Altered Mental Status in a U.S. Army Special Forces Soldier

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Abstract

Special Operations medical provider must be familiar with the differential diagnosis for a patient with altered mental status since it includes multiple life-threatening illnesses. Potential diagnoses include meningitis, encephalitis, malaria and many others. While preparing to evacuate to definitive care from an austere location, they must also be prepared to initiate empiric therapy that is specific to the patient and the area of operations. We present a case of a U.S. Army Special Forces Soldier that developed limbic encephalitis of presumed Herpes Simplex Virus (HSV) origin. We will review the key differential diagnoses for this presentation with a focus on infectious etiologies. We will also summarize current diagnostic and therapeutic strategies. Our recommendation is to initiate oral acyclovir when IV acyclovir is not available and this diagnosis cannot be excluded.

Introduction

Encephalitis is a predominantly viral infection of the central nervous system (CNS). Multiple different viral etiologies are possible and the ultimate cause may not be identified. A broad spectrum of presentations may occur. Frequently encountered symptoms include altered mental status, fever, and a variety of neurologic deficits. These may range from minor deficits to flaccid paralysis or coma. Memory deficits, personality changes and seizures may also be present. Potential pathogens vary considerably based on seasonal variation and geographic considerations. MRI of the brain is the ideal imaging modality and the diagnosis can be confirmed with polymerase chain reaction (PCR) testing of the cerebrospinal fluid (CSF).

Case Report

A 35-year-old male U.S. Army Special Forces Soldier self-referred to the Emergency Department (ED) of his local military treatment facility with the chief complaint of headache, disorientation and increasing memory difficulties. He had noticed these symptoms 12 hours prior to presentation and they had been progressing throughout the day without any other associated symptoms. He had recently returned from a 6-month temporary duty assignment in Hawaii, but had no other recent deployments or international travel. He had no preceding illness.

On presentation to the ED, the patient was confused and was noted to have obvious difficulty forming new memories. He reported having difficulty focusing. He denied fever, headache or other symptoms. The patient had no significant past medical history. Vital signs were all found to be within the normal range and he was afebrile. His physical exam was unremarkable, to include the absence of nuchal rigidity, petechiae or other rashes. His Glasgow Coma Scale was 15. A consult was placed from the ED to the on-call Neurologist who arranged to see the patient in his clinic within the next 72 hours. The Neurologist requested an MRI be completed prior to the outpatient visit, but recommended deferring the lumbar puncture and all other studies. His diagnosis on discharge was Transient Global Amnesia.

The following day, the Soldier presented to his Special Forces Medical Sergeant (18D) and complained of a febrile illness at that time. At 24 hours after initial presentation, the 18D and the Battalion Surgeon escorted the Soldier back to the ED. At that time, he was noticeably more confused and he began confabulating. His only other complaint at that time was several episodes of emesis. Again, his physical exam was unremarkable, and his vital signs to include temperature were all within normal limits.

The patient was immediately started on IV acyclovir, ceftriaxone, and dexamethasone to empirically treat both meningitis and encephalitis. Encephalitis was suspected due to the patient's rapidly worsening short-term memory. A lumbar puncture (LP) was performed, the results of which were consistent with a viral process (WBC 93, RBC 2, glucose 55, protein 66). He was admitted for further treatment and evaluation due to concern for encephalitis. PCR testing for both HSV 1 and 2 was negative, as were all other tests run on the CSF. A head CT without contrast was unremarkable. A MRI performed four days post onset revealed abnormalities in the bilateral medial temporal lobes, caudate heads, left putamen, and both mammillary bodies. These findings were considered atypical for HSV encephalitis, but more typical for an autoimmune etiology. Extensive additional testing and imaging to rule out rheumatologic or paraneoplastic causes was negative. Post-vaccinial encephalitis was considered as the Soldier had received his small pox vaccine two weeks prior; however, additional PCR for this etiology was also negative. Serum was positive for HSV IgM with HSV IgG being negative suggesting an acute infection. No epileptiform activity was detected on an EEG. The patient underwent a repeat lumber puncture that demonstrated a decline in his WBC count to 53 while on acyclovir (RBC 2, Protein 45, Glucose 7), but all other CSF studies to include repeat PCR testing were again negative. A follow-up MRI performed at seven days post-presentation revealed stable lesions.

