A 39-Year-Old Man with Acute Mental Status Changes

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The incidence of herpes simplex virus (HSV) encephalitis exceeds that of other forms of acute viral encephalitis. It is widely acknowledged that the use of PCR amplification for the detection of HSV DNA in cerebrospinal fluid (CSF) has increased our diagnostic sensitivity for this illness, leading to the diagnosis of HSV encephalitis in a wide range of clinical presentations. It is important to distinguish HSV from other viral encephalitides because it is the only form of viral encephalitis for which effective treatment exists. Prognosis is greatly improved with early treatment.

A 39-year-old man presented to the emergency department complaining of fatigue for 3 weeks and a headache for 4 days. The patient also reported a fever. The headache was described as bifrontal, throbbing, constant, 8/10 in intensity, and unrelieved by ibuprofen. The patient reported no radiation of this pain, no neck stiffness, and no photophobia. The patient also reported a 7-pound unintentional weight loss over the past month. He denied cough, chills, night sweats, dyspnea on exertion, diar-

CME INFORMATION

TARGET AUDIENCE

The September/October Clinical Case of the Month is intended for family physicians, general internists, general practitioners, emergency medicine physicians, pediatricians, dermatologists, radiologists, and neurologists.

EDUCATIONAL OBJECTIVES

After reading this article, physicians should be able to identify and understand the epidemiology, clinical presentation, diagnosis, and treatment of herpes simplex virus encephalitis.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Billingsley has nothing to disclose.
Ms. Hovland has nothing to disclose.
Dr. Agcaoili has nothing to disclose.
Dr. Long has nothing to disclose.
Dr. Borne has nothing to disclose.
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.

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rhea, nausea, or vomiting. He also denied any sick contacts or history of tuberculosis exposure. The patient emigrated from Pakistan in 1992 and last visited that country in 1997.

The patient's past medical history was significant only for an impacted kidney stone requiring surgery 15 years prior. He was married for 5 years, had one child, and reported one episode of homosexual intercourse approximately 7 years earlier. He denied tobacco, alcohol, or illicit drug use. The only medications used by the patient were acetaminophen and ibuprofen as needed for pain relief.

Vital signs included a temperature of 101.0°F, a heart rate of 100 beats per minute, blood pressure of 134/103 mmHg, and a respiratory rate of 20 breaths per minute. He was 5'1" tall and weighed 120 pounds; his body mass index (BMI) was 22.7. The patient was diaphoretic, weak, and ill appearing, but was alert and oriented. The physical exam including the neurological exam revealed no apparent abnormalities.

Serum chemistries on presentation were significant for a sodium of 134 mmol/L (135-146 mmol/L) and a potassium of 3.5 mmol/L (3.8-5.2 mmol/L). A complete blood count revealed a hemoglobin of 11.3 gm/dL (13.5-17.5 gm/dL), a hematocrit of 33.1% (40%-51%), a mean cell volume of 83.3 fL (76-96 fL), a platelet count of 102,000/ µL (130,000-400,000/µL), and a white blood cell count of 2,900/µL (6000-1100/µL) with a differential of 80% neutrophils (35%-65%), 11% lymphocytes (25%-35%), and 9% monocytes (3%-10%). An immunodeficiency panel demonstrated an absolute CD4 count of 9/µL (600-1500/µL), a CD4 percentage of 2.1% (36%-54%), and a CD4:CD8 ratio of 0.1 (1.1-2.9). Human immunodeficiency virus (HIV) testing was positive. Serum cryptococcal antigen, rapid plasma reagin (RPR), and hepatitis A, B, C panels were non-reactive. A lumbar puncture was performed. The cerebrospinal fluid (CSF) white blood cell count was 2/µL (<5/µL) with a differential of 8% neutrophils (none), 76% lymphocytes (60%-70%), and 16% monocytes (30%-50%). The CSF contained 17 RBCs/µL (<5/µL), a total protein of 66 mg/dL (20-50mg/dL), and glucose of 58 mg/dL (40- 70 mg/dL). The india ink stain revealed no cryptococcal organisms, and the cryptococcal antigen test was negative. Routine blood cultures, fungal blood cultures, mycobacterial blood cultures, and urine cultures were sent. A computed tomographic (CT) scan of the head with contrast showed only mild diffuse cerebral atrophy.

