Clinical Reasoning: A 27-year-old man with acute-onset ataxia

SECTION 1
A 27-year-old man with a history of diabetes mellitus (DM) and asthma presented to the emergency department 1 month after the onset of dysarthria and ataxia. The symptoms were noted abruptly upon waking. He swayed on standing, fell easily, and noted tremor when manipulating objects. His speech was nearly unintelligible. He also had 1 month of mild distal paresthesias and a 30-pound unintentional weight loss. He denied diplopia, dysphagia, preceding illness, or other systemic symptoms. Over the course of the month, his dysarthria improved but his imbalance remained unchanged. His delay in seeking medical attention was due to lack of health insurance.

The patient’s type 2 DM was diagnosed in adolescence. It was initially controlled with metformin and then insulin. As an adult, he lost health insurance coverage. He subsequently self-medicated with sporadic doses of insulin. He had a 3-pack-year tobacco smoking history, consumed 3 ounces of alcohol per week, and used marijuana once per week. He worked in construction, fireproofing, and insulating old buildings.

Examination revealed saccadic visual pursuit with intact voluntary saccades. There were no square wave jerks or nystagmus. Speech was dysarthric. Cranial nerve examination was otherwise normal. Strength was preserved, but the patient’s tone was diffusely diminished. Vibratory sensation was 2 seconds at the toes with otherwise preserved sensation. Deep tendon reflexes were absent in upper and lower extremities. Plantar responses were flexor bilaterally. The patient had marked ataxia on finger-to-nose and heel-to-shin with intention tremor, dysrhythmokinesia on hand tapping, and dysdiadochokinesia with rapid alternating movements. Stance was stable with no truncal ataxia. Romberg was positive with subtle sway with eye closure. Gait was wide based; he was unable to tandem walk.

Questions for consideration:
1. Where does this process localize?
2. What is the differential diagnosis for acute-onset ataxia?
SECTION 2

The patient’s examination revealed cerebellar dysfunction and peripheral polyneuropathy. Severe proprioceptive deficits can result in a sensory appendicular ataxia. In this patient, the degree of sensory impairment did not account for the severity of the appendicular ataxia. Cerebellar dysfunction was supported by the presence of dysdiadochokinesia, dysrhythmokinesia, intention tremor, saccadic pursuits, and dysarthria.

The differential diagnosis for cerebellar ataxia can be narrowed by the timing of clinical onset. Causes of acute-onset ataxia include 3 categories of pathology: vascular, toxic, and infectious. Both ischemic and hemorrhagic posterior circulation strokes should be considered. Acute-onset ataxia can also result from exposure to medications (antiepileptics, antineoplastics, lithium salts, metronidazole), recreational drugs (alcohol, phencyclidine), and environmental toxins (carbon tetrachloride, bromides, toluene, mercury, manganese). Our patient worked in old buildings, which can be a source of mercury intoxication. Postinfectious viral cerebellitis typically occurs in children, yet has also been described in young adults secondary to Epstein-Barr virus.

Since our patient also had a peripheral neuropathy, diagnoses unifying it and the cerebellar ataxia should be considered. His history of unintentional weight loss raises concern for malignancy and an associated paraneoplastic syndrome. Classically, anti-Hu manifests with cerebellar degeneration and neuropathy. Vitamin deficiencies can also cause both cerebellar and peripheral nerve involvement (B₁, B₁₂, E). In contrast to our case, these disorders present subacutely.

Questions for consideration:
1. What investigations would you order?
2. Can the peripheral neuropathy and cerebellar ataxia be accounted for by a unifying diagnosis?
SECTION 3
The patient was admitted to the hospital for an expedited workup. MRI of the brain showed symmetric signal abnormalities in the pons and cerebellum (figure). Laboratory testing identified uncontrolled DM. His blood glucose peaked at 708 mg/dL early in his hospital course and his HbA1c was 15.9%. A lumbar puncture revealed elevated protein (207 mg/dL) and elevated glucose (194 mg/dL) but no pleocytosis. The remainder of his workup was unremarkable: complete blood count, basic metabolic panel, vitamin B₁₂, vitamin E, heavy metals (mercury and lead), CSF paraneoplastic panel, and CSF viral PCR for Epstein-Barr virus, herpesvirus, and varicella-zoster virus were normal or negative.

EMG revealed a moderate, length-dependent motor and sensory, predominantly axonal, polyneuropathy. This was compatible with a diabetic neuropathy, in the context of uncontrolled hyperglycemia. There were no clinical features that conflicted with this possibility, such as asymmetry, rapidly progressive coarse, motor greater than sensory deficits, or proximal greater than distal deficits. Other testing for the neuropathy was unremarkable: antinuclear antibody, anti-Ro, anti-La, serum and urine protein electrophoresis, HIV, and syphilis were normal or negative.

