Clinical Reasoning: A 37-Year-Old Man With Involuntary Movements, Gait Disturbance, and Hyperesthesia

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SECTION 1

A 37-year-old right-handed Indigenous Canadian man presented with 2.5 years of progressive involuntary movements, gait instability, and hyperesthesia. He complained of constant, involuntary head and trunk movements, severe speech disturbance, dysphagia, blurred vision, and binocular diplopia in all directions. He took no regular medications and drank no alcohol. Past medical history was noncontributory. Family history was notable for a great uncle who died in his fifties from an unspecified gait disorder.

On examination, vital signs were normal. MMSE was 28/30, losing points for writing a sentence and copying a figure, largely due to involuntary limb movements. He had leftward square wave jerks on primary gaze, saccadic pursuit, bilateral horizontal gaze-evoked nystagmus, and impaired upgaze. He had significant dysarthria with staccato speech. The remainder of the cranial nerve examination was unremarkable. He had an 8 cm amplitude, 3-4Hz frequency, rhythmic, oscillatory titubation of the head.
and trunk with rest and posture as well as a 3 cm amplitude, 3-4Hz frequency, postural and action (up to 5Hz) tremor of the hands and feet bilaterally. He had an exaggerated startle response without spontaneous myoclonus. Muscle bulk, tone, and power were otherwise normal without fasciculations. Muscle stretch reflexes were 2+ throughout. He had widespread hyperesthesia throughout his limbs and trunk which precluded more detailed sensory testing. Coordination testing revealed bilateral, lower more than upper limb dysmetria. He had dysdiadokinesia and uncoordinated fine finger movements bilaterally, right more than left, and severe truncal ataxia when sitting upright that worsened when standing. Gait was broad-based with lateropulsion.

Question 1: Where does this process localize?

Question 2: What clinical tests and investigations would you consider?
The patient presents with a slowly progressive pan-cerebellar syndrome affecting speech, eye movements, and prominent truncal and appendicular ataxia. A pan-cerebellar syndrome is usually caused by infectious or parainfectious processes, immune-mediated, or metabolic etiologies. Figure 1 demonstrates an approach to ataxia in adults. In this case, given the slowly progressive symptoms, the main considerations were genetic, metabolic, or immune-mediated causes, whereas vascular and infectious etiologies were considered less likely. However, diffuse hyperesthesia suggests involvement beyond the cerebellum, and may be localized to disruption to any part of the central or peripheral somatosensory pathway.

Further review of systems revealed diffuse pruritus, poor sleep with frequent awakening, alternating constipation and diarrhea, and urinary hesitancy. He described a 20lb weight loss with no fevers or night sweats. He ate a regular diet and had no toxic environmental exposures.

Complete blood count, basic metabolic panel, thyroid stimulating hormone, vitamin B12, vitamin E, iron profile, urinary copper, tissue transglutaminase IgA, and a rheumatologic panel were unremarkable. MRI head without contrast showed isolated, diffuse cerebellar atrophy (Figure 2A-B). A paraneoplastic panel (amphiphysin, Ma2/Ta, CV2.1, Ri, Recoverin, SOX1, Titin, Yo, Hu, GAD65, and Tr/DNER), and bacterial and viral cultures in serum and cerebrospinal fluid (CSF) were negative. Enhanced CT of the chest, abdomen, and pelvis as well as fluorodeoxyglucose-positron emission tomography were negative for malignancy. CSF showed elevated protein and positive oligoclonal banding. Targeted genetic testing was performed for Friedrich’s ataxia and spinocerebellar ataxias 1, 2, 3, 4, and 6 as these are the most common adult-onset genetic ataxias. Testing revealed a heterozygous trinucleotide expansion in the frataxin gene, with a point mutation on the other allele.

**Question 1:** Do these findings explain his symptoms?

**Question 2:** What other investigations would you consider?
SECTION 3

The differential diagnosis for diffuse cerebellar atrophy is wide and includes toxin exposure, neurodegenerative disorders, hereditary cerebellar ataxias, paraneoplastic degeneration, and infectious or inflammatory cerebellitis.

Friedreich ataxia (FA) is the most common inherited ataxia, and is usually caused by a homozygous GAA trinucleotide expansion in the frataxin (FXN) gene on chromosome 9q13.2 Most patients present before age 20, with larger GAA expansions correlating to earlier age of onset and severity. Although true heterozygotes are asymptomatic, compound heterozygotes (such as our patient) and those with smaller GAA expansions may present with late-onset Friedreich ataxia (LOFA), typically after the age of 20. LOFA presents similarly to FA, although with milder phenotypes and without characteristic skeletal deformities. Spinal cord atrophy is typically seen regardless of age of onset, but LOFA may have cerebellar vermian atrophy and fourth ventricular enlargement. LOFA should be considered in the work-up of progressive ataxia in young adults given a high prevalence of carriers, estimated at 1 in 50,000 in Caucasian populations.

Cases describing cerebellar atrophy have been reported for many neurodegenerative disorders such as Alzheimer’s Disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple system atrophy, and progressive supranuclear palsy. Given the patient’s age, preserved cognition, and lack of other hallmark clinical or imaging features, these diagnoses were considered less likely. The patient also had no known exposure to alcohol, medications, or other toxins. Therefore, the primary considerations in this case were hereditary cerebellar ataxias, paraneoplastic cerebellar degeneration, and immune-mediated cerebellitis. The concurrent sensory hyperesthesia and autonomic dysfunction suggested either a systemic process or an additional parallel process.