Intravenous antibiotics were begun for the possibility of bacterial meningitis, but were discontinued after 72 hours when all CSF cultures remained negative. Trimethoprim/sulfamethoxazole and azithromycin were initiated for prophylaxis against *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, and Toxoplasmosis.

Blood, CSF, and urine cultures remained negative. Low-grade fever and headache persisted. On hospital day eight, the patient became more lethargic, confused, and disoriented. A lumbar puncture revealed a white blood cell count of 25/µL with a differential of 87% neutrophils, 9% lymphocytes, and 4% monocytes. The CSF manifested a red blood cell count of 30/µL, a protein continent of 114 mg/dL, and a glucose of 57 mg/dL. Cerebral spinal fluid was also sent for herpes simplex virus (HSV) polymerase chain reaction (PCR) and empiric acyclovir was initiated. A MRI of the head with and without contrast was obtained (Figure 1).

The CSF HSV PCR test was positive. The patient completed a 21-day course of intravenous acyclovir. The headache and fever slowly resolved although some disorientation persisted. After completion of his treatment, the patient returned home to be cared for by his family.

DISCUSSION

Herpes simplex virus (HSV) accounts for 10% to 20% of all cases of viral encephalitis in the United States and has an estimated incidence of 2 to 4 cases per million per year.[1] It is a relatively uncommon illness given the ubiquity of the herpes simplex virus in the general population. In fact, as many as 95% of individuals are seropositive for antibodies to HSV-1 by 15 years of age.[2] Reported cases of HSV encephalitis appear to be sporadic, both seasonally and geographically. There is no racial or sex predominance, but it is more common in children.[3] The capacity of HSV to establish lifelong latency in sensory ganglia of infected individuals leads to continuous circulation of the virus in the human population. Serologic data indicate that infection of the brain occurs as a primary infection in about 50% of patients and as recurrent infection, as evidenced by preexisting antibodies or clinical history of herpes labialis, in the other half.[2] HSV-2 infections, by maternal transmission from genital disease, occur most commonly in neonates.[1,3,2]

Although HSV-1 is the most common cause of HSV encephalitis in the adult population, the detection of HSV-2 DNA in CSF is more frequent in the HIV-positive population compared to immunocompetent populations.[3] Perhaps this is related to the increased prevalence of HSV-2 genital infections in the HIV-positive population. HSV encephalitis, caused by either HSV-1 or HSV-2, does not appear to occur more frequently in the HIV-population as compared to the immunocompetent population. Immunodeficiency has not been implicated as a predisposing condition to the development

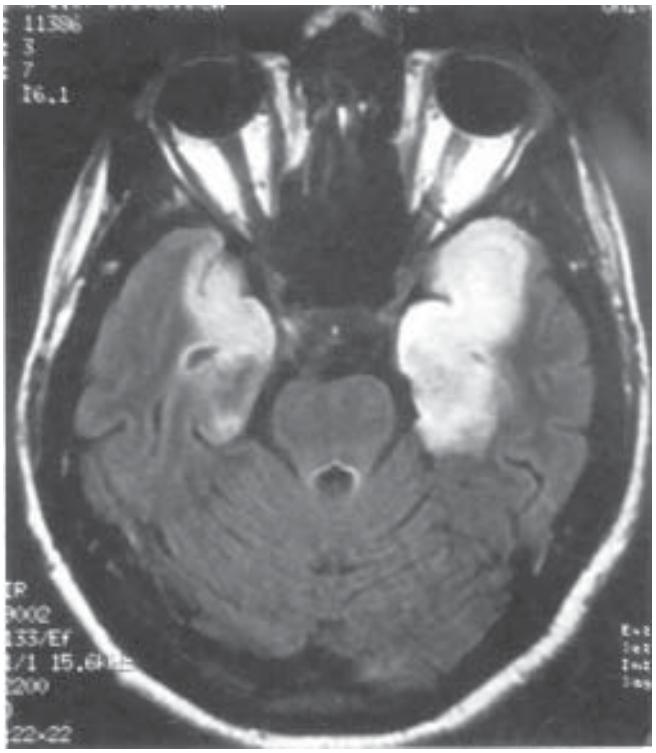

Figure 1. Brain MRI. T-1 weighted axial plane through the midbrain showing extensive bilateral high signal intensity in the temporal lobes.

of HSV encephalitis. However, HSV encephalitis in HIV-infected individuals seems to recur more often and have a more severe course.

