

# Clinical Reasoning:

## A 35-year-old man with 2 episodes of meningoencephalitis associated with flu-like illnesses

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### SECTION 1

A 33-year-old man with an unremarkable medical history presented to an outside hospital emergency department (ED) in January 2011 with altered mental status and a seizure. Four days prior to his admission, his children experienced fevers and body aches that self-resolved. The patient developed similar symptoms 3 days later that he treated with acetaminophen and ibuprofen. On the morning of admission, he became disoriented and unable to answer simple questions. Paramedics were called, and he had a witnessed generalized tonic-clonic seizure on their arrival. He had a second witnessed generalized seizure in the ED and was intubated for airway protection.

CT of the brain had normal results. CSF analysis revealed 7 leukocytes/ $\mu$ L (62% lymphocytes), 41 erythrocytes/ $\mu$ L, glucose 69 mg/dL, and protein

83 mg/dL. CSF Gram stain and bacterial cultures were negative. MRI of the brain with and without contrast and magnetic resonance angiography of the brain had normal results. EEG done while the patient was intubated showed nonspecific diffuse slowing and sedative changes but no epileptiform activity. Herpes simplex virus (HSV) PCR was negative. He was placed on empiric ceftriaxone, vancomycin, and acyclovir. He was extubated and slowly returned to normal within 3 days. He was discharged on hospital day 4 on phenytoin.

### Questions for consideration:

1. Based on the clinical presentation and CSF results, what are the differential diagnoses?
2. What additional CSF and serum diagnostic studies could be ordered?

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## SECTION 2

The clinical picture and CSF results suggest an aseptic meningitis or encephalitis. Whereas seizure and altered mental status suggest encephalitis, they can also occur in meningitis. Thus the more inclusive term meningoencephalitis is applicable to this case. The broad differential includes viral, atypical bacteria, other infectious agents, autoimmune, paraneoplastic/neoplastic, drugs/toxins, or a structural issue (table). Partially treated acute bacterial meningitis can also present with a lymphocytic CSF. The patient's clinical resolution within 4 days with the only treatment being empiric ceftriaxone, vancomycin, and acyclovir makes a neoplastic, fungal, or atypical infectious

process unlikely. Normal imaging helps exclude structural abnormalities. Several medications can cause drug-induced aseptic meningitis. A rare, self-limited syndrome of transient headaches and focal neurologic deficits with CSF lymphocytosis (HaNDL) has been reported<sup>1</sup>; however, our patient did not report a headache. He is immunocompetent and denies drug or alcohol use. Even without further studies, the clinical and CSF profile of this patient is most suggestive of a viral process.

Brain imaging during CNS viral infections causing aseptic meningitis may or may not be remarkable. The clinical course typically runs about 1–2 weeks, depending on the agent. The causative agent often goes unidentified. In one New York Public Health study, PCR was positive in only 36% of presumed viral meningitis or encephalitis cases.<sup>2</sup> Agents more likely to produce a meningitis picture include enteroviruses, HSV-2, varicella-zoster virus (VZV), and lymphocytic choriomeningitis virus (LCMV).<sup>3,4</sup> HSV-1 and arboviruses are more likely to cause encephalitis.<sup>3,5</sup> HSV-1 often shows imaging abnormalities in the temporal and inferior frontal lobes. It carries a high morbidity, and empiric acyclovir treatment is required in suspected cases. Of the arboviruses, West Nile virus (WNV) is now the most common cause of epidemic meningoencephalitis in North America. Neuroinvasive WNV can present in a variety of ways, including meningitis, encephalitis, and acute flaccid paralysis.<sup>6</sup> Enteroviruses and arboviruses occur more often in the warmer seasons.<sup>3</sup>

In our patient, additional CSF studies were negative for HSV-1, HSV-2, VZV, cytomegalovirus, Epstein-Barr virus, influenza, enteroviruses, arboviruses including WNV, LCMV, measles, and mumps. Serum HIV and rapid plasma reagin were negative. Extensive serum viral serology testing revealed no positive immunoglobulin M levels, and there was no change in immunoglobulin G antibody titers in acute and 3 weeks postonset convalescent samples. He was diagnosed with an unspecified viral encephalitis by the outside hospital.