Repeat MRI of the head and cervical spine with contrast performed ten months later revealed progression of the diffuse cerebellar atrophy with no significant atrophy of the spinal cord (Figure 2C-E) and no
abnormalities on T2-FLAIR. The inflammatory CSF pattern, systemic symptoms not commonly
associated with LOFA and lack of hallmark imaging findings suggested an alternative or additional
diagnosis. The compound heterozygotic mutation was considered a variant of uncertain significance,
potentially contributing to, but not fully explaining the patient’s syndrome. Given FA is an untreatable
condition, it is important to consider other potentially treatable contributors to his presentation.

Serum autoimmune encephalitis antibody panel was sent which revealed a high positive titer for anti-
dipeptidyl peptidase-like protein 6 (DPPX). The patient was trialed on immunosuppressive therapy for
presumed anti-DPPX encephalitis with oral prednisone, intravenous immunoglobulin (IVIg), and
rituximab induction. His exaggerated startle significantly improved. He experienced transient
improvement in his involuntary movements and hyperesthesia with each of these treatments but continued
to have overall gradual progression of his symptoms. He therefore underwent five sessions of plasma
exchange (PLEX) which further improved his involuntary movements, pruritus, and hyperesthesia.
Truncal and appendicular ataxia mildly improved, but he could still not stand unassisted. There was no
improvement in speech. Symptoms remained stable six weeks after PLEX and he is planned for
maintenance PLEX and rituximab therapy.
DISCUSSION

In 2012, Boronat et al described a novel cell surface autoantigen mediated encephalitis secondary to autoantibodies against dipeptidyl peptidase-like protein 6 (DPPX). DPPX is a regulatory subunit of the voltage gated rapidly inactivating potassium channel Kv4.2. It is important in somatodendritic signal integration and inhibition of back-propagation of action potentials. Reduced expression due to autoantibody binding leads to hyperexcitability.

DPPX is highly expressed in the hippocampus, striatum, cerebellum and myenteric plexus. Patients present with a constellation of symptoms attributable to dysfunction in these areas, including cognitive impairment, movement disorders, cerebellar and brainstem dysfunction, and diarrhea with profound weight loss. Abnormal movements described in previous case series include parkinsonism, orobuccolingual dyskinesia, tremor, myoclonus, rigidity, and hyperekplexia. Postural hypotension and sleep disturbances have also been reported. Hyperexcitability in the central and peripheral nervous systems are reported to cause seizures, pruritus, and dysesthesias. Patients may occasionally present with a picture similar to progressive encephalomyelitis with rigidity and myoclonus (PERM) or stiff person syndrome.

Symptoms typically progress over months to years. Diagnosis is often delayed, due to non-specific clinical features and frequently unremarkable neuroimaging. Association with neoplastic processes have been reported, particularly B-cell lymphoma. CSF analysis may show pleocytosis and increased IgG synthesis rate. Detection of the auto-antibody is diagnostic, with higher sensitivity on cell based assays than immunofluorescence. Treatment consists of immunotherapy, mainly corticosteroids, though maintenance with tacrolimus, rituximab, IVIG and PLEX have also been used.

In one review of 53 patients, 48% experienced marked improvement after immunotherapy. Cessation of therapy led to relapse of symptoms in two out of nine patients in a small case series. Delay in treatment initiation may correlate with poorer outcomes, as highlighted in a case of a 53-year-old man who began...
treatment with corticosteroids, PLEX, and rituximab 2 years following symptom onset with relatively poor results. Untreated inflammation over time may lead to irreversible atrophy, which is less likely to respond to immunotherapy, as seen in our case.

This case illustrates the broad approach to a patient with a constellation of symptoms including a pan-cerebellar syndrome. An important takeaway from this case is that premature closure after an initial possible diagnosis may result in missed diagnosis of additional pathology. Though the results of the patient’s initial genetic testing potentially contributed to his presentation, it did not fully explain his presentation - particularly with hyperesthesia and systemic symptoms. Therefore, it was important to consider additional diagnoses. This is particularly important when a presumed diagnosis is untreatable and there is clinical uncertainty.
References


Figure Captions

Figure 1: Etiologies of ataxia in adults.

<table>
<thead>
<tr>
<th>Etiologies of ataxia</th>
<th>Acute</th>
<th>Subacute</th>
<th>Chronic</th>
<th>Episodic</th>
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<tr>
<td>Infectious</td>
<td>Bacterial meningitis, viral cerebellitis, cerebellar abscess, tick paralysis</td>
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<tr>
<td>Degenerative</td>
<td>Creutzfeldt-Jakob disease</td>
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**Genetic**

- Autosomal dominant: Spinocerebellar ataxia 1-31, episodic ataxia 1-6
- Autosomal recessive: Friedreich ataxia, ataxia telangiectasia, vitamin E deficiency, Wilson disease, many others
- X-linked: Fragile X tremor ataxia syndrome (FXTAS), X-linked adrenoleukodystrophy

**Mitochondrial**

- MEIAS, MERFF, NARP, Kearns-Sayre syndrome and many others

**Acquired**

- Multiple system atrophy, superficial siderosis, hypothryoidism, autoimmune or paraneoplastic cerebellar degeneration, non-Langerhans cell histiocytosis, idiopathic late-onset cerebellar ataxia

**Immune mediated**

- Demyelinating disease (multiple sclerosis, NMO spectrum disorders, anti-MOG)

**Genetic**

- Episodic ataxia 1 and 2, familial hemiplegic migraine (+/- basilar migraine)

**Metabolic**

- Rare in adults, porphyria, mitochondrial disorders
Figure 2: Initial MRI brain and repeat MRI brain and cervical spine with contrast ten months later.

MRI T2-weighted axial brain (A,B), sagittal cervical spine (C), and T1-weighted sagittal and coronal brain (D) show cerebellar atrophy with prominence of the folia (small arrows). There is marked progression over 10 months (A compared B) and no cord atrophy (C). There was no enhancement with gadolinium in the brain or cervical spine (not shown).
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