Clinical Reasoning: A 72-year-old man with rapid cognitive decline and unilateral muscle jerks

A 72-year-old man presented with cognitive decline and unilateral muscle jerks. Three months prior to presentation, the patient suddenly developed violent muscle jerks involving the right side of his body and face that impaired his gait and balance. Approximately 1 week later, he acutely developed confusion and memory loss. Over the following weeks, he experienced fluctuating symptoms of confusion, memory impairment, insomnia, and paranoid delusions. His muscle jerks and unstable gait were intermittent with return to baseline in between attacks, but they increased in frequency and occurred many times throughout the day. He was found to be mildly hyponatremic and was eventually admitted to a psychiatric ward for treatment of acute psychosis.

On neurologic examination, the patient was alert and oriented to person only. He registered 3 items but was unable to recall them at 5 minutes and was unable to complete serial 7s. He had no language deficits and could follow 3-step commands without difficulty. His cranial nerve, motor, and sensory examination results were normal. He had a wide-based gait with prominent right lateral pulsion and retropulsion, without any observed muscle jerks during gait examination. Occasional myoclonus involving the right side of his face and right upper extremity were observed, which were associated with loss of awareness and dystonic posturing of the right arm.

The patient was admitted to the general neurology ward and an MRI of the brain was performed (figure).

Questions for consideration:
1. Based on the history and physical examination, what is the differential diagnosis? How does the MRI narrow the differential?
2. What further workup would you order at this time?

Fluid-attenuated inversion recovery sequences show hyperintensity in (A) bilateral hippocampi and amygdalae and (B) the left caudate and putamen.

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SECTION 2
This patient presents with a subacute encephalopathy of fluctuating intensity, with myoclonus and gait abnormalities preceding the development of cognitive symptoms. Though the right-sided myoclonus may be cortical or subcortical, the localization can be narrowed based on other findings. Retropulsion is an extrapyramidal sign often due to loss of postural reflexes and is seen in disorders that involve the basal ganglia; the asymmetric right lateral pulsion localizes this to the left basal ganglia. The patient also displays cognitive deficits in orientation, memory, and attention, which indicate that there might be further cortical or subcortical involvement. The differential diagnosis should consider subacute encephalopathies that present with this constellation of findings.

The patient’s rapid cognitive decline, myoclonus, and gait instability raise concern for Creutzfeldt-Jakob disease (CJD) and other prion diseases; other neurodegenerative conditions are common in this age group but less likely given the rapid clinical progression. Limbic encephalitis can mimic CJD and may result from a paraneoplastic syndrome or autoantibodies in the absence of cancer. Additional diagnostic categories to consider are autoimmune conditions (e.g., Sjögren syndrome, lupus, Hashimoto encephalopathy, sarcoidosis, CNS vasculitis), infections (tuberculosis, Lyme disease, *Listeria*, Whipple disease, *Cryptococcus*, toxoplasmosis), and neoplasms. Potentially reversible causes of encephalopathy can be ruled out with simple blood tests, including complete blood count (CBC), general chemistries, thyroid-stimulating hormone (TSH), vitamin B₁₂, and rapid plasma reagin, and an EEG can be performed to rule out seizures.

The MRI showed T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in bilateral hippocampi and amygdalae, with FLAIR hyperintensity and postcontrast enhancement in the left caudate and putamen. There was no cortical ribboning or diffusion restriction on diffusion-weighted imaging, making CJD less likely. The MRI confirms the suspected basal ganglia involvement, and the hyperintensities in the limbic region may explain the patient’s cognitive symptoms. These findings are consistent with limbic encephalitis; however, other autoimmune and infectious etiologies should be ruled out.

Plasma sodium level on admission was 132 mM (normal range 135–145 mM) with a nadir of 122 mM during his hospitalization; otherwise his CBC and chemistry panel were unremarkable. TSH and vitamin B₁₂ were normal. CSF studies showed a mildly elevated protein of 69 mg/dL (normal range 15–40 mg/dL) but were otherwise unremarkable, including immunoglobulin G synthesis rate and index with no inflammatory cells or oligoclonal bands. Serum autoimmune and inflammatory workup including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, rheumatoid factor, Sjögren syndrome A/Sjögren syndrome B, angiotensin-converting enzyme, antithyroid peroxidase, and antithyroglobulin were unremarkable. Infectious workup was negative for herpes simplex virus, HIV, syphilis, and a meningoencephalitis panel. A paraneoplastic antibody panel (table e-1 on the Neurology® Web site at Neurology.org) of the serum and CSF was pending, although anti-Hu and anti-NMDA receptor were negative by outside records. A 16-hour continuous EEG showed diffuse slowing and was negative for epileptiform discharges. Whole-body PET/CT scan, a serum lymphoma panel, and a scrotal ultrasound were all negative for neoplasm.

