Episodic Receptive Aphasia Associated with HSV-2 Encephalitis

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Abstract— Herpes Simplex Virus type 2 (HSV-2) is a rare cause of encephalitis beyond neonatal period. HSV-2 encephalitis typically produces global encephalitis with significant neurologic impairment. We report a case of HSV-2, which was confirmed by PCR in CSF, encephalitis presenting with a focal partial seizure manifested as episodic receptive aphasia in an immunocompromised cancer patient. His receptive aphasia was completely resolved after he was treated with Acyclovir and Levetiracetam. Focal seizures presenting as episodic receptive aphasia are rare but can be the only clinical manifestation of HSV-2 encephalitis. Early recognition of the spectrum of HSV-2 encephalitis in adults and initiation of prompt anti-viral and anti-epileptic treatment are critical in reducing mortality and morbidity associated with HSV-2 encephalitis.

Keywords — Encephalitis, HSV-2, focal seizure, receptive aphasia.

I. INTRODUCTION

Herpes Simplex Encephalitis (HSE) is the most common non-epidemic encephalitis, and the most common cause of sporadic lethal encephalitis. The majority (~90%) of HSE are caused by HSV-1. HSV-2 is a rare cause of encephalitis beyond neonatal period. Patients with HSV-2 encephalitis typically present with global encephalitis and rapid deterioration of neurological status. Untreated HSE is associated with a high mortality and morbidity rate, and early diagnosis and prompt antiviral therapy can lead to reduction of the morbidity and mortality associated with HSE. We report a case of HSV-2 encephalitis in an immunocompromised elderly patient presenting with episodic receptive aphasia. In contrast to classic pathological and electrographic findings in HSE patients, our patient had no abnormal EEG or MRI findings. Our patient rapidly responded to treatment with Acyclovir and Levetiracetam.

II. CASE REPORT

A 78 year old right-handed Vietnamese male with history of thoracic bone metastatic non-small cell lung cancer presented with two episodes of transient language disturbance. These two episodes of language disturbance occurred a day apart, and there were no other associated neurological symptoms. Each event lasted for 3-4 hours and was resolved spontaneously. He was completely normal in-between these episodes, and unable to recall the details during the events. On day three of hospitalization, the patient had his third episode that was witnessed by our neurology inpatient service team. During this episode, he was awake, alert, attentive, and speaking in clear sentences. However, he failed to answer the questions appropriately. For example, when he was asked “Do you want to go to the bathroom?” the patient replied “What is bathroom and why would I go there?” His language repetition was also impaired, but the fluency and naming remained intact, and other neurological examination was non-focal. An EEG that was done during the episode just revealed diffuse background slowing with no electroencephalographic seizures or epileptiform discharges (Figure 1A). A therapeutic trial of Ativan (2 mg) was given during the episode and the patient’s language comprehension improved rapidly. Given the findings of clinical manifestation, neurological examination, and symptomatic improvement after Ativan administration, his clinical presentations were consistent with the events of a focal seizure manifesting as receptive aphasia. He was treated with Levetiracetam (500 mg, BID), and there was no further recurrent event. MRI of the brain with and without contrast a day after the initial event was unremarkable (Figure 1B). CSF studies revealed high WBC count at 66 with predominant lymphocytes, elevated protein at 82, and normal glucose. CSF PCR analysis confirmed HSV-2. The rest of work-up including other viruses, bacteria, fungus, and malignancy were unrevealing. Notably, the patient had no previous or current history of oral or genital herpetic lesions. He was treated with intravenous Acyclovir for two weeks followed by oral Valacyclovir for permanent prophylaxis. Due to intolerance to Levetiracetam, his anti-epileptic drug was switched to Lacosamide, and he has been free of any further episodes of receptive aphasia. Follow up EEG was normal.

III. DISCUSSION

Usually HSV-1 is responsible for virtually all cases of HSE in people older than 3 months. HSV-2 is a rare cause of encephalitis beyond neonatal period, and it accounts for about

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Temporal lobe abnormalities on brain imaging.

In immunocompromised patients, early recognition with promptly appropriate diagnosis, particularly in elderly and immunocompromised patients.

False negative PCR results can occur in more than 80% of HSV-1 encephalitis patients, typically showing prominent intermittent high amplitude slow waves and, occasionally, continuous periodic lateralized epileptiform discharges (PLEDs) in the affected region.

To our knowledge, no previous studies indicated the exact percentage of abnormal EEG occurred in HSV-2 encephalitis patients. Our patient presented with episodic expression aphasia, a clinical manifestation of partial seizure. The EEG on our patient showed mild diffuse background slowing.

Although about 5% of patients with HSE have a normal CSF profile, CSF analysis usually shows a classic viral profile in acute HSE patients.

CSF HSV by PCR can be detected within 24 hours of the onset of symptoms and the PCR test remains positive for at least 5–7 days after the start of antiviral therapy. False negative PCR result most likely occurs when the CSF is collected either too early within the first 24–48 hours or too late after 10–14 days of the illness.

In our patient, CSF was collected three days after the initial episode and CSF PCR was positive for HSV-2.

CSF cytology was negative for malignant cells but showed increased pleomorphic lymphocytes that are consistent with viral encephalitis.

We report this unique case of viral encephalitis that was caused by the rare HSV-2 virus without abnormal brain MRI or focal EEG findings.

Histopathological examination showed prominent intermittent high amplitude slow waves in the temporal lobes.

1.6% to 6.5% of HSE cases (1). HSV-2 HSE usually can be seen in immunocompromised individuals and neonates (1). HSE typically has an abrupt onset with rapid progression over a few days, but there are no particular features that can be used to differentiate it from other viral causes of encephalitis (2).

