Clinical Reasoning: A 22-year-old postpartum woman with new-onset seizures and headache

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Section 1

A 22-year-old right-handed woman with no relevant medical history presented 7 days after delivery of her first child with new-onset seizures. Her pregnancy was unremarkable and she received standard prenatal care. During spontaneous vaginal delivery of her healthy full-term baby, she developed fever (39.6°C), tachycardia, and cough. Influenza B antigen was detected on nasopharyngeal swab consistent with respiratory influenza and she was started on a 5-day course of oseltamivir. She was discharged home after 2 days and her respiratory symptoms resolved. On postpartum day 7, she had 2 generalized convulsions lasting 1–2 minutes each. Her family noticed right elbow flexion and head version to the left at onset, but did not recall any movements of her left upper extremity. Afterwards she was confused and somnolent for several hours and did not recall either event. Review of systems was notable for a new-onset headache which was moderate intensity, bifrontal, nonpositional, with a pressure/throbbing quality starting 1 day prior to presentation. Family history was unremarkable. She had normal development, completed high school, and worked full-time as a cashier.

On examination, the patient was afebrile with a blood pressure of 175/105 mm Hg and a heart rate of 81 beats per minute. She was alert, in no acute distress, and without nuchal rigidity. Funduscopic examination revealed no papilledema. She was fully oriented and able to repeat sentences and follow commands without difficulty. She had decreased verbal fluency (able to name only 4 words starting with the letter “F” in 1 minute) and had difficulty with basic arithmetic (unable to calculate number of quarters in $2.25). She also had difficulty following the Luria 3-step test. Sensory and visual neglect were absent. The rest of her neurologic examination was unremarkable.

Questions for consideration:
1. Where would you localize this process?
2. What would be your differential diagnosis?

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Section 2

This patient’s history is suggestive of new focal-onset seizures with secondary generalization. Her ictal semiology lateralizes to a seizure involving her right frontal lobe, specifically the supplementary motor area. Classically, patients with seizures emanating from this region display the fencing posture in which one elbow is extended and raised, while the opposite elbow is flexed with abduction and external rotation of the shoulder. Typically the patients display head version ipsilateral to the extended elbow. Ictal onset is contralateral to the extended arm in 92% of cases and is associated with involvement of the supplementary motor area.

Our patient’s cognitive examination suggests frontal lobe dysfunction. The Luria 3-step test, developed by neuropsychologist Alexander Luria (1902–1977), involves asking the patient to repeat a series of 3 hand motions, including a fist, a cutting motion, followed by a slap posture. Patients with frontal lobe disorders often have difficulty alternating between the different hand motions, suggesting deficits in motor planning. In addition, our patient’s decreased verbal fluency suggests a lesion in her dominant inferior frontal lobe.

Eclampsia is highest on the differential in a postpartum patient with new-onset seizures and hypertension. Although eclampsia is often considered in pregnant patients after 20 weeks gestation, it can also occur up to 4 weeks postpartum. Electrolyte derangements, including fluctuations in sodium, glucose, calcium, and magnesium, are also important to consider in postpartum patients presenting with seizures. Another related condition to consider is posterior reversible encephalopathy syndrome (PRES). PRES refers to a disorder of partially reversible subcortical vasogenic edema in patients with acute neurologic symptoms including seizures, encephalopathy, headache, and visual disturbances. PRES is thought to be secondary to endothelial injury related to abrupt changes in blood pressure or the direct effects on cytokines on the endothelium, which leads to breakdown of the blood–brain barrier and subsequent cerebral edema. Diagnosis of PRES is made clinically in patients with supportive radiographic findings.

Given the recent diagnosis of influenza, a postinfectious encephalitis was also high on our differential. Encephalitis can result from infectious, postinfectious, or autoimmune etiologies, and patients often present with new-onset headache, altered mental status, or seizures. Another diagnostic consideration is cerebral venous thrombosis given the higher risk of thrombosis in pregnant patients, particularly in the postpartum period. Patients with cerebral venous thrombosis often present with new-onset headaches and approximately 44% present with new-onset seizures.

Questions for consideration:
1. How would you manage this patient?
2. What investigations would you want to perform next?
Section 3

Upon admission, initial laboratory studies demonstrated proteinuria and a neutrophil-predominant leukocytosis (white blood cells 12.3 × 1,000/mm³, 84% neutrophils). A comprehensive metabolic panel and coagulation studies were normal. For suspected eclampsia, the patient was started on a magnesium infusion and nifedipine. Her seizures were diagnosed clinically and managed using levetiracetam. MRI brain with and without IV contrast revealed a T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity in the right middle frontal gyrus involving the premotor and supplementary motor cortices with mild leptomeningeal enhancement (figure). Magnetic resonance angiography/magnetic resonance venography (MRV) revealed no evidence of vascular abnormality or venous thrombosis. EEG was not performed as it would not change management. Lumbar puncture on hospital day 1 revealed an opening pressure of 17 cm H₂O, red blood cell count of 500/mm³ in tube 1 and 600/mm³ in tube 4, white blood cell count 10/mm³ in tube 1 and 10/mm³ in tube 4 (33% lymphocytes, 28% neutrophils, 39% monocytes), protein 33 mg/dL, and glucose 65 mg/dL. Seven unique oligoclonal bands were detected in the CSF compared to serum. Bacterial, fungal, and viral CSF cultures were negative. NMDA receptor antibodies and paraneoplastic workup were negative. A broad viral infectious workup was negative, including evaluation for herpes simplex virus (HSV), West Nile virus, Epstein-Barr virus, cytomegalovirus, and arboviruses. Influenza PCR in the CSF was negative. Cytology showed no atypical cells. Rheumatologic workup was notable for an erythrocyte sedimentation rate of 54 mm/h and C-reactive protein 4.40 mg/dL, but was otherwise unremarkable.