The patient remained hospitalized for 14 days while receiving IV acyclovir and further evaluation. During his stay, he developed a systemic reaction to IV acyclovir

that manifested as a diffuse erythematous rash. Due to the presumption of HSV encephalitis, the decision was made to continue the medication and the addition of diphenhydramine reduced his symptoms dramatically. His anterograde amnesia mildly improved during this time. He was discharged and received a total of 21 days IV acyclovir with improvement in both clinical status and laboratory values. The patient did not display seizure activity at any time. The only other symptom he reported was occasional moderate headaches, which were relieved with either ibuprofen or acetaminophen. The patient scored 28/30 on a mini-mental status exam eight days after discharge. The final diagnosis was limbic encephalitis of HSV origin although PCR was negative on both occasions. This patient was presumed to have HSV encephalitis due to his improvement while on acyclovir. The possibility that the patient's encephalitis was caused by a herpes virus other than HSV 1 or 2 also exists (e.g., human herpes virus 6 or HHV 6).

Follow-on care was performed on an outpatient basis that included cognitive rehabilitation at Stanford University for four months. He was returned to full duty 9 months post onset with minimal neurological sequelae. He continues to function on an Operational Detachment - Alpha without any duty restrictions.

Discussion

Herpes Simplex Virus is the most common cause of severe sporadic encephalitis in North America and in the world. Although it has the highest mortality rate, it is also the most treatable form of encephalitis.[1,2,3] It is known for the serious, often long-term, neurological sequelae that affect many survivors even after receiving treatment. However, prompt recognition and early treatment can still provide good patient outcomes. Mortality reaches 70% in untreated cases of HSV encephalitis, but decreases to 19-28% with appropriate diagnosis and treatment.[4,5]

Primary signs and symptoms may include fever, headache, nuchal rigidity, focal neurologic deficits or memory loss. Altered mental status or seizure activity may also be present. Altered mental status may refer to many alterations in brain function; these effects can range from minimal to encephalopathy and coma. They may include: confusion, loss of orientation, delirium, lethargy, emotional lability, psychomotor retardation and others. Onset can be acute, or present with the prodrome of a flu-like illness. This patient's presentation is unusual in that he never exhibited any focal neurologic signs or seizures. He complained of subjective fever upon his second presentation, but did not exhibit objective fever prior to admission to the hospital. It is unknown if he was taking antipyretics due to his difficulties with short-term recall at that point.

The differential diagnosis for this presentation is extensive, especially within the spectrum of medicine in Special Operations where Soldiers travel throughout the world. A thorough travel and exposure history must be elicited. Numerous infectious etiologies for viral encephalitis exist and are often endemic to specific regions or show seasonal variation. Many other viruses can cause encephalitis and their clinical presentation is the same as HSV encephalitis. Most infections by viruses that cause encephalitis are subclinical, and encephalitis from HSV is itself a rare complication. These include the St. Louis encephalitis, West Nile encephalitis, Eastern Equine encephalitis, Japanese encephalitis (in Asia) or encephalitis from other herpes viruses. Meningitis, especially if caused by tuberculosis, may have a similar presentation. Malaria must be considered in a patient with history of potential exposure, even with appropriate prophylaxis. Other differential diagnoses include subdural hematoma or empyema, intracranial neoplasms (primary or secondary), vasculitis, brain abscess, rabies and drug-induced encephalopathy.

HSV appears to infect cerebral tissue through the trigeminal nerve or the olfactory route, but may also develop secondarily to viremia. Infection can result from a primary HSV infection of the oropharynx, a recurrent HSV infection, or without any previously identified HSV infection as in this patient. The predominant result is hemorrhagic necrosis and petechial hemorrhage in the inferior and medial temporal lobes and portions of the frontal lobes. Either HSV-1 or HSV-2 can cause encephalitis in the neonatal period, but HSV-2 is more common and is usually caused by contact with infected maternal secretions during birth. HSV-1 is the predominant cause of HSV encephalitis in the vast majority patients past this period.