HSV-1 encephalitis is usually localized to the temporal lobe, and temporal lobe abnormalities on brain imaging are considered as strong evidence for HSE in appropriate clinical settings.

However, extra temporal involvement on brain imaging is also common in HSE. In a retrospective chart review, Wasay and colleagues reported that extra temporal involvement occurs in 55% patients with HSE, and 15% of HSE patients have exclusive involvement of extra temporal areas (3).

However, this is not clear that how many of those patients with HSE were related to HSV-1 or HSV-2 in that study.

HSV-2 encephalitis usually produces more global encephalitis and spares the medial temporal and inferior frontal lobes (4).

Hemorrhagic insult and early involvement of white matter in HSV-2 HSE are typical. In immunocompromised patients, central involvement can be more diffuse, and it is more likely to affect the brain stem which differs from the classic pattern commonly seen in immunocompetent patients (i.e., medial temporal lobes, insular cortex, and inferolateral frontal lobes) (5).

Abnormal brain MRI findings were reported in 60% of patients with HSV-2 encephalitis, and 40% of them have temporal lobe involvement that is consistent with limbic encephalitis (6). In our case, no significant brain MRI abnormalities were identified (Figure 1B).

Focal electroencephalogram (EEG) abnormalities can occur in more than 80% of HSV-1 encephalitis patients, typically showing prominent intermittent high amplitude slow waves and, occasionally, continuous periodic lateralized epileptiform discharges (PLEDs) in the affected region (7).

To our knowledge, no previous studies indicated the exact percentage of abnormal EEG occurred in HSV-2 encephalitis patients. Our patient presented with episodic expression aphasia, a clinical manifestation of partial seizure. The EEG on our patient showed mild diffuse background slowing (Figure 1A).

Although about 5% of patients with HSE have a normal CSF profile, CSF analysis usually shows a classic viral profile in acute HSE patients. CSF PCR analysis for HSV has extremely high sensitivity (94-98%) as well as specificity (98-100%) (9).

CSF HSV by PCR can be detected within 24 hours of the onset of symptoms and the PCR test remains positive for at least 5–7 days after the start of antiviral therapy. False negative PCR result most likely occurs when the CSF is collected either too early within the first 24–48 hours or too late after 10–14 days of the illness (4).

In our patient, CSF was collected three days after the initial episode and CSF PCR was positive for HSV-2.

CSF cytology was negative for malignant cells but showed increased pleomorphic lymphocytes that are consistent with viral encephalitis.

We report this unique case of viral encephalitis that was caused by the rare HSV-2 virus without abnormal brain MRI or focal EEG findings. His only clinical presentation was focal seizures manifesting as receptive aphasia. The most common causes for receptive aphasia are ischemic/hemorrhagic stroke, tumor, vascular malformation, and infections that affect dominant temporal lobe. As an elderly cancer patient who is immunocompromised from chemotherapy and steroid treatment, he might have a previous indolent infection. A high index of suspicion is crucial to make prompt diagnosis of HSV-2 encephalitis in adults, particularly in elderly and immunocompromised patients. Patients with suspected HSV-2 encephalitis should be treated with empiric Acyclovir while waiting for CSF confirmation, as delay in treatment would have a notorious outcome on prognosis. It should be aware that even with appropriate treatment, prognosis is not always favorable in HSE patients (6).

The numbers of reported cases of HSV-2 encephalitis in adults still remain very limited. Further investigations such as a large scale of retrospective study, literature-based meta-analysis, and mechanistic studies are needed for us to better understand the clinical courses/presentations, and underlying pathology of this disease.

In summary, focal CNS deficits, such as episodic receptive aphasia, can be an initial presentation of HSV-2 encephalitis, and HSV-2 HSE should be considered in the differential diagnosis, particularly in elderly and immunocompromised patients. Early recognition with promptly appropriate diagnostic studies and treatment can decrease mortality and morbidity associated with HSV-2 encephalitis.
References


Questions (please choose one single answer):

1. Which of the following is incorrect regarding HSV-2 encephalitis?
   A. It is commonly seen in immunocompromised patients.
   B. It usually localizes to the temporal lobes.
   C. EEG findings could be non-specific.
   D. False negative CSF PCR for HSV-2 can occur within the first 24-48 hrs of illness.

2. Which of the following is incorrect regarding HSV encephalitis?
   A. HSV encephalitis is the most common cause of sporadic lethal encephalitis.
   B. High clinical suspicion, timely treatment with acyclovir is necessary in both HSV-1 and HSV-2 encephalitis.
   C. HSV-1 encephalitis is more common in neonates while HSV-2 encephalitis is more common in adult population.
   D. HSV-1 encephalitis usually localizes to the temporal lobe while HSV-2 encephalitis produces more global encephalitis.

3. Which of the following is correct regarding HSV2 encephalitis?
   A. MRI brain shows abnormalities in 90% of the cases.
   B. Typically present with global encephalitis, but can present as a focal neurological symptom such as episodic receptive aphasia.
   C. Focal EEG findings such as periodic lateralized epileptiform discharges (PLEDs) can be seen in 80% of patients.
   D. CSF PCR for HSV-2 has a sensitivity of 55% and a specificity of 90%.

4. Which of the following statement is correct regarding the timing of collecting cerebrospinal fluid (CSF) samples for PCR to produce relatively high yield in HSV2 encephalitis?
   A. When the CSF is collected at 24–48 hours after the onset of the symptoms.
   B. When the CSF is collected at 3-10 days after the onset of the symptoms.
   C. When the CSF is collected first 3 weeks after the onset of the symptoms.
   D. When the CSF is collected first 4 weeks after the onset of the symptoms.