Questions for consideration:
1. What is the diagnosis?
2. What is the prognosis?

Figure Axial head MRI

(A) Axial T2 brain MRI shows symmetric hyperintensity of the pons with relative sparing of the corticospinal tracts and hyperintensity of the paramedian cerebellar folia; (B) T1 contrast enhancement within a similar pontine distribution; and (C) a diffusion-weighted image shows restricted diffusion within a similar cerebellar distribution.
SECTION 4

Our patient’s MRI revealed symmetric signal abnormalities within the pons and cerebellum. The symmetry suggests toxic, metabolic, and genetic categories of pathology. Metronidazole and methyl bromide intoxications can produce symmetric imaging findings in the pons and cerebellum, among other structures. Pontine involvement is limited dorsally and cerebellar involvement limited to deep nuclei. These intoxications are unlikely in our patient, given the lack of exposure and incompatible imaging. Genetic causes are also unlikely, given the clinical course of acute-onset symptoms followed by improvement. Among metabolic disorders, osmotic demyelination syndrome (ODS) frequently affects the pons and can also affect the cerebellum. In this disorder, the pons characteristically has a trident-shaped signal change due to relative sparing of the corticospinal tract. This pattern of injury was present in our patient (figure, A).

Our patient was diagnosed with ODS and peripheral neuropathy from uncontrolled DM. His delayed presentation to the hospital posed a diagnostic challenge. It is unclear what his metabolic homeostasis was at the time of injury. Nevertheless, his diagnosis was made in the context of characteristic imaging, the risk of rapid fluctuations in osmolarity, and by negative tests for alternate causes of acute-onset ataxia.

ODS is the degeneration of oligodendrocytes and their myelin caused by a rapid rise in extracellular osmolarity. Cells normally adapt to changes in extracellular osmolality by shifting their ions and organic solutes. This process maintains cells isotonic to their surroundings and protects them from swelling or shrinking. Cellular injury occurs when the rate of rising extracellular osmolarity outpaces the rate of cellular adaptation.

Clinically, ODS results from the rapid correction of chronic hyponatremia. It can also occur with a rise in extracellular osmolality, without preceding hyponatremia. This has been described in hyperosmolar hyperglycemia from uncontrolled DM and dehydration from severe burns.1–3 Several factors appear to increase the susceptibility to ODS. Alcoholism is the main associated condition, followed by cirrhosis and malnutrition.4 Our patient was likely exposed to hyperosmolar states from uncontrolled DM and sporadic insulin use.

The process of osmotic demyelination can affect various brain structures and produce diverse clinical manifestations. Isolated pontine injury occurs in half of patients. This can manifest with encephalopathy, dysarthria, dysphagia, oculomotor dysfunction, and spastic quadriparesis. Extrapontine injury occurs in the remaining half of patients, with or without associated pontine involvement.5 Extrapontine injury can occur in the cerebellum, thalamus, basal ganglia, hippocampus, or mesencephalon. Injury of these structures can manifest with ataxia, behavioral changes, parkinsonism, dystonia, or chorea.3,6–8 Presentations range in severity from mild symptoms to coma. Relevant to our patient, the cerebellum is the most common extrapontine structure affected in ODS.

MRI has become essential in establishing a diagnosis of ODS. The imaging hallmark is strikingly symmetric signal abnormalities, accounted for by diffuse metabolic pathophysiology. Restricted diffusion is the earliest and most sensitive acute finding. T2 hyperintensity is commonly seen, yet can be delayed for weeks after the symptom onset. Thus, follow-up imaging may be required in patients with normal initial imaging. Both T1 hypointensity and contrast enhancement are seen in a minority of cases.9

Our understanding of the prognosis in ODS has evolved over time. When first recognized in autopsy cases, ODS was thought to be rare and invariably fatal. Advances in imaging have allowed the recognition of this disorder’s spectrum. Half of affected patients recover and regain independent function, one-quarter remain disabled, and one-quarter die.4 Favorable outcomes are predicted by higher Glasgow Coma Scale scores on presentation (>10 points), less severe hyponatremia (>115 mEq/dL), and the absence of concomitant hypokalemia.4 The extent of signal abnormalities on MRI does not predict clinical outcome.10

Our patient was started on insulin (glargine 15 units/d with sliding scale lispro 0–20 units/meal) and discharged home. At follow-up, 3 months later, his dysarthria had resolved, he had only slight dysmetria on finger-to-nose testing, his gait had normalized, and he was able to tandem walk.

AUTHOR CONTRIBUTIONS
Jorge Risco was involved in drafting and revising the manuscript for content. Menachem Weiss was involved in drafting and revising the manuscript for content.

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