Section Editor

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Clinical Reasoning: A 35-year-old woman with acute seizures and behavior change

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SECTION 1

A previously healthy 35-year-old Sudanese woman was admitted with new-onset right hemispheric seizures with secondary generalization. The patient's vital signs were temperature 100.2°F, blood pressure 133/96 mm Hg, pulse 83 beats per minute, respirations 18 per minute, and oxygen saturation 100% on room air. Additionally, a complete neurologic examination was within normal limits. She was discharged on phenytoin and levetiracetam but returned 4 days later with repeated generalized tonic-clonic seizures and altered behavior. Shortly after admission, she became progressively confused with severe insomnia, amnesia, cognitive decline, and delirium, which included bouts of hypersexuality,

hyperreligiosity, and auditory hallucinations; her neurologic examination continued to be unremarkable other than mental status fluctuations. Continuous EEG revealed several subclinical seizures along with 3 clinically evident seizures. These seizures progressed to become bilateral with 10-Hz rhythmic spike-and-wave complexes involving the left frontotemporal head region, and this spread to the left hemisphere and evolved to 4- to 5-Hz theta activity with amplitude of 60 μ V.

Questions for consideration:

1. What constitutes encephalopathic behavior?
2. What would be the differential diagnosis at this point in her care?

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SECTION 2

The hallmark of encephalopathic behavior includes pronounced deficits in attention, concentration, memory, judgment, and level of consciousness. These may occur alone or in some combination, sometimes associated with auditory and visual hallucinations. A patient's mental status will often fluctuate and delusions and hallucinations are common. This patient's presentation with new-onset temporal lobe seizures, amnesia, and encephalopathy fits the pattern of limbic encephalitis described as "the rapid development of irritability, depression, sleep disturbances, seizures, hallucinations, and short-term memory loss."¹

The differential diagnosis includes various paraneoplastic etiologies as well as CNS tumors (table). It has been noted that several specific limbic encephalitides

are more common in patients with certain cancers.² For example, anti-Hu antibody limbic encephalitis is more frequently seen in small-cell lung cancers, anti-Ma antibody with testis or lung cancers, and amphiphysin antibody with breast and small-cell lung cancers. Another very important disorder to recognize is herpes simplex encephalitis. Herpes simplex virus (HSV) PCR using the patient's CSF yields a sensitivity of 94% and a specificity of 98% for this condition.² The recognition of various common cancers as well as HSV will be important in the management of patients with complex partial seizures, encephalopathy, and amnesia.

Questions for consideration:

1. What laboratory tests should be ordered?
2. What imaging should be performed?

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Table Focused differential diagnosis for the symptom constellation of complex partial seizures, encephalopathy, and amnesia

Infectious	Miscellaneous
Viral	Mitochondrial disorders
Herpes simplex virus 1/2	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) disorder
Cytomegalovirus	<i>POLG</i> disorder
Varicella-zoster virus	Endocrine
HIV	Hashimoto thyroiditis
Human herpes viruses	Vascular
West Nile	Stroke
Japanese B encephalitis	Subdural hematoma
Bacterial	Subarachnoid hemorrhage
<i>Neisseria meningitidis</i>	Tumors
Pneumococcus	CNS metastasis
<i>Mycobacterium tuberculosis</i>	CNS gliomas
Lyme disease	CNS lymphomas
<i>Bartonella henselae</i>	Others
<i>Treponema pallidum</i>	Toxins
Fungal	Wernicke encephalopathy
Cryptococcal meningitis	
<i>Candida</i>	
Miscellaneous	
Toxoplasmosis	
Creutzfeldt-Jakob disease	
Autoimmune	
Paraneoplastic	
Voltage-gated potassium channel	
<i>N</i> -methyl-D-aspartate receptor	
2-Amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid	
γ -Aminobutyric acid receptor encephalitis	
Glutamic acid decarboxylase-65 antibodies	
Anti-Ma	
Anti-Hu	
Collapsin response mediator protein 5 antibody	
Amphiphysin antibody	
Systemic autoimmune disorders with CNS involvement	
Systemic lupus erythematosus	
Lupus cerebritis	
Lupus anticoagulant syndrome	
Sjögren syndrome	
Behçet disease	
Vasculitis	
Systemic Wegener granulomatosis	
Churg-Strauss syndrome	
Polyarteritis nodosa	
Nonsystemic isolated CNS angiitis	

SECTION 3

The initial diagnostic evaluation for this patient included laboratory evaluation, urgent MRI of the brain with and without gadolinium, and EEG. Continuous video EEG proved useful for the recognition of subclinical seizures.

