CLINICAL VIGNETTE

A Case of Atypical Herpes Simplex Virus Type 2 Encephalitis

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A 69-year-old female with a history of rheumatoid arthritis (RA) and hypertension presented with fevers and altered mental status for two days.

One day prior to admission, the patient had gotten lost driving home from a friend's birthday party. She missed her usual exit by 30 miles and needed to be picked up at a grocery store by her husband. The patient remained confused the following day and was unusually flat and quiet per her husband. She then had a syncopal episode while eating lunch. Her temperature at that time was 103^{o}F, so her husband and son brought her to the ER for evaluation.

Past medical history is significant for lumbosacral spondylosis status post L2-L5 spinal fusion, rheumatoid arthritis for which she was taking prednisone 5 mg daily, and HTN for which she was taking amlodipine and irbesartan.

Family history was significant for Alzheimer's dementia, diagnosed in her mother in the early 70s and in her brother in his late 60s. Social history was insignificant; patient denied the use of tobacco, alcohol, or any recreational drugs.

Review of systems was significant for flu-like symptoms (cough, fatigue, body aches, and general malaise) she had developed the month prior. All symptoms had resolved by admission except for a mild cough. She denied headaches, neck stiffness, and photophobia as well as recent travel or sick contacts.

Initial presentation showed a temperature of 39.1, heart rate of 110, blood pressure of 148/97, respiratory rate of 20, and O2 saturation of 98% on room air.

On physical exam, patient was pleasant and conversant but oriented to person only. She had difficulty with finger-to-nose testing, more due to difficulty comprehending the task than performing the task. Neurological exam was otherwise benign, with a supple neck, negative Brudzinski's and Kernig's signs, and intact cranial nerves.

Initial laboratory evaluation revealed a normal CBC and UA. CT brain showed mild cerebral atrophy with no acute intracranial pathology.

A lumbar puncture was attempted in the ED but was unsuccessful. She was started empirically on vancomycin, ceftriaxone, ampicillin, and acyclovir for presumed meningitis or encephalitis. The following day the patient was afebrile and alert and oriented x 3 with no focal deficits found on neurological exam. When asked, she denied a history of cold sores or genital ulcers.

MRI brain showed no evidence of an acute process. EEG was normal. IR-guided LP was performed with cerebrospinal fluid (CSF) analysis showing 42,000 red blood cells and 83 white blood cells with 64% neutrophils, 29% lymphocytes, and 7% monocytes. Glucose was 64 and protein was elevated 63. Initial bacterial, fungal, and acid-fast cultures of CSF were negative. Herpes simplex virus-2 PCR of the CSF came back positive, confirming the diagnosis of HSV-2 encephalitis.

Antibiotics were discontinued, and therapy was narrowed to intravenous acyclovir 10 mg/kg every 8 hours. Patient remained at neurological baseline throughout the rest of her hospitalization, and she was subsequently discharged with a 21-day course of intravenous acyclovir that she completed with no issues.

Epidemiology

Herpes simplex encephalitis (HSE) accounts for almost 20% of all cases of encephalitis with an estimated annual incidence of 1 in 250,000 to 500,000.[1,2] HSV-1 is responsible for 90% of adult cases. HSV-2 is more commonly seen in neonates and the immunosuppressed, and only responsible for 10% of adult cases.[3] There are only scattered case reports and small studies documenting its presence in the literature.[4-8]

Pathogenesis

The pathogenesis of herpes simplex encephalitis is not well understood. It is known that replicating virus causes ballooning of cells and the degeneration of cellular nuclei. Mononuclear cells infiltrate the infected tissue, resulting in acute inflammation, edema, and even eventual necrosis.[4] HSE can occur both from primary and recurrent HSV infection, although it is unclear how the virus enters the CNS. It is possible that latent virus may travel from the trigeminal ganglia.[9] One-third of the cases of HSE occur through primary infection, and the remaining two-thirds occur in those with pre-existing HSV antibodies. Only 10% of HSE patients have a history of recurrent herpes labialis.[4] Host immunity plays an important role as HSE is extremely rare despite the high seroprevalence of both HSV-1 and HSV-2.[10]