The pathogens causing acute encephalitis are separated into two categories: those transmitted by vectors and those spread by human-to-human contact. Many viral and rickettsial infections have seasonal and regional variations due to the life cycles of their arthropod vectors. The arboviral meningoencephalitides transmitted by mosquitoes (eg, Eastern and Western equine encephalitis, St. Louis encephalitis) occur most commonly in summer months.[2] Tick-borne infections, such as Rocky Mountain spotted fever and Lyme disease, are most common in spring and early summer.[2] Rabies virus is transmitted by direct inoculation from the bite of an infected animal. A careful history, including recent travel to endemic areas, exposure to animal or insect bites, and seasonality, is the most important factor in establishing a diagnosis.

Herpes simplex virus is in the category of human-to-human transmissible agents that include measles-virus, mumps-virus, and enteroviral infections of the CNS. These pathogens are transmitted by intimate person-to-person contact or droplet exposure, occur worldwide, and have no definitive seasonal variation. Humans are the only natural reservoir of HSV, and no vectors are involved in its transmission; thus no epidemiologic patterns have been established.[2] The lack of active skin or genital lesions may also further obscure the diagnosis of HSV encephalitis. In one study, only 39% of patients with HSV encephalitis had active lesions or a history of previous local lesions.[3] Patients presenting with one of the other encephalitides may have a viral exanthem as is seen in enteroviral encephalitis or the petechial rash characteristic of Rocky Mountain spotted fever.

The most common symptoms of HSV encephalitis are difficult to distinguish from other forms of acute viral encephalitis. These include fever, headache, personality change, and generalized seizures, in decreasing order of incidence.[2,4] Of the presenting signs, reduced level of consciousness and disorientation are the most common, but are nonspecific.[2,4] Localization of neurological findings to the temporal lobe is typically associated with HSV encephalitis; however, this finding is also not specific for HSV.[2] Changes referable to the HSV-infected areas of the temporal and frontal lobes include memory loss, peculiar behavior, expressive aphasia, olfactory or gustatory hallucinations, focal seizures, and, rarely, anosmia.[2] Electrolyte imbalances result secondary to the syndrome of inappropriate secretion of antidiuretic hormone. Cerebral edema contributes to the neurological signs and symptoms, the degree of which largely determines the outcome of the illness. Poor prognostic indicators include the presence of stupor or coma, delay of therapy, age greater than 54 years old, bilateral epileptiform abnormalities on EEG, and abnormalities visualized on head CT.

DIAGNOSIS

Analysis of cerebrospinal fluid obtained by lumbar puncture is usually non-specific. In viral meningitis, CSF protein content is typically increased (>45 mg/dL) and glucose content is normal (50-80 mg/dL) or slightly low. In such cases when glucose is found to be low, repeat CSF analysis is recommended to exclude tuberculous meningitis. A white blood cell count of 50 to 300 cells/mm^3 is not uncommon, often lymphocytic in predominance although a neutrophilic pleocytosis may be present early in infection.[5] Xanthrochromasia secondary to hemorrhagic necrosis is more common in HSV encephalitis than in other encephalitides.[2] These CSF findings are found also in infections other than viral encephalitis including tuberculosis, cryptococcosis, or toxoplasmosis in a patient with AIDS.[2] Attempts should be made to rule-out these infections when clinically indicated. HSV is rarely cultured from cerebrospinal fluid; however, detection of HSV DNA with PCR amplification provides a definitive diagnosis. The sensitivity and specificity of HSV

DNA detection by CSF-targeted PCR has been estimated to be 100% and 99.6%, respectively, and the test has replaced brain biopsy as the "gold standard" for diagnosis of HSV encephalitis.[3] Furthermore, CSF PCR is an excellent diagnostic tool to confirm mild or atypical cases of HSV encephalitis.

