



Untreated herpes simplex virus encephalitis without a fatal outcome

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Abstract

Herpes simplex virus encephalitis (HSE) is the most common sporadic fatal encephalitis. Although timely administered acyclovir treatment decreases mortality, neuropsychiatric sequelae is still common among survivors. Magnetic resonance imaging is frequently utilized for the diagnosis of HSE, which typically involves temporal lobe(s) and can be mixed with brain tumors involving the same area. Here, we report a case of HSE, who received acyclovir with a delay of 90 days because of presumptive tumor diagnosis and survived with minimal sequelae.

Keywords Herpes virus · Encephalitis · Treatment

Introduction

Herpes simplex virus encephalitis (HSE) is the most common sporadic fatal encephalitis (Hjalmarsson et al. 2007). The incidence is estimated to be 2–4 cases per 1,000,000, and HSV-1 is responsible for almost 90% of cases (Steiner and Benninger 2013). HSE cases typically present with fever, headache, mental status changes, and seizures. Magnetic resonance imaging (MRI) is frequently utilized for the diagnosis of HSE, which typically involves temporal lobe(s). The gold standard for confirming diagnosis is the detection of viral DNA by polymerase chain reaction (PCR) in cerebrospinal fluid (CSF). Untreated HSE has high mortality and morbidity rates, about 70% and 50%, respectively (Boivin 2004; Whitley and Kimberlin 2005). With the use

of acyclovir for HSE, the mortality rate decreased to 5–15% but neuropsychiatric sequelae is still common (Stahl et al. 2012). Here, we report a case of HSE, which did not progress to fatality despite failure to administer timely antiviral treatment and eventually the infected tissue was removed by surgery.

Case

A 41-year-old female was admitted to the emergency service with complaints of nausea, vomiting, headache, confusion, and behavioral changes. Nausea and vomiting first started 9 days before admission with addition of throbbing headache localized to the left side of cranium four days later. Once agnosia (she failed to recognize other family members or call their names; could not locate toilet at home) and dysosmia (everything smelled the same) developed, she was brought to emergency service. During this period, she had no fever or shaking chills. The complaints of nausea and vomiting had regressed 2 days before presentation. On physical examination, she was in good general condition, fully cooperative; meningeal irritation signs include nuchal rigidity, Kernig and Brudzinski signs were absent, and no pathological findings including focal neurological deficits and seizure were detected on admission. Her previous medical history was unremarkable except surgery for scoliosis 2 years ago. Laboratory values were within normal ranges. As there was no papilledema or a space-occupying lesion in computerized tomography imaging of brain, lumbar puncture (LP) was performed. Cerebrospinal fluid (CSF) was

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