Clinical Manifestations

HSE typically manifests with non-specific symptoms of encephalopathy and fever. This encephalopathy can range from overall cognitive impairment, personality changes, and seizures to focal neurological defects such as aphasia and focal weakness.[11,12] Meningeal signs such as photophobia and nuchal rigidity are typically absent. Review of early case reports and series suggest the presentation of HSV-2 encephalitis may be clinically indistinguishable from HSV-1 encephalitis.[5,7]

Diagnosis

The mainstay of diagnosis is detection of virus by HSV PCR. The sensitivity and specificity of PCR of the CSF is about 96% and 99%, respectively.[13] PCR diagnosis can be supplemented by neuroimaging, ideally with MRI, which typically shows characteristic enhancement from inflammation in the temporal and frontal lobes, insular cortex, and angular gyrus.[14]

Treatment

For patients with HSE, treatment with intravenous acyclovir has been shown to have a substantial mortality benefit compared to vidarabine.[15] Differences between HSV-1 and HSV-2 have not been described in treatment studies. The current therapy of choice is intravenous acyclovir 10 mg/kg three times daily for a minimum of 14-21 days.[2,4] Delay in starting acyclovir of 48 hours or more has been shown to result in a significantly worse prognosis.[16]

Prognosis

The mortality from HSE in adults is as high as 70%. Acyclovir decreases the mortality rate to 20% six months after therapy. Morbidity is high regardless of treatment. Less than 40% of patients return to normal function after HSE; patients are often left with significant neurological impairment.[4] There is some evidence that morbidity for HSE caused by HSV-2 may be even higher than that for HSV-1 in both adults and neonates.[5,17]

Discussion

The literature thus far has been overwhelmingly focused on HSE caused by HSV-1, which is warranted given the rarity of HSV-2 encephalitis. As such, our case provides valuable insight into the clinical manifestations and treatment of HSV-2 encephalitis. To our knowledge, this is the first described case of HSV-2 encephalitis in an adult with rheumatoid arthritis on corticosteroids. The effect of corticosteroid immunosuppression is unclear. The patient had only been taking physiological doses of corticosteroids for her RA, but it may have increased her risk of developing HSV-2 encephalitis.

Looking back, the patient's flu-like illness a month prior may have been primary HSV infection, although patient denied any history of cold sores or genital ulcers. She presented with normal brain imaging without the characteristic MRI findings in the temporal lobes. In addition, despite the high incidence of significant neurological impairment after infection, our patient returned to neurological baseline after only one night of intravenous acyclovir treatment. The similar clinical presentation and successful treatment with acyclovir in our case provides compelling evidence that there is substantial overlap between HSE caused by HSV-1 or HSV-2.

