SPS), an autoimmune disorder associated with GAD-65 antibodies and type 1 diabetes mellitus that can lead to generalized rigidity, muscle spasms, and a wide-based gait. Serum GAD-65 antibodies were within normal limits. Due to concern for possible seronegative SPS, he was started on empiric IVIg 2gm/kg monthly for 4 months without improvement. Additional diagnostic workup for other treatable causes of myelopathy and ataxia was unrevealing, including serum (e.g., copper, ceruloplasmin, vitamin E, anti-tissue transglutaminase, HTLV, HIV, RPR) and CSF (e.g., routine studies, oligoclonal bands, IgG index, GAD-65) testing. Repeat brain and spinal cord imaging were reportedly unremarkable, but further review showed subtle atrophy in the superior cerebellar vermis (Figure). He was subsequently referred to the movement disorders clinic.

Is other genetic testing indicated?

Section 5

His focused ataxia exam was notable for normal oculomotor function, mild cerebellar dysarthria, dysmetria in all four extremities, and a wide-based gait with forward flexion of the arms and waist (Video). Other findings included hyporeflexia in his arms and hypertonia and hyperreflexia in his legs. Strength testing was normal and sensory exam was notable for distally-predominant hypoesthesia to pinprick and vibration in all extremities. Due to concern for inherited conditions not detected by ES, he was referred for genetic testing. The University of Chicago ataxia repeat expansion panel showed a pathogenic GAA allelic expansion without a normal allele in the frataxin (*FXN*) gene, suggesting two expanded alleles of the same length consistent with Friedreich ataxia (FRDA). Additional testing to determine the size of the GAA expansion(s) was not performed due to insurance constraints. His screening echocardiogram was normal.

Discussion

FRDA is the most common cause of hereditary ataxia, with an estimated incidence of 1 per 50,000-100,000 persons.⁶ FRDA is an autosomal recessive condition associated with biallelic GAA expansions or point mutations in the *FXN* gene on chromosome 9, leading to reduced production of the mitochondrial protein frataxin.⁷ The exact role of frataxin in the pathogenesis of FRDA is unclear, but the normal protein has been linked to the biogenesis of iron-sulfur clusters, iron chaperoning and storage, and control of iron-mediated oxidative stress.⁸ FRDA is considered a multi-system disorder with neurologic, cardiac, endocrine, and musculoskeletal involvement.⁹

Similar to other trinucleotide repeat disorders, the clinical phenotype of FRDA can vary based on GAA expansion number, with larger GAA repeats contributing to earlier age at onset

and faster disease progression.⁶ Individuals with onset before 8 years progress twice as quickly as those with onset after 15 years.⁹ While the majority of cases develop in adolescence, 25% of cases are associated with atypical or late-onset symptoms, defined as late-onset FRDA (LOFA) in individuals ages 26-39, and very late-onset FRDA (VLOFA) in individuals age 40 and older.¹⁰ Cases of FRDA and LOFA/VLOFA often differ phenotypically. Typical FRDA is characterized by progressive dysarthria, limb and gait ataxia, impaired vibration and proprioception with areflexia in the lower extremities, and extensor plantar responses. Common non-neurologic manifestations include hypertrophic cardiomyopathy, diabetes mellitus, and skeletal abnormalities, such as kyphoscoliosis and pes cavus. In contrast, persons with LOFA are more likely to develop lower limb spasticity with preserved or increased deep tendon reflexes and less likely to develop cardiomyopathy.¹ Spastic ataxia has also been reported as the presenting symptom of VLOFA.¹¹ These atypical findings can mimic HSP, SPS, or spinocerebellar ataxias, leading to diagnostic errors or delays.

With regard to workup, neuroimaging is typically normal. However, LOFA has been associated with superior cerebellar vermis atrophy (Figure), and both FRDA and LOFA are associated with cervical cord atrophy.¹ Electrodiagnostic studies may also show an axonal sensory neuropathy or sensory ganglionopathy.^{1,12} Commercially-available CSF studies are unremarkable but help exclude alternative infectious, autoimmune, and paraneoplastic causes. Diagnosis is based on confirmatory genetic testing, and the choice of gene panel has important clinical implications. In our case, HSP panel, ES, and mitochondrial testing were non-diagnostic. Although ES is often considered the gold standard for genetic testing, its methodology is not designed to detect the abnormal nucleotide repeat expansions associated with many forms of ataxia.¹³ Therefore, clinical suspicion for ataxia should prompt discussion with a geneticist and

consideration of targeted single- or multi-gene nucleotide repeat expansion panels to avoid diagnostic delays.

FRDA surveillance includes annual cardiac assessments, diabetes and scoliosis screening, swallowing and urodynamic testing, and ophthalmology and audiology evaluations.¹⁴ Treatment is symptomatic, and omaveloxolone, an activator of the mitochondrial Nrf2 pathway, was FDA-approved in February 2023 as a disease-modifying therapy for FRDA.¹⁵ Genetic counseling is also encouraged for patients and families. Although prenatal testing exists, predicting the clinical phenotype based on GAA repeat length alone is difficult.¹⁴

In conclusion, the diagnosis of progressive spasticity and ataxia is challenging. Clinicians must be cognizant of the varying presentations of FRDA and other trinucleotide repeat disorders based on age at onset. Careful examination and ancillary testing can help narrow the differential diagnosis and tailor genetic testing.

