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Authors

Joo, Esther

Ly, Alexandra

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CLINICAL VIGNETTE

A Rare Complication of Herpes Simplex Virus Encephalitis

Esther Joo, MD and Alexandra Ly, MD

Case Presentation

A 42-year-old man with no known past medical history was brought into the Emergency Department from home after having a seizure witnessed by his wife. The day preceding admission, the patient had complained of a posterior headache, nausea and myalgias along with a fever to 100.5F. He denied any recent known sick contacts or recent travels. He has only been sexually active with his wife and has no known history of oral or genital vesicular lesions.

On exam, vital signs included: febrile to 38.4C, pulse of 86/min, respiratory rate of 16/min, blood pressure of 122/72 and 97% O₂ saturation on room air. He was initially in a post-ictal state, but gradually improved mentation and was alert and oriented to person, place, date and situation. His neurologic exam was otherwise grossly intact with a supple neck. He had no oral or genital lesions. His cardio-pulmonary exam was normal and abdominal exam benign.

Laboratory studies revealed only a mild leukocytosis (11.3K/cumm), with normal hemoglobin and platelets, chemistries showed normal sodium and potassium with an elevated creatinine (1.29 mg/dL). Urine toxicology was negative as were blood levels for acetaminophen, salicylate and ethanol. A CT head without contrast showed no acute intracranial findings. An MRI brain with and without contrast demonstrated increased signal on the T2 weighted and FLAIR sequences in the left medial temporal lobe and insular cortex without evidence of hemorrhage. CSF analysis demonstrated pleocytosis (94/cumm) with neutrophil predominance, mildly elevated protein (56 mg/dL) and mildly elevated glucose (79 mg/dL). Blood and CSF cultures were negative. PCR performed on the CSF detected HSV-1 and patient was diagnosed with Herpes Simplex Virus encephalitis (HSVE).

The patient was initiated on acyclovir 10mg/kg IV every eight hours and with improvement in his headache. He was also started on levetiracetam for secondary seizure prevention. On hospital day 3, the patient became intermittently somnolent. A CT head demonstrated edema within the medial left temporal lobe and insular cortex without evidence of hemorrhagic transformation. He continued to have fevers, slow speech, word finding difficulties and waxing and waning mental status. On hospital day 7, a repeat LP was performed given the persistence of fevers and headache and lack of improvement of mental status without new neurologic deficits. The repeat CSF analysis demonstrated 8,550/cumm RBC, 93/cumm nucleated cell count

with lymphocytic predominance, normal glucose count and elevated protein 157 mg/dL. The elevated RBC count prompted a repeat CT that revealed interval development of an intraparenchymal hemorrhage within the left temporal lobe with extension of the hemorrhage into the left lateral ventricular system, and midline shift toward the right. Neurosurgery was consulted but did not recommend surgical intervention. He was transferred to the medical ICU for closer monitoring and serial CT head imaging was obtained remained stable. The patient was transferred to the wards and remained stable. On hospital day 20, the patient was ready for discharge with plans to complete a 21-day total course of IV acyclovir. At discharge, the patient had regained full orientation but continued to have slow speech and word-finding difficulties.

Discussion

Acute encephalitis is important to recognize promptly because delayed inadequate treatment can lead to poor prognosis with high morbidity and mortality. Prior to the development of antiviral treatment for HSVE, the mortality rate was about 70% with 50% significant morbidity.¹ The incidence of HSVE both worldwide, and in the US, is 2-4 cases/1,000,000, with HSV-1 making up roughly 90% of all HSV encephalitis cases. Men and women are affected equally with a bi-modal distribution affecting both young children up to 3 years old and a greater majority affecting those >50 years old.² HSVE can be caused by reactivation of latent herpes simplex virus or from primary infection.¹

HSVE should be considered in patients who present with features typical of encephalitis, which may include various combinations of fever, seizures, neurologic deficits, lethargy, irritability, behavioral or personality changes, along with EEG or neuroimaging findings suggestive of encephalitis.^{3,4} MRI results typically show lesions in the inferomedial regions in one or both temporal lobes.⁵ However, the critical component in the diagnosis of HSVE is the evaluation of cerebrospinal fluid obtained by lumbar puncture. CSF fluid analysis typically demonstrates a pleocytosis (>5 WBC x 10⁹/L) that is predominantly lymphocytic, though can be neutrophilic early in the disease. normal to moderately elevated protein level, and normal glucose level.⁴ While PCR for HSV-1 and 2 in the CSF has a sensitivity and specificity >95% and is considered the gold standard in diagnosing HSVE, it can be negative early in the course of infection and thus may need to be repeated in 3-7

days despite acyclovir therapy, if suspicion remains high.^{2,4} CT head can be completed prior to LP if indicated but should not delay initiation of treatment with antiviral therapy if suspicion for HSVE is high.^{1,3}

Standard treatment for HSVE is acyclovir IV 10mg/kg every 8 hours for adults. It should be initiated as early as possible when viral encephalitis is suspected, as PCR for HSV in the CSF will remain positive for a few days after initiation of therapy.^{3,6} A typical course of treatment is between 14-21 days.⁶ Given the risk of renal toxicity, it is recommended to provide IV fluids before each dose. There is poor-quality evidence for use of glucocorticoids in the treatment of HSVE.

Monitoring for improvement during the treatment of HSVE can be challenging given as many as 89% of patients have persistent neuropsychiatric symptoms at the time of discharge.¹ These persistent symptoms can often mask acute-phase CNS complications of HSVE such as intracranial hemorrhage. While intracranial hemorrhage is rare, occurring in roughly 2.7% of cases, this particular complication is becoming more recognized as it is associated with increased in-hospital mortality in adults and can be associated with HSV-1 encephalitis.^{7,8} ICH occurred with a median time of 10 days after clinical onset of symptoms with the location of the hemorrhage predominantly located in the temporal lobe involving the area of encephalitis.^{8,9} Patients often do not exhibit any new symptoms but rather a lack improvement or have worsening of initial symptoms during the course of therapy. Those that develop symptoms exhibited decreased level of consciousness, third-nerve palsy and hemiparesis.⁹

In summary, early diagnosis and timely initiation of appropriate antiviral therapy is critical in the treatment of HSVE encephalitis in order to decrease the morbidity and mortality. While the patient presented in this case was initiated on appropriate therapy quickly, his neurologic exam failed to improve despite treatment which prompted repeat LP and brain imaging, leading to the diagnosis of intracranial hemorrhage.

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