The only abnormalities in admission labs were a platelet count of $422,000/\text{mm}^3$ and a blood urea nitrogen of 6 mg/dL; otherwise, complete blood count and basic metabolic panel were within normal limits. A series of 3 lumbar punctures revealed no abnormalities with the exception of an elevated white blood cell count of $23/\text{mm}^3$ and red blood cell count of $91/\text{mm}^3$ on the first attempt; the protein and glucose were 29 mg/dL and 74 mg/dL, respectively. Cultures were negative (bacterial, fungal, and acid fast); PCR for varicella-zoster virus, HSV-1, and HSV-2 were negative; Lyme titers were below threshold; Venereal

Disease Research Laboratory test was nonreactive; and the cryptococcal antigen assay was also negative. MRI revealed no intracranial abnormalities. The following antibody assays were performed, which were all negative: NMDA receptor antibody (tested twice), striated muscle antibody, acetylcholine receptor binding antibody, acetylcholine receptor ganglionic antibody, neuronal potassium channel antibody, antihuman tissue transglutaminase antibody, deamidated gliadin peptide antibody, and thyroid peroxidase and thyroglobulin antibodies. However, P/Q-type calcium channel and N-type calcium channel antibodies were positive.

Questions for consideration:

1. What is the diagnosis?
2. What are the usual causes of this disorder?
3. What medications should be used?
4. What is the prognosis?

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SECTION 4

At this point, the patient was diagnosed with anti-voltage-gated calcium channel (VGCC) limbic encephalitis.¹ The possibility of malignancy was high. Therefore, a full evaluation was performed including a CT of the chest, abdomen, and pelvis, a pelvic ultrasound (positive only for uterine leiomyoma), mammogram, and a full-body PET scan—all of which revealed no underlying neoplasm. The classic syndrome associated with VGCC is Lambert-Eaton myasthenic syndrome (LEMS), and approximately half of the LEMS cases are associated with small-cell lung cancer. P/Q-type calcium channel antibodies are pathogenic in LEMS, and there may be other autoantibodies to calcium channels that have pathogenicity in other, yet to be described, syndromes.³ This patient did not have any features of LEMS, and a thorough malignancy workup was negative; her presentation with isolated limbic encephalitis is, therefore, distinctly unusual.

She was started on IV immunoglobulin (IVIg) 2 g/kg in 5 divided doses. In patients presenting with features of autoimmune limbic encephalitis, treatment should begin as soon as possible; the alternatives to IVIg include corticosteroids and plasma exchange.⁴ Our patient showed much improvement with the IVIg therapy, exhibiting improved mental status and seizure control, and was subsequently started on prednisone 80 mg daily, which was tapered to 60 mg daily upon discharge.

On follow-up at 2 months, 4 months, and 6 months after the initial illness, she continued to show steady improvement. She received a second course of IVIg 2 g/kg 2 months into the illness with further improvement. She was gradually tapered to prednisone 10 mg/d 6 months later. Steroid-sparing therapy was considered but not initiated because she became pregnant shortly after discharge. Antiepileptic therapy was tapered with discontinuation of clonazepam and lacosamide 2 months into the illness and a gradual taper of levetiracetam to 1,000 mg twice a day and zonisamide to 200 mg/d. She has continued to remain seizure free since discharge and has near-normal mental status. She continues to show subtle abnormalities in executive function, especially tasks such as clock drawing, which remain slow and imprecise 6 months into the illness. Memory, as tested by 3-object recall, is normal.

DISCUSSION This case represents an unusual entity in the etiology of limbic encephalitis. An isolated limbic encephalitis presentation in association with VGCC antibodies is markedly uncommon. The success of IVIg and prednisone draws similarities to well-established plans of care for other antibody-associated encephalopathies⁵ and would suggest similarity in the autoimmune pathophysiology of this disorder. Additionally, if a patient exhibiting symptoms of limbic encephalitis has a known neoplasm, early intervention and possible empiric therapy should be considered.⁶ Recognizing the signs and symptoms of limbic encephalitis is important given the fact that this is a treatable condition in which rapid and striking recovery is possible. An acute or subacute change in behavior, mood, emotion, sleep, and amnesia, accompanied by new-onset seizures, is suggestive of limbic encephalitis.

AUTHOR CONTRIBUTIONS

Contributed to conceptualization of the study, literature review for the study, and final review and submission of the study: J.J. Rejeski, J.C. Morris, F.O. Walker, and N. Balakrishnan. Contributed to the draft of the study: J.J. Rejeski and N. Balakrishnan.

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