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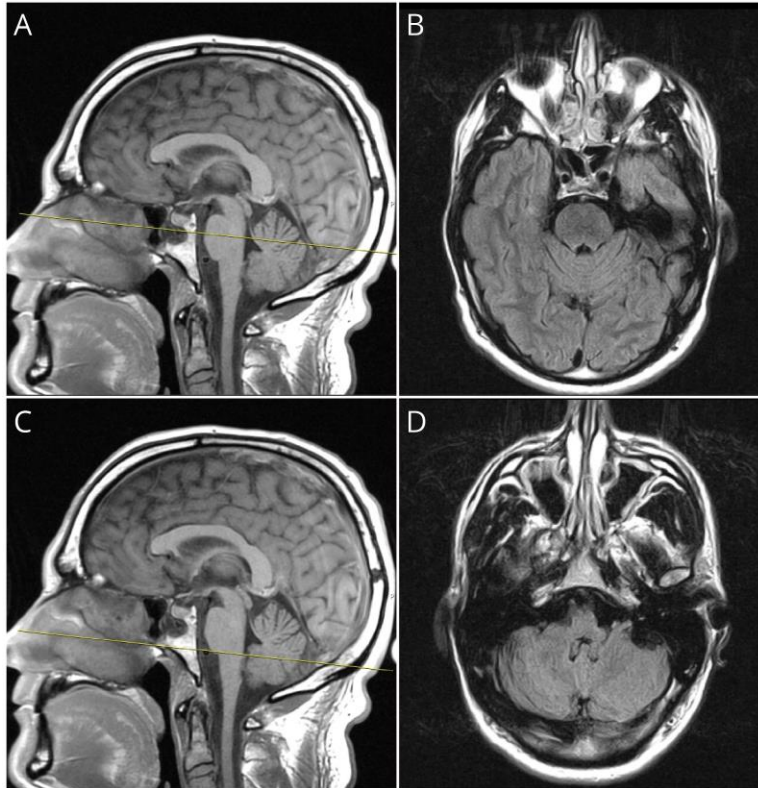
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Legends

Figure: MRI brain without contrast

Sagittal T1-weighted (A,C) and axial T2 FLAIR (B,D) images captured 8 years after symptom onset showed mild atrophy in the superior cerebellar vermis (A,B) more than inferior cerebellar vermis (C,D).



Video: Movement disorders examination

Neurological exam shows mild dysmetria with finger-nose-finger and overshoot with mirroring, mild dysmetria with heel-to-shin on the left more than right, 3+ patellar reflexes bilaterally, and a wide-based gait with flexion of the arms and forward trunk and pelvis tilt. Speech and oculomotor exams are not shown.

Table 1. Differential diagnosis for progressive adult-onset ataxia and sensory changes

| Category | Diagnosis | Cardinal Clinical and Laboratory Findings | MRI Findings |
|-------------------------------------|----------------------|---|--|
| Hereditary (Autosomal recessive) | ARCA | Type 1: isolated ataxia. Type 2: myoclonus, epilepsy, mental retardation. | Type 1 and 2: cerebellar atrophy. Type 2: stroke-like cerebral lesions. |
| | ARSACS | Neuropathy, spastic paraparesis, demyelination. | Cerebellar atrophy. T2 linear pontine hypointensities. |
| | AOA | Type 1 and 2: Neuropathy, variable oculocephalic dissociation, chorea, dystonia. Type 1: elevated serum LDL cholesterol, decreased serum albumin. Type 2: Elevated serum alpha-fetoprotein. | Type 1 and 2: Cerebellar atrophy. |
| | AVED | Neuronopathy, hyperreflexia, hypertonia. Low serum vitamin E. | No cerebellar atrophy, cervical cord atrophy. |
| | CANVAS | Neuronopathy, vestibular areflexia, chronic cough. | Cerebellar vermis and crus I atrophy. |
| | HSP | SPG7: Sensorimotor neuropathy, spastic ataxia, urinary sphincter dysfunction, amyotrophy. | Cerebellar atrophy. |
| | LGG | Neuropathy, spasticity, weakness, dystonia, epilepsy, dementia, psychosis, anterior horn cell involvement. | Cerebellar atrophy. |
| | LOFA | Neuronopathy, lower limb hyperreflexia and hypertonia. | Superior cerebellar atrophy, cervical cord atrophy. |
| | Adult Refsum disease | Sensorimotor neuropathy, retinitis pigmentosa, sensorineural hearing loss, ichthyosis. | No cerebellar atrophy. |
| | Iatrogenic | Chronic alcohol abuse | Neuropathy, hemoglobin macrocytosis, cardiac arrhythmias, cirrhosis, pancreatitis. |
| Phenytoin toxicity | | Neuropathy, osteomalacia, hirsutism, gum hypertrophy. | Cerebellar atrophy. |
| Neurodegenerative | MSA-C | Neuropathy, parkinsonism, dysautonomia, non-motor symptoms (e.g., anosmia, constipation, rapid eye movement sleep behavior disorders). | Putaminal, middle cerebellar peduncle, and pontine atrophy. |

ARCA, autosomal recessive cerebellar ataxia; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; AOA, ataxia with oculomotor apraxia; AVED, ataxia with vitamin E deficiency; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; GAD, glutamic acid decarboxylase; HSP, hereditary spastic paraplegias; LGG, late-onset GM2 gangliosidosis; LOFA, late-onset Friedreich ataxia; MSA-C, multiple system atrophy-cerebellar type

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