Questions for consideration:
1. What is the most likely diagnosis?
2. How would you manage this patient?
Section 4

This patient’s clinical picture is most consistent with influenza-associated encephalitis (IAE). After correcting for the elevated red blood cells in her CSF, she had a mild monocyte-predominant pleocytosis. This is a nonspecific finding, but can be seen in a variety of viral meningoencephalitides. Although a pleocytosis can be seen in the setting of seizure, this is a diagnosis of exclusion. Her CSF profile is most suggestive of an infectious or inflammatory CNS process, making PRES or eclampsia as the cause alone unlikely. MRV showed no evidence of cerebral venous thrombosis. A broad infectious and autoimmune evaluation was unrevealing. Finally, this patient’s clinical presentation, MRI abnormalities, and confirmed respiratory influenza infection are all consistent with the diagnosis of IAE.

Given our initial concern for eclampsia, the patient was treated with a magnesium infusion for 24 hours. Repeat urine studies showed resolution of her proteinuria and her hypertension resolved on hospital day 2 (suspected to be due to postictal autonomic dysfunction). After starting levetiracetam 500 mg twice daily, she did not have any further seizures. She was treated with a 7-day course of IV acyclovir while awaiting HSV PCR results. Completion of one course with oseltamivir was deemed sufficient treatment for her influenza infection. Her cognitive deficits slowly improved during her admission. She did not receive any immunomodulation given her improving clinical picture and she was discharged home after 10 days. On follow-up examinations at 1 and 4 months, she continued to be seizure-free with continued improvement of her cognitive deficits. Repeat MRI 3 months later showed interval improvement of T2/FLAIR hyperintensities.

Discussion

IAE most often occurs in children and is associated with a high degree of morbidity and mortality. Cases of IAE in adults are exceedingly rare, with an estimated incidence of 0.21 per million population per year. Patients often present with seizures (27%), altered mental status (23%), and fever (93%) up to 3 weeks following a respiratory influenza infection. A recent literature review identified 44 cases of IAE identified in adults, of which 68% were male, median age at presentation was 46 years (range 20–86 years), and none of the patients was immunocompromised. Of note, children can present with a severe form of IAE known as acute necrotizing encephalopathy, characterized by symmetric lesions involving the thalami, brainstem, cerebellum, and corpus callosum. The pathophysiology of IAE is not well-understood but appears to involve a hyperactivated cytokine response instead of direct viral invasion. This mechanism is supported by the notion that influenza virus is rarely isolated from the CNS and high levels of cytokines (interleukin-6, soluble tumor necrosis factor–1) can be consistently found in CSF/serum specimens. This cytokine response causes direct neurotoxic effects, cerebral metabolic derangements, and breakdown of the blood–brain barrier. The delay between our patient’s respiratory illness and the onset of her encephalopathy supports the notion that IAE is related to a postinfectious immune-mediated process as opposed to direct viral invasion.

The diagnosis of IAE proves to be challenging given the lack of well-defined diagnostic and clinical criteria. Diagnosis is established in patients presenting with encephalitis in the setting of recent respiratory influenza infection. In patients presenting with sepsis, it can be difficult to distinguish IAE from septic encephalopathy. Initial evaluation should include nasopharyngeal testing for influenza, MRI brain, and lumbar puncture. MRI abnormalities are found in the majority of cases (62%) and include T2 hyperintensities in the cerebellum, brainstem, and subcortical white matter. CSF should be tested for influenza PCR; however, it is positive in only 16% of cases. Rising influenza antibody titers have been detected in a few case reports, but its frequency is not well-established.

Currently there are no established therapies for IAE. Cerebral edema and seizures require prompt evaluation and supportive management. Given the high levels of cytokines in this condition, one might speculate that steroids would be beneficial. Treatment with oseltamivir and immunomodulation have been proposed, but evidence of their efficacy is lacking. Data on the prognosis of IAE are scarce. A recent study found that 61% of adults with IAE made a full recovery, 21% had permanent neurologic deficits, and 18% died. Given its morbidity and mortality, IAE should be considered in all patients with encephalitis in the setting of recent respiratory illness.

Author contributions

Kevin McGehrin: manuscript concept and initial draft. Chandra Konersman: revision of manuscript for intellectual content. Ronald Ellis: revision of manuscript for intellectual content.

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Disclosure

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References


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