REFERENCES

1. **Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, Cunningham R, Zuckerman M, Mutton KJ, Solomon T, Ward KN, Lunn MP, Irani SR, Vincent A, Brown DW, Crowcroft NS; UK Health Protection Agency (HPA) Aetiology of Encephalitis Study Group**. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. *Lancet Infect Dis*. 2010 Dec;10(12):835-44. doi:10.1016/S1473-3099(10)70222-X. Epub 2010 Oct 15. Erratum in: Lancet Infect Dis. 2011 Feb;11(2):79. PubMed PMID: 20952256.
2. **Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, Holland M, Easton A, Buckley C, Kneen R, Beeching NJ; National Encephalitis Guidelines Development and Stakeholder Groups**. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. *J Infect*. 2012 Apr;64(4):347-73. doi:10.1016/j.jinf.2011.11.014. Epub 2011 Nov 18. PubMed PMID: 22120595.
3. **Chaudhuri A, Kennedy PG**. Diagnosis and treatment of viral encephalitis. *Postgrad Med J*. 2002 Oct;78(924):575-83. Review. PubMed PMID: 12415078; PubMed Central PMCID: PMC1742520.
4. **Whitley RJ**. Herpes simplex encephalitis: adolescents and adults. *Antiviral Res*. 2006 Sep;71(2-3):141-8. Epub 2006 Apr 25. Review. PubMed PMID: 16675036.
5. **Mateen FJ, Miller SA, Aksamit AJ Jr**. Herpes simplex virus 2 encephalitis in adults. *Mayo Clin Proc*. 2014 Feb;89(2):274-5. doi: 10.1016/j.mayocp.2013.12.003. PubMed PMID: 24485138.
6. **Aurelius E, Johansson B, Sköldenberg B, Forsgren M**. Encephalitis in immunocompetent patients due to herpes simplex virus type 1 or 2 as determined by type-specific polymerase chain reaction and antibody assays of cerebrospinal fluid. *J Med Virol*. 1993 Mar;39(3):179-86. PubMed PMID: 8385702.
7. **Omland LH, Vestergaard BF, Wandall JH**. Herpes simplex virus type 2 infections of the central nervous system: A retrospective study of 49 patients. *Scand J Infect Dis*. 2008;40(1):59-62. Epub 2007 Jul 10. PubMed PMID: 17852910.
8. **Harrison NA, MacDonald BK, Scott G, Kapoor R**. Atypical herpes type 2 encephalitis associated with normal MRI imaging. *J Neurol Neurosurg Psychiatry*. 2003 Jul;74(7):974-6. PubMed PMID: 12810797; PubMed Central PMCID: PMC1738518.

9. **Levitz RE**. Herpes simplex encephalitis: a review. *Heart Lung*. 1998 May-Jun;27(3):209-12. Review. PubMed PMID: 9622408.
10. **Kennedy PG, Steiner I**. Recent issues in herpes simplex encephalitis. *J Neurovirol*. 2013 Aug;19(4):346-50. doi: 10.1007/s13365-013-0178-6. Epub 2013 Jun 18. Review. PubMed PMID: 23775137.
11. **Kennedy PG, Chaudhuri A**. Herpes simplex encephalitis. *J Neurol Neurosurg Psychiatry*. 2002 Sep;73(3):237-8. PubMed PMID: 12185148; PubMed Central PMCID:PMC1738005.
12. **Whitley RJ, Gnann JW**. Viral encephalitis: familiar infections and emerging pathogens. *Lancet*. 2002 Feb 9;359(9305):507-13. Review. PubMed PMID: 11853816.
13. **Steiner I, Schmutzhard E, Sellner J, Chaudhuri A, Kennedy PG; European Federation of Neurological Sciences; European Neurologic Society**. EFNS-ENS guidelines for the use of PCR technology for the diagnosis of infections of the nervous system. *Eur J Neurol*. 2012 Oct;19(10):1278-91. doi:10.1111/j.1468-1331.2012.03808.x. Epub 2012 Aug 6. PubMed PMID: 22882231.
14. **Steiner I, Budka H, Chaudhuri A, Koskiniemi M, Sainio K, Salonen O, Kennedy PG**. Viral meningoencephalitis: a review of diagnostic methods and guidelines for management. *Eur J Neurol*. 2010 Aug;17(8):999-e57. doi:10.1111/j.1468-1331.2010.02970.x. Epub 2010 Mar 3. Review. PubMed PMID: 20236175.
15. **Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ**. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med*. 1986 Jan 16;314(3):144-9. PubMed PMID: 3001520.
16. **Raschilas F, Wolff M, Delatour F, Chaffaut C, De Broucker T, Chevret S, Lebon P, Canton P, Rozenberg F**. Outcome of and prognostic factors for herpes simplex encephalitis in adult patients: results of a multicenter study. *Clin Infect Dis*. 2002 Aug 1;35(3):254-60. Epub 2002 Jul 10. PubMed PMID: 12115090.
17. **Corey L, Whitley RJ, Stone EF, Mohan K**. Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. *Lancet*. 1988 Jan 2-9;1(8575-6):1-4. PubMed PMID: 2891886.

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