

Don't Let Herpes Melt Your Brain!

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ANNALS CASE

A 16-year-old previously healthy female adolescent presented with fever, headache, and word-finding difficulties. She had developed a cold sore 2 weeks before, followed by intermittent headaches, vomiting, and fever to 39°C (102.2°F). On examination, she had an erythematous lesion on her lip, which initially appeared vesicular. Her neurologic examination result was nonfocal. Her WBC count was normal. Lumbar puncture revealed xanthochromic cerebrospinal fluid (CSF). Magnetic resonance imaging (MRI) (T2 and fluid-attenuated inversion recovery sequences) showed edema, petechial hemorrhage, and gray matter enhancement within the median left temporal lobe.¹

WHAT'S THE DIAGNOSIS AND WHAT'S THE TREATMENT?

The patient received a diagnosis of herpes simplex virus (HSV) encephalitis and treatment of intravenous acyclovir.

KEEPING DEFINITIONS STRAIGHT

There are a lot of things to inflame in the human body, eh? In a fit of genius (or drunkenness), our predecessors decided to name things wildly differently, depending on where the inflammation digs in. But that has utility in this case because the clinical presentations are different too. Meningitis and encephalitis are distinct disease processes, in which meningitis involves inflammation of the meninges (the membrane covering the brain and spinal cord) and encephalitis involves inflammation of the brain itself. And there are more Scrabble words like myelitis that involve inflammation of the spinal cord (eg, transverse myelitis). You can also have meningoencephalitis, in which both membrane and brain are inflamed.^{2,3} When I start a punk rock cover band, I'm going to name it the Meningoencephalitides because it's hard to say, and that's punk.

WHY IS IT ALWAYS THE YOUNG AND THE OLD?

One in 10 encephalitis cases is due to HSV, the most common cause of sporadic fatal encephalitis in the United States.⁴ HSV encephalitis affects all ages, but predominates in the young and old (thanks a lot, herpes): 33% of cases are in patients younger than 20 years, whereas 50% are in patients older than 50 years. HSV-1 is more common in adults; HSV-2, in neonates.⁵

WHY SHOULD WE CARE?

Well, HSV encephalitis causes acute inflammation, congestion, and hemorrhage of the brain, which most often leads to frank necrosis and liquefaction of the involved brain tissue (insert zombie joke here).⁶ So if you can prevent the inflammation from spreading from a small amount of brain inflammation to a bigger amount, that would be a good thing. In fact, of all the different types of viral encephalitis, HSV encephalitis is one of the few viral causes of the disease for which we actually have accurate diagnostic testing and relatively cheap treatment, all readily available! Research suggests that administering acyclovir to HSV encephalitis patients reduces mortality from greater than 70% in untreated patients to less than 20% in treated patients.^{4,6} And the downside of treating in the scenario of brain inflammation? Not much. If my brain is inflamed and you're my physician, consider this my consent to acyclovir therapy.

HOW NOT TO MISS IT

So what are the red flags that should clue you in to diagnosing HSV encephalitis?

- Fever+headache+neurologic abnormality=think encephalitis!

But, what does "neurologic abnormality" really mean (I mean, I'm pretty sure my uncle Jim has that at baseline)? Well, the bummer is it can be subtle and can lead you down other diagnostic paths. It can be as subtle as behavioral change that may mimic psychiatric disorders, or mild cognitive impairment that may mimic early dementia. It can present as seizures or even strokelike lateralizing neurologic deficits. I swore I'd never say the phrase "have a high clinical suspicion," so I'm not going to say it...but, you know, maybe have one anyway.

One interesting study found some interesting stats on what HSV encephalitis patients presented with: viral prodrome (fever [90%], headache [81%], and nausea/vomiting [46%]) with associated neurologic impairment (behavioral change [71%], confusion [24%], focal neurologic deficits [33%], and seizure [67%]).⁴

OK, I'M CONCERNED: WHAT DO I DO?

If you're concerned about HSV encephalitis, what do you have to do? Well, a lumbar puncture is mandatory and, ideally, an MRI if possible or available. The MRI can give you a nice bit of information, but I know not everyone can get one. If you're the hero working in an emergency department at 3 AM in a hospital unequipped with MRI at that time, then, first, thank you; and second, it's OK to get computed tomography with and without contrast, if you remember the sensitivity decreases to 50% early in the disease course.^{4,5,7} When you perform the lumbar puncture, don't forget to order a CSF HSV polymerase chain reaction (PCR) assay. And also empirically administer acyclovir, in addition to appropriate antibiotics you'd administer for run-of-the-mill meningitis.

WHAT'S THE MRI SUPPOSED TO SHOW?

MRI of the brain, assuming you can get it, should be ordered with fluid-attenuated inversion recovery and diffusion-weighted imaging sequences. And, no, nobody knows exactly what the heck that means, so write it down and chat with your radiologist, but classically the MRI demonstrates high signal in the medial temporal lobe(s) or frontal lobe(s). For some reason, herpes likes the temporal lobe. A scientific analogy: herpes is to the temporal lobe as the Dark Side of the Force is to Darth Vader (you're welcome).

WHAT'S THE BIG DEAL ABOUT LUMBAR PUNCTURE?

Lumbar puncture classically demonstrates elevated CSF WBCs, specifically lymphocytes, mildly elevated CSF protein levels, and normal CSF glucose levels. If HSV encephalitis is hemorrhagic, which it often is, CSF RBCs or xanthochromia may be present as well. All of that being said, the definitive diagnosis is classically obtained by PCR assay testing for CSF HSV (What? You don't have that on your order sheet?).⁷

Now to deflate our balloon a little: initial MRI and CSF analyses (including HSV PCR) may be normal in up to 10% of cases, so if you have a very high—ahem—clinical suspicion for viral encephalitis, be sure someone rechecks them in 1 to 2 days.⁷ Also, CSF viral cultures are extremely low yield, and the Infectious Disease Society of America does not recommend routinely ordering them.⁷

GIVING ACYCLOVIR EARLY STOPS THE BRAIN FROM MELTING!

I said it above, but I'll say it again: give acyclovir early to prevent the unchecked herpes virus from melting the brain. Acyclovir inhibits viral replication and prevents further disease progression in the brain. In adults, acyclovir should be empirically started at 10 mg/kg intravenously every 8 hours for 14 to 21 days, assuming normal renal function.⁷ And add appropriate antibiotics to cover for bacterial causes until some dude who doesn't work nights and weekends runs your PCR to confirm your diagnosis upstairs.

THE BOTTOM LINE

Fever+headache+neurologic deficit=think encephalitis=think MRI+lumbar puncture (don't forget CSF HSV PCR)=empiric antibiotics+acyclovir.

Let's take a look again at this case and see whether we can pick out the red flags:

Patient Case

A 16-year-old **previously healthy female** adolescent presented with **fever, headache, and word-finding difficulties**. She had developed a **cold sore** 2 weeks before, followed by **intermittent headaches, vomiting, and fever** to 39°C (102.2°F). On examination, she had an erythematous lesion on her lip, which initially appeared **vesicular**. Her neurologic examination result was nonfocal. Her WBC count was normal. Lumbar puncture revealed **xanthochromic CSF**. MRI (T2 and fluid-attenuated inversion recovery sequences) showed edema, petechial hemorrhage, and gray matter enhancement within the **median left temporal lobe**.

Diagnosis: HSV encephalitis. The patient was admitted while receiving intravenous acyclovir pending CSF PCR, which returned positive for HSV-1.

If you want to read more but don't have a lot of time, Sabah et al⁵ is a great, brief article.

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