In March 2011, the patient was diagnosed with influenza and treated with oseltamivir. He did not develop any neurologic symptoms, and his flu symptoms resolved in 1 week. By November 2012, his phenytoin was tapered by his physician to 100 mg daily.

In December 2012, the patient's wife and children became sick with an apparent viral gastroenteritis. A few days later he too began experiencing fever, nausea, vomiting, and fatigue, for which he took ibuprofen. The next day he became disoriented and unable to answer simple questions correctly. The wife noted these symptoms were similar to the prior episode. Paramedics were called and he was admitted to the

**Table** Differential diagnosis of lymphocytic meningoencephalitis

<b>Infectious</b>
Viral
Atypical bacteria (Lyme, tuberculosis, syphilis, others)
Fungal
Partially treated acute bacterial meningitis
Parameningeal bacterial focus
Protist (granulomatous amoebic encephalitis, <i>Naegleria</i> )
Helminth (varies with geographic location)
<b>Autoimmune/Inflammatory</b>
Postinfectious encephalitis
Voltage-gated potassium channel complex encephalitis (leucine-rich glioma-inactivated protein 1, contactin-associated protein-like 2 antibodies)
NMDA receptor encephalitis
Steroid-responsive encephalopathy associated with autoimmune thyroiditis
Systemic lupus erythematosus
Rheumatoid pachymeningitis
Neurosarcoidosis
Behçet disease
Primary CNS vasculitis
<b>Neoplasm</b>
CNS malignancy
Leptomeningeal spread
Paraneoplastic
<b>Anatomic issue</b>
Skull base defect
Epidermoid cyst rupture
<b>Drug-induced</b>
Nonsteroidal anti-inflammatory drugs
Antibiotics
IV immunoglobulin
OKT3 antibodies
Toxins/illicit drugs
<b>Migraine-related</b>
Headaches and focal neurologic deficits with CSF lymphocytosis (HaNDL)

same hospital as in 2011. He again had a witnessed generalized tonic-clonic seizure in the ED. He was intubated for airway protection and put on the same empiric antimicrobial course as in 2011. CT of the brain was normal. CSF revealed 35 leukocytes/ $\mu\text{L}$  (76% lymphocytes), 0 erythrocytes/ $\mu\text{L}$ , glucose 76 mg/dL, and protein 105 mg/dL. MRI brain with and without contrast and EEG were again unremarkable. CSF Gram stain and culture, HSV PCR, Lyme antibodies, and Venereal Disease Research Laboratory were negative. Extensive CSF and serum viral studies were again unrevealing. Serum antinuclear antibodies, rheumatoid factor,

C-reactive protein, complements, and quantitative immunoglobulins were all within normal limits. He gradually returned to normal within 4–5 days. Upon discharge, he was switched from phenytoin to levetiracetam 750 mg BID. His discharge diagnosis was again viral encephalitis, with the specific infectious agent unknown.

**Questions for consideration:**

1. What are the likely differential diagnoses now?
2. What infectious agent is most likely to cause benign recurrent lymphocytic meningitis?
3. What are the next steps in management?

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### SECTION 3

The patient presented to our neurology clinic 1 month after the second episode. He had no symptoms and a normal neurologic examination. At this point, he had had 2 episodes of fever-associated lymphocytic meningoencephalitis without residual clinical deficits. The etiology of recurrent aseptic meningitis in this case includes Mollaret meningitis, an autoimmune disorder, or a drug-induced aseptic meningitis.

Mollaret meningitis, also known as benign recurrent lymphocytic meningitis, is characterized by 3 or more self-resolving episodes of fever, meningeal signs, and possibly transient focal neurologic symptoms. Episodes typically last 2–5 days.<sup>7</sup> The underlying agent in most cases is HSV-2. Pathogenesis is linked to viral reactivation. Our patient's CSF was negative for both HSV-1 and -2; serum immunoglobulin G was positive for HSV-1 only.

