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Clinical Reasoning: A 57-year-old woman who developed acute amnesia following fever and upper respiratory symptoms

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SECTION 1

A 57-year-old woman with a history of depression and hyperlipidemia presented with 2 days of confusion and memory loss. Four days prior to presentation, she developed fevers, myalgias, and rhinorrhea. On the day prior to presentation, the patient began having memory difficulties and was noted by her husband to have completely forgotten many events and details of the previous days. She presented to an outside hospital where a comprehensive neurologic

examination disclosed a nonfluent expressive aphasia but was otherwise unremarkable. Basic laboratory tests including electrolytes, complete blood count, and liver function tests had normal results.

Questions for consideration:

1. What is the differential diagnosis for subacute memory disturbances and confusion in this patient?
2. What are the initial steps in evaluation?

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SECTION 2

The differential diagnosis for the subacute onset of amnesia and speech difficulties is broad. In a patient with recent fevers, meningitis or encephalitis must be considered. Seizures with postictal confusion or exposure to psychoactive medications or drugs of abuse could produce the changes described. Stroke or cerebral hemorrhage must be considered, but the purely cognitive abnormalities without associated motor or sensory changes on examination would be atypical. Finally, transient global amnesia is a consideration, but is a diagnosis of exclusion. The initial workup would include intracranial imaging to assess for mass lesion, stroke, or hemorrhage. Lumbar puncture and systemic infectious workup should be considered

given the recent fevers, upper respiratory symptoms, and changes in cognition. Urine and blood toxicology could also be helpful.

Chest X-ray and CT scan of the head were unremarkable. Infectious workup was notable for a rapid influenza swab that was positive for influenza A. The following day, the patient had a generalized tonic-clonic seizure. MRI of the brain showed symmetrical T2 hyperintensities of the bilateral mesial temporal lobes, thalami, and cingulate cortex.

Questions for consideration:

1. What is the differential diagnosis of subacute altered mental status and seizures in association with mesial temporal lobe changes?
2. What are the next steps in management?

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SECTION 3

The acute abnormalities of the temporal lobes are concerning for a viral or bacterial encephalitis. The constellation of seizures and temporal lobe abnormalities is suggestive of herpes simplex virus (HSV) encephalitis, but this typically produces asymmetric inflammation and hemorrhage of the medial temporal lobes rather than the symmetric changes as in this case. Seizure activity itself can lead to transient T2 hyperintensities in the medial temporal lobes. However, seizures could not account for the other MRI abnormalities; thus, the seizures should be viewed as symptomatic of another pathologic process until proven otherwise. Other considerations in this patient would be a paraneoplastic or autoimmune encephalitis, but the acute onset and rapid decompensation is atypical. Given the concern for an acute infectious process, the patient needs urgent lumbar puncture and empiric antiviral therapy for HSV encephalitis. An antiepileptic drug should be administered and EEG monitoring should be considered, especially if there is concern for ongoing seizures.

The patient was treated with acyclovir and levetiracetam. EEG showed generalized slowing without epileptiform activity. Lumbar puncture showed total

protein of 443 mg/dL, glucose of 98 mg/dL, with 4 leukocytes and 11 erythrocytes per mm³. The patient became progressively more somnolent, requiring transfer to an intensive care unit, and she was transferred to our hospital for further evaluation and management.

On arrival, the patient had a rectal temperature of 101.9°F and was somnolent, only opening her eyes to deep nasopharyngeal suctioning, but not to sternal rub or nail bed pressure. Her cranial nerves were normal, and she was able to localize to noxious stimuli in all extremities. Reflexes were brisk, measuring 3/4 in all 4 extremities, and the patient had positive Hoffman signs, flexor plantar response on the right, and equivocal response with fanning of the toes on the left. Repeat MRI showed interval progression and worsening of the previously noted T2 signal abnormalities with new multifocal hemorrhage within the hippocampi and thalami and worsening contrast enhancement throughout the hippocampal heads (figure).

Questions for consideration:

1. How do you interpret the results of lumbar puncture?
2. What additional CSF studies could be useful in determining the cause of this patient's encephalitis?

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Figure MRI of the brain shows symmetric bilateral T2 signal hyperintensity involving multiple deep structures as well as hemorrhage and contrast enhancement

(A) T2 hyperintensity of the mesial temporal lobes, hippocampi, and amygdala. (B) T2 hyperintensities of insular cortex and thalami. (C) Susceptibility artifact in the mesial temporal lobes consistent with microhemorrhage and necrosis. (D) T1 postcontrast enhancement of the mesial temporal lobes consistent with active inflammation.