PCR testing of the CSF is rapid and highly sensitive and specific, and has become the standard of diagnosis for HSV encephalitis.[6,7] PCR should be positive within 24 hours of onset, with a sensitivity of 98% and a specificity of 94-100%. It remains positive throughout the first seven days of antiviral therapy.[3,7] Cranial CT scan may demonstrate temporal lobe hypodensity, but only has an early sensitivity of 50%.[3] CT imaging may be useful to rule out other differentials, such as space-occupying lesions. MRI is the most sensitive and specific imaging modality for HSV encephalitis and can help expedite the diagnosis. It shows abnormalities in almost all cases, especially when conducted early in the disease process. It frequently shows very characteristic temporal lobe lesions. Brain biopsy should be considered for patients with a negative PCR that still present with a high suspicion for HSV encephalitis.[2,3] Regardless of the efficacy or availability of laboratory testing or imaging, antiviral chemotherapy must not be delayed.

Intravenous acyclovir is the standard for treatment of HSV encephalitis. It must be initiated as soon as Herpes encephalitis is clinically suspected to maximally reduce mortality and improve neurologic outcomes in survivors.[2,3] This is especially true in clinical environments that are more austere where MRI and CSF studies aren't possible and there may be delays in definitive diagnoses. The patient's age and state of consciousness at the time of initial therapy greatly impact the mortality rate as well as morbidity. Most patients who survive will still have some degree of neurological dysfunction. The normal duration of IV therapy is 14-21 days and the drug is generally well tolerated. Although this pa-

tient exhibited a systemic reaction, it was well controlled with the addition of diphenhydramine and he was able to continue therapy.

Although IV acyclovir is rarely carried by SOF medical providers, oral acyclovir is more readily available. Oral acyclovir has a bioavailability of only 10%-30%.[8,9] In our opinion, however, oral acyclovir should be considered until the appropriate treatment and diagnosis can be provided when encephalitis is suspected. We were only able to find one case report in the literature documenting the treatment of suspected HSV encephalitis with oral acyclovir.[8] No trials were found. This patient from India, however, responded dramatically to a 10-day oral course even when it was started on the 6th day of symptoms. An oral preparation was used in that child due to the parent's inability to afford the IV medication. In addition, adding PO or IV acyclovir to the treatment protocol for meningitis is reasonable if the means are not available to narrow the diagnosis.

This patient had an excellent outcome despite developing a potentially devastating disease. His presentation was highly unusual in that his only objective symptom at the time treatment was severe difficulty with short-term memory. The vast majority of patients with encephalitis will be febrile. It is difficult to estimate the degree to which he would have manifested other typical symptoms such as fever, focal neurologic deficits, seizures, or other forms of altered mental status if he had not received treatment in the early stages of his disease process. It is, however, highly probable that his outcome was greatly improved with the prompt and empiric initiation of acyclovir. Acyclovir is the only treatment option for HSV encephalitis. As this is the only treatable form of encephalitis, any suspected encephalitis should be treated empirically with acyclovir. The potential differential diagnoses for a patient with altered mental status are myriad and may include multiple infectious and non-infectious causes. For this reason, a thorough consideration of the area of operations, the patient's risk factors, and potential consultation with expert medical providers can help taylor therapy and improve patient outcomes. If the patient presents in an austere area, it may be necessary to treat empirically for more than one possible disease (e.g. encephalitis and meningitis) by combining acyclovir with other medications while the patient is being evacuated for further evaluation and treatment.

Conclusion

HSV Encephalitis is a potentially catastrophic disease that should be considered in any patient altered mental status, especially if they present with fever. The prognosis for a patient with this disease can be dramatically improved with prompt recognition and the initiation of IV acyclovir. Acyclovir should be started immediately and continued until the diagnosis can be ruled in or excluded. When IV acyclovir is not available, we recommend starting PO acyclovir while the patient is being evacuated to definitive care. Recognition of this disease, and initiating treatment are within the scope of practice for the SOF Medic. Based on the potential mortality and morbidity associated with this diagnosis, this disease should receive increased emphasis in training and certification programs for the SOF Medic.

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