A variety of autoimmune conditions, both primary CNS and systemic, can cause recurrent meningoencephalitis. Postinfectious encephalitis usually occurs days to weeks after the prodromal infection, unlike in our case, where symptoms occurred within a day of the viral-like syndrome. Recent investigations have identified 2 specific antibodies to proteins associated with the voltage-gated potassium channel (VGKC) complex (but not to the potassium channel itself): leucine-rich glioma-inactivated protein 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). LGI1 antibodies are more often associated with seizures and encephalitis, and CASPR2 antibodies with peripheral nerve excitability.<sup>8</sup> Although VGKC complex antibodies were not tested in our patient, the improvement without immunosuppressive therapy and lack of subsequent recurrence makes this etiology unlikely. A variety of systemic autoimmune or inflammatory conditions can also cause meningoencephalitis. However, the normal serologic studies, normal neuroimaging, and rapid return to baseline without any immunosuppressive treatment makes etiologies such as systemic lupus erythematosus (SLE) or neurosarcoidosis unlikely.

Given the patient's return to baseline within 5 days and his preceding ibuprofen use on both occasions, we suspected drug-induced meningoencephalitis. Whereas he did have viral syndromes prior to his CNS symptoms, his onset to recovery time was more rapid than usual for viral meningitis or encephalitis. In addition, the extensive viral testing came back unremarkable. Furthermore, he had not taken any nonsteroidal anti-inflammatory drugs (NSAIDs) between the January 2011 and December 2012 episodes. An infectious disease specialist consultation concurred that his symptoms were unlikely of infectious etiology.

Our patient has had no additional episodes since December 2012 while strictly avoiding NSAIDs. Since both of his apparent seizures were provoked by ibuprofen use, his levetiracetam was weaned off. Prior to discontinuation of levetiracetam, a routine EEG showed no abnormal activity.

**DISCUSSION** The most commonly implicated drugs in drug-induced aseptic meningitis are NSAIDs, antibiotics, IV immunoglobulin, and OKT3 antibodies. Among the NSAIDs, ibuprofen is more likely than other agents in this class to cause meningitis.<sup>9</sup> The interval between drug intake and meningitic symptoms varies. Seizures are seen in 5%–10% of cases.<sup>9</sup> The condition is more likely to occur in patients with underlying autoimmune disorders, most commonly SLE. However, it has also been associated with Sjögren syndrome, rheumatoid arthritis, and mixed/undifferentiated connective tissue disease. This could be due to the widespread use of NSAIDs in these patients or an inherent tendency to autoreact. Some authors suggest screening for these autoimmune conditions in healthy patients developing NSAID meningitis.<sup>10</sup> The pathogenesis of NSAID meningitis is not clearly understood, but may relate to a hypersensitivity mechanism confined to the CNS based on symptoms worsening on re-exposure and 20%–25% of cases involving allergic signs such as facial edema, conjunctivitis, and rash. A type III or IV hypersensitivity reaction has been postulated based on findings of increased intrathecal synthesis of immunoglobulin G and immune complex formation.<sup>9</sup> However, other studies suggest the mechanism relates to direct toxicity on the meninges or activation of the innate immune system.<sup>11</sup> A total of 75% of patients with NSAID-induced aseptic meningitis have a neutrophilic CSF, while about 25% have a lymphocytic CSF. Mean CSF protein in NSAID meningitis is around 124 mg/dL, and can increase on subsequent exposures.<sup>9</sup> Brain imaging is usually normal. Prognosis is good if the offending agent is identified and discontinued.

Excluding CNS infection (particularly viral) is often difficult when diagnosing drug-induced aseptic meningitis. The 2 largest classes of responsible drugs, NSAIDs and antibiotics, are commonly given to patients with fever or suspected infection. A key feature of drug-induced aseptic meningitis is that it typically resolves more quickly (within 5 days of drug discontinuation vs 1–2 weeks for viral meningitis). In addition, CSF cultures and viral PCRs must be negative.

Drug challenge is the classic confirmatory test for adverse drug reactions. In one case report, a 50-mg double-blinded administration of ibuprofen elicited meningeal signs that resolved within 24 hours.<sup>12</sup>

However, drug challenge in cases of severe reactions is controversial and not routinely recommended. This is particularly true for NSAIDs (as opposed to antibiotics), since they are usually nonessential medications.

### AUTHOR CONTRIBUTIONS

Dr. Amin: study concept and design, drafting and revising the manuscript. Dr. Lewis: study concept and design, drafting and revising the manuscript.

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