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Clinical Reasoning: A 54-year-old woman with dementia, myoclonus, and ataxia

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SECTION 1

A 54-year-old woman was referred for a second opinion regarding a 3-month history of subacute onset progressive cognitive decline. She complained of memory difficulties particularly with short term recall. Decision-making and organizational skills were increasingly difficult. She also developed sudden brief jerking movements of her body and progressive gait imbalance and incoordination leading to falls. Three months after onset, she could not work, drive, cook, or perform activities of daily living. She had not had episodes suggestive of seizures. Her medical history was remarkable for celiac disease diagnosed 9 years previously, which resolved with a gluten-free diet, collagenous colitis, Raynaud syndrome, osteopenia, anxiety, and prior episodes of hyponatremia related to polydipsia. Current medications included amitriptyline, venlafaxine, and Pepto-Bismol. She worked as a financial analyst, had never consumed tobacco products, and drank 3–4 alcoholic beverages per week. Her father had myasthenia gravis but there was no family history of dementia. General examination revealed a restless woman with pseudobulbar affect who was unable to provide a meaningful history. Neurologic examination revealed multiple abnormalities. Mental status testing revealed a mild to moderate degree of encephalopathy including abnormalities in attention, frontal lobe function, and comprehension. Kokmen short test of mental status score was 23 out of 38 (29/38 or less consistent with dementia). There was multifocal myoclonus and postural tremor. Cerebellar examination revealed appendicular and gait ataxia. Muscle strength and reflexes were normal. Sensory examination was unreliable due to dementia.

Question for consideration:

1. What is the differential diagnosis?

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SECTION 2

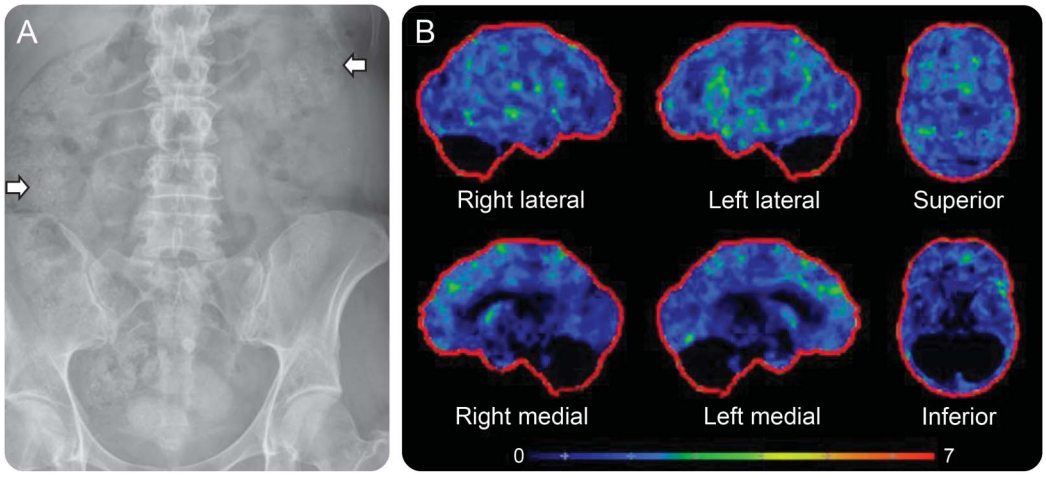
Differential diagnoses included various potential mechanisms for a rapidly progressive dementia.

1. Prion disease (e.g., Creutzfeldt-Jakob disease [CJD])
2. Autoimmune/paraneoplastic encephalopathy
3. Toxic/metabolic encephalopathy (e.g., medication-induced, electrolyte disturbance, serotonin syndrome, heavy metal toxicity)
4. Neoplasm (e.g., gliomatosis cerebri, neoplastic meningitis, intravascular lymphoma)
5. Infectious etiologies (e.g., HIV, syphilis, Whipple)
6. Vascular disorders (e.g., CNS vasculitis, β-amyloid-related angiitis)
7. Other neurodegenerative etiologies (e.g., early-onset Alzheimer disease)
8. Other systemic or extraneurologic autoimmunity that can be accompanied by neurologic manifestations (e.g., celiac disease)