Electroencephalography (EEG), another potentially helpful diagnostic tool, usually reveals periodic sharp waves from focal abnormalities in HSV PCR-positive patients. The EEG is sensitive, but less specific for diagnosing HSV encephalitis, except in cases in which abnormalities of the temporal regions are observed, a finding strongly associated with HSV encephalitis.[4] Magnetic resonance imaging (MRI) of the brain is the most useful radiographic diagnostic test in suspected HSV encephalitis. In one study, 88.9% of patients with PCR-positive HSV encephalitis had characteristic lesions of one or both temporal lobes.[4] Compared to computed tomography, MRI is better able to visualize inflammation in the temporal lobes due to the high-sensitivity of the T2-weighted technique in detecting edema and the enhanced visualization of the temporal-basal lobes without artifact from the skull base.[6] Brain biopsy remains a diagnostic option in some patients, specifically those in which treatment with acyclovir results in no improvement in clinical status and the physician is left searching for another causative agent. Findings of intranuclear inclusion bodies and hemorrhagic necrosis predominately in the medial temporal and inferior frontal lobes support the diagnosis of HSV encephalitis.[1,5] Open craniotomy is necessary for biopsy of the involved portions of the brain, and the inherent complications of such a procedure limit its use. In addition, because of the focal nature of the disease, false-negative results occur in approximately 4% of patients.[1]

TREATMENT

Early treatment is important to improve clinical outcome. Intravenous acyclovir (30 mg/kg/day divided into eight hour doses for 14 to 21 days) is the antiviral of choice. Mortality is reduced to 19% 6 months after treatment compared to 70% in those patients without treatment.[1] IV vidarabine (15 mg/kg/day) is an alternative agent for HSV encephalitis. However, it is more toxic and less effective than acyclovir. In HIV-infected individuals, there is an increased incidence of concomitant CMV meningo-encephalitis.[3] The clinical significance of HSV-CMV coinfection is not known. IV forscarnet (40-60 mg/kg every 8 hours), which penetrates the CSF, can be used to treat HSV-CMV coinfection. More than 5% of patients suffer from clinical relapse despite appropriate therapy.[2] Neurologic sequelae, like chronic fatigue, severe anxiety, emotional liability, poor motivation, and upper motor neuron abnormalities are common, and their severity depend on the extensiveness of the infection.

CONCLUSION

HSV encephalitis remains a significant infection causing morbidity and mortality despite advances in diagnosis and treatment. A high index of suspicion and early initiation of acyclovir therapy may increase survival, decrease morbidity, and prevent neurologic sequelae. The higher incidence of CMV meningoencephalitis in AIDS patients with HSV encephalitis has important clinical implications with regards to diagnosis and choice of treatment.

MRI follow-up may not correlate with clinical recovery and improvement. In stable patients, there seems to be no indication for MRI after completing the whole course of treatment. In the few cases where there is continuous clinical deterioration, however, repeat MRI of the brain may help guide further treatment.

REFERENCES

1. Tang Y, Mitchell PS, Espy MJ, et al. Molecular diagnosis of herpes simplex virus infections in the central nervous system. *J Clin Microbiol* 1999;37:2127-2136.
2. Oxman MN. Herpes simplex viruses. In: Gorbach SL, Bartlett JG, Blacklow NR. *Infectious Diseases*, Second edition. Philadelphia:W.B. Saunders; 1998:2022-2062.
3. Cingue P, Vago L, Marenzi R, et al. Herpes simplex virus infections of the central nervous system in human immunodeficiency virus-infected patients: clinical management by polymerase chain reaction assay of cerebrospinal fluid. *Clin Infect Dis* 1998;27:303-309.
4. Domingues RB, Tsanaclis AM, Pannuti CS, et al. Evaluation of the range of clinical presentations of herpes simplex encephalitis by using polymerase chain reaction assay of cerebrospinal fluid samples. *Clin Infect Dis* 1997;25:86-91.
5. Dudgeon JA. Pathology of herpes encephalitis. *Postgrad Med J* 1969;45:386-391.
6. Schroth G, Gawehn J, Thron A, et al. Early diagnosis of herpes simplex encephalitis by MRI. *Neurology* 1987;37:179-183.

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CME QUESTIONS

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For each question, choose the one answer that is most correct.

1. HSV Encephalitis is more common in:
   a) Asian women
   b) Native Americans
   c) Children
   d) African-americans

2. All of the following causes of encephalitis have seasonal variation except:
   a) Rocky Mountain spotted fever
   b) St. Louis Encephalitis
   c) Lyme Disease
   d) Mumps-virus

3. The most common symptoms of HSV encephalitis include:
   a) Headache
   b) Personality change
   c) Seizures
   d) A & C
   e) All of the above

4. Which of the following has replaced brain biopsy as the "gold standard" for diagnosis of HSV Encephalitis:
   a) Cerebrospinal fluid culture
   b) Electroencephalography
   c) CSF-targeted PCR
   d) Magnetic resonance imaging of the brain