SECTION 4

The patient has a markedly elevated total protein concentration in the CSF but an overall noninflammatory profile with normal leukocyte and erythrocyte counts. This is inconsistent with most typical bacterial and viral forms of meningitis. A comprehensive workup for viral encephalitis and atypical CNS infections should be initiated. CSF testing should include Gram stain, bacterial culture, and serology for HSV and varicella-zoster virus (VZV). Additional serum and CSF testing could include cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus-6 (HHV6), adenovirus, mycoplasma, *Legionella*, influenza, and *Cryptococcus* as well as testing for enteroviruses or arboviruses depending on the season. In addition, further immunologic CSF studies including testing for oligoclonal bands and measuring CSF immunoglobulins and cytokines could be useful in defining the nature of the cerebral pathology.

Acyclovir was continued, and the patient was empirically treated for bacterial meningitis with vancomycin and ceftriaxone. Repeat lumbar puncture showed total protein of 794 mg/dL, glucose of 84 mg/dL, with 4 leukocytes and 19 erythrocytes per mm³. Opening pressure was 8 cm of water. Repeat CSF testing was negative for HSV, VZV, EBV, CMV, HHV6, adenovirus, and *Cryptococcus*; serum was negative for HHV6 and mycoplasma, and urine was negative for *Legionella* antigen. HSV PCR was also negative from the CSF obtained at the referring hospital. CSF oligoclonal bands and immunoglobulins were not tested. CSF Gram stain and culture were negative, and vancomycin and acyclovir were stopped. Influenza A testing was repeated and was again positive, but CSF PCR testing for influenza virus was negative. Chest X-ray demonstrated a left lower lobe opacity, and the patient was treated with a 7-day course of ceftriaxone and azithromycin for pneumonia.

Based on the patient's prodromal viral illness, positive influenza A testing, and negative workup for other bacterial or viral encephalitides, her presentation was believed to be most consistent with a subtype of so-called influenza-associated encephalitis/encephalopathy (IAE) known as acute necrotizing encephalopathy (ANE). She was enrolled in a clinical trial comparing oseltamivir to zanamivir for treatment of influenza. However, her condition continued to deteriorate despite antiviral therapy, and she required intubation for airway protection. Over the next several days, her examination results worsened such that she no longer spontaneously moved her extremities and only demonstrated stereotyped movements in response to noxious stimuli. Studies of IAE have generally failed to show direct viral infection of the CNS, suggesting an

immune-mediated mechanism of tissue injury rather than direct viral toxicity.¹⁻³ Based on these observations and limited case reports of success of immune-modulating therapy in IAE, the patient was treated with a 5-day course of IV methylprednisolone 1000 mg daily as well as 1 mg/kg IV immunoglobulin (IVIg) given over 2 days. She demonstrated some purposeful movements on hospital day 9 and was extubated on hospital day 11. Her condition slowly improved over the next week, and she was discharged to a rehabilitation facility on hospital day 21. On discharge, she was alert, was able to speak in 2-word sentences, could follow simple commands, and was able to walk with assistance. On follow-up 8 months later, the patient was fully ambulatory without residual aphasia, but had significant persistent deficits in anterograde and retrograde memory.

DISCUSSION We present the case of a 57-year-old woman who developed influenza A infection followed by amnesia and encephalopathy that progressed rapidly to coma. Brain MRI showed symmetric changes in the mesial temporal lobes and thalami consistent with necrotizing encephalitis. Additional extensive workup for infectious encephalitis was negative. She was treated with a course of steroids and IVIg for presumed influenza A encephalitis and her condition improved significantly.

CNS complications of influenza are rare and diverse, and include seizures, Reye syndrome, Guillain-Barré syndrome, movement disorders, numerous forms of encephalopathy or encephalitis, and cerebral hemorrhage.^{1,2} IAE is a rare complication of influenza infection, most commonly described in children under 5 years of age (82.6% of 1998–1999 Japanese cases), and the ANE variant is defined by its association with symmetric hemorrhagic brain lesions.³ The most common clinical features of ANE are generalized seizures and alterations of mental status including reduced level of consciousness, abnormal speech, and delirium.^{1,3} Radiographic findings include symmetrically distributed lesions of the cerebral white matter and deep structures including the thalami and brainstem, with bilateral necrotic or hemorrhagic thalamic lesions being characteristic.^{3,4} Multiple case series of IAE have demonstrated that CSF is generally noninflammatory, and virus can seldom be detected in CSF or in brain tissue.^{1,3,4} Neuronal injury in IAE is thought to relate to robust cytokine release and immune activation rather than direct CNS virus penetration.⁵ Based on this putative model of pathogenesis, severe cases of IAE have been treated with immune-modulating therapies with some anecdotal reports of success. However, the rarity of IAE has precluded any controlled trials to assess the efficacy of such approaches.

AUTHOR CONTRIBUTIONS

Brett A. McCray cared for the patient presented, wrote the text, and helped to assemble the figures. Deborah Forst cared for the patient presented, helped edit the text, and helped to assemble the figures. Jenelle Jindal cared for the patient and helped in discussion of the manuscript. Galen V. Henderson cared for the patient presented and helped edit the text.

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