Given the concomitant use of a tricyclic antidepressant (amitriptyline) and serotonin and norepinephrine reuptake inhibitor (venlafaxine) accompanied by confusion and myoclonus, serotonin syndrome was a consideration. However, there were no recent medication adjustments, no fever was present, and the presentation over 3 months was felt to be too insidious. MRI brain with gadolinium contrast and magnetic resonance angiogram of the brain were both normal at an outside facility prior to referral to our institution. The normal imaging excluded primary brain neoplasm or metastatic lesions as the cause and made vasculitis and meningitis unlikely. There were no radiologic features suggestive of CJD (cortical ribboning on diffusion-weighted images or T2 hyperintensities in the caudate were not found) despite a high clinical suspicion given the rapidly progressive dementia accompanied by ataxia and myoclonus. Similarly, imaging did not reveal changes suggestive of an autoimmune encephalopathy, such as mesial temporal lobe signal abnormalities. Initial laboratory testing at an outside facility revealed a sodium level of 118 mmol/L (normal 135–145) a few weeks prior to our evaluation and repeat testing after fluid restriction revealed a level of 129 mmol/L with a serum osmolality of 262 mOsm/kg (normal 275–295). However, the patient's confusion persisted and hence her referral to Mayo Clinic for further evaluation. Thyroid function was normal. Systemic autoimmune disease with nervous system involvement was also a consideration but antinuclear, SSA/SSB, myeloperoxidase, and PR-3 antibodies were all negative. Celiac disease has been linked to ataxia and rarely dementia. Celiac serology was negative, consistent with serologic remission from her gluten-free diet. To further evaluate nutritional deficiencies, particularly given the potential of malabsorption, vitamin B^{12}, folate, vitamin B_6, and vitamin E were all assessed and within normal limits. Serum levels of arsenic, mercury, cadmium, lead, magnesium, copper, and zinc were also normal.

An abdominal X-ray performed as part of the workup for any relationship to her gastrointestinal conditions revealed multiple radio-opaque deposits (figure, A). ^{18}F-fluorodeoxyglucose (FDG) PET scan of the brain was done to evaluate for primary neurodegenerative disorders and showed a generalized mild to moderate reduction of FDG uptake in both cerebral hemispheres, consistent with a nonspecific encephalopathy and not suggestive of Alzheimer or

Figure **Abdominal X-ray and brain FDG-PET findings**



(A) Abdominal X-ray shows speckles of scattered speckled radio-opaque deposits throughout but most prominent in the ascending and sigmoid colon (arrows). (B) FDG-PET brain shows diffuse nonspecific mildly reduced uptake consistent with metabolic encephalopathy as opposed to a specific neurodegenerative disorder (normal uptake = blue/black; mildly reduced uptake = green; moderately reduced uptake = yellow; markedly reduced uptake = red).

Lewy body disease (figure, B). EEG showed normal posterior rhythm, diffuse intermittent slowing in the delta frequency range, but no periodic sharp waves that can occur with CJD. CSF analysis revealed a normal cell count, protein, and glucose; oligoclonal bands were not present and neuron-specific enolase was normal. CSF infectious parameters were unrevealing and included herpes simplex virus, varicella-zoster virus, and Whipple PCR and syphilis testing. Comprehensive neural autoantibody testing in serum revealed elevated voltage-gated potassium channel complex (VGKCc) autoantibodies at 0.06 nmol/L (normal ≤0.02 nmol/L). VGKCc testing in the CSF was normal. All other neural antibodies in serum and CSF including glutamic acid decarboxylase 65 autoantibodies, NMDA, AMPA, and GABA-B receptor autoantibodies, anti-neuronal nuclear autoantibodies type 1 (anti-Hu) and 2 (anti-Ri), and Purkinje cell autoantibody type 1 (anti-Yo), 2, and Tr were all negative.

Question for consideration:

1. How could the clinical significance of the VGKCc autoantibody be further clarified?

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SECTION 3

While the subacute encephalopathy, myoclonus, family history of autoimmunity, and hyponatremia could fit anti-leucine-rich glioma inactivated-1 (LGI1) autoantibody encephalitis, VGKCc autoantibody subtyping for LGI1 and anti-contactin-associated protein-2 (Caspr2) antibodies were negative. A positive VGKCc autoantibody with negative LGI1 and Caspr2 antibody testing is of uncertain clinical significance.

Questions for consideration:

1. What is the diagnosis?
2. How was the diagnosis confirmed?

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SECTION 4

The patient carried a diagnosis of collagenous colitis, for which she took bismuth subsalicylate 1,048 mg daily for approximately 2 years preceding presentation. Whole blood bismuth level at 948 ng/mL and urine bismuth level at >406.5 ng/mL were in the toxic range (normal <50; toxic >200 ng/mL). The abdominal X-ray findings were a clue suggestive of bismuth accumulation in the gut. The diagnosis was bismuth neurotoxicity causing rapidly progressive dementia, myoclonus, and ataxia. The patient's initial hyponatremia could have resulted from secretory diarrhea from collagenous colitis, excess water drinking in the setting of the disinhibition, or syndrome of inappropriate antidiuretic hormone secretion from bismuth neurotoxicity. We recommended discontinuation of all bismuth subsalicylate use and maintenance of regular bowel movements to facilitate excretion. At 10 weeks follow-up visit, the patient was cognitively back to near normal functioning, other than very mild difficulty with complex arithmetic. She was able to return to work and function independently in all activities of daily living. Myoclonus and gait ataxia resolved. Whole blood bismuth level returned to normal at 9.5 ng/mL, whereas the urine level declined to 8.6 ng/mL (normal <50; toxic >200 ng/mL).

DISCUSSION This case highlights the importance of considering a broad differential diagnosis when evaluating patients with subacute onset rapidly progressive cognitive syndromes and avoiding premature closure if a nonspecific elevation of a neural autoantibody is found. Second, it is very important to obtain a good history of medication and toxin exposure. Third, bismuth neurotoxicity is a rare but well-described clinical entity that our patient demonstrated.

Bismuth has been reported to cause a reversible syndrome characterized by myoclonus, ataxia, and cognitive decline.[1] Another report of 45 patients describes stages of bismuth-related neurotoxicity. A prodromal stage of neuropsychiatric symptoms such as depression, anxiety, and somnolence may be seen. This is followed by memory difficulties, inattention, and subsequently myoclonus, ataxia, and more obvious encephalopathy. In most of these patients, EEG was negative for epileptiform abnormalities, but can rarely show myoclonic status, as evidenced by a single case.[2] In patients who died, cerebellum, thalamus, and frontal and occipital cortices showed the highest accumulation of bismuth.[3] The syndrome has been likened to prion disease.[4] Bismuth absorption through the gut is variable, and may be increased in states of abnormal gut permeability. The half-life of bismuth described in humans varies from 3.5 minutes to 17–22 years.[5] Our patient was potentially at higher risk of bismuth absorption through the gastrointestinal tract due to comorbid conditions of microscopic colitis and possible celiac disease. Both of these conditions have been linked to altered mucosal permeability and conceivably increased bismuth absorption.[6]

Various mechanisms of neurotoxicity have been postulated primarily based on mouse model experiments. Bismuth has been shown to travel retrogradely through the axons to cell bodies after intramuscular instillation.[7] In vitro rat brain tissue experiments have also shown accumulation of bismuth in astrocytes.[8] Once in a nervous system cell, mechanism of injury is postulated to be via genotoxic effects with impairment of DNA repair.[9]

In addition, our patient had positive VGKCc autoantibodies, raising the possibility of an autoimmune encephalopathy, but the negative subtyping for LGI1 and Caspr2 antibodies raised concern. A recent study showed that autoimmune neurologic disease was much more prevalent among patients with positive antibodies to LGI1 or Caspr2 and an isolated positive VGKCc antibody with negative testing for LGI1 and Caspr2 was not a clear marker of autoimmune encephalopathy, which is further emphasized by our case.[10]

AUTHOR CONTRIBUTIONS

Dr. Ali: manuscript draft. Dr. Flanagan: manuscript editing and supervision. Drs. Murray and Adams: manuscript editing.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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