Questions for consideration:
1. Can a diagnosis of paraneoplastic limbic encephalitis be made in the absence of cancer or a paraneoplastic antibody?
2. Would you initiate presumptive treatment at this point, or wait for more results?
SECTION 3
According to an international guideline developed in 2004, this patient meets the definition of probable (rather than definite) paraneoplastic neurologic syndrome (PNS) given a classic neurologic syndrome (limbic encephalitis) in the absence of antibodies or cancer.1 If a paraneoplastic antibody is identified and initial cancer screening is negative, the European Federation of Neurological Societies Task Force recommends repeat cancer screening (targeting cancers associated with the identified antibody) at 3–6 months and then every 6 months up to 4 years.2 Starting treatment for probable PNS is reasonable while awaiting the identification of an antibody or tumor because of the potential for rapid, often irreversible neurologic decline.

The patient received 5 days of plasma exchange and was discharged. Corticosteroids were not given at this time due to his diabetes, psychiatric symptoms, and availability of plasma exchange. The myoclonic jerks resolved at home, and his other symptoms persisted. During a follow-up visit, the patient was initially alert but became progressively drowsy and unresponsive. Right-sided myoclonic jerks were apparent in his face, arm, and leg. He was readmitted to the hospital, with concern for status epilepticus or worsening of his underlying condition.

An EEG and MRI showed no changes from previous studies. The paraneoplastic panel returned positive for voltage-gated potassium channel (VGKC) antibodies with a level of 190 pM. The patient finished 3 days of IV immunoglobulin (IVIg) treatment and then received 1 g of IV methylprednisolone for 4 days. He was discharged home with a diagnosis of limbic encephalitis associated with VGKC complex antibodies. He received 1 g of IV methylprednisolone weekly, with an additional course of plasma exchange, and started 500 mg of mycophenolate twice daily, which was uptitrated to 1,000 mg twice daily. He also received levetiracetam, which required up titration to 1,500 mg twice daily to achieve control of the myoclonus. Four months after his discharge from the hospital, he experienced almost complete resolution of symptoms, with only sporadic myoclonus associated with insomnia.

Question for consideration:
1. What prognosis does this diagnosis carry?

DISCUSSION
Limbic encephalitis is an autoimmune process affecting the medial temporal lobes or limbic structures that can present either acutely or subacutely with symptoms of confusion, memory impairment, sleep disturbance, seizures, and psychiatric disturbance.1 The cause may be paraneoplastic or nonparaneoplastic, and the diagnosis is usually made with neuroimaging and identification of the associated antibody. CSF studies are typically normal or have a mildly elevated protein level.3 In general, the well-characterized paraneoplastic antibodies (e.g., anti-Hu, anti-Yo) are directed at intracellular antigens, affect older individuals, are more often associated with cancer, and have a poor response to immunotherapy; antibodies targeting cell surface antigens (e.g., VGKC, NMDA receptor) can affect all ages, are less likely to be associated with cancer, and often respond well to immunotherapy.4

VGKC antibodies identified on radioimmunoassay have antigenic targets other than the VGKC itself and are therefore more accurately referred to as VGKC complex antibodies.4 At least 2 targets are well described: leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein related 2 (Caspr2). LGI1 antibodies typically produce limbic encephalitis, hyponatremia, and myoclonic-like movements, whereas Caspr2 antibodies can produce encephalitis, Morvan syndrome, painful neuropathy, or neuromyotonia.4

Our patient presented with limbic encephalitis, hyponatremia, and myoclonic jerks and was found to be VGKC complex antibody-positive, likely LGI1. The myoclonic jerks are termed faciobrachial dystonic seizures (FBDS), which are highly associated with LGI1 antibodies and can precede cognitive symptoms.5,6 Although only a minority of patients with FBDS show basal ganglia involvement on MRI, abnormalities are commonly seen on PET.3 FBDS typically show a poor response to standard antiepileptic drugs but may respond to early immunotherapy.5,6 A recent prospective study suggests that early recognition of FBDS and treatment with immunotherapy may reduce the frequency of FBDS attacks and prevent the development of cognitive symptoms.6

Prognosis is generally favorable, as 80% of patients respond to immunotherapy with improvement in memory and executive functions.7,8 Cancer is rarely reported with LGI1 antibodies, and a series of 55 patients with confirmed LGI1 antibodies revealed no cancer after a median follow-up of 3 years; therefore, the utility of cancer screening in these patients is questionable. Though evidence is limited as to the optimal treatment regimen, most patients respond well to initial treatment with corticosteroids, plasma exchange, or IVIg, with maintenance options including corticosteroids or steroid-sparing agents such as mycophenolate, rituximab, or cyclophosphamide.6,7,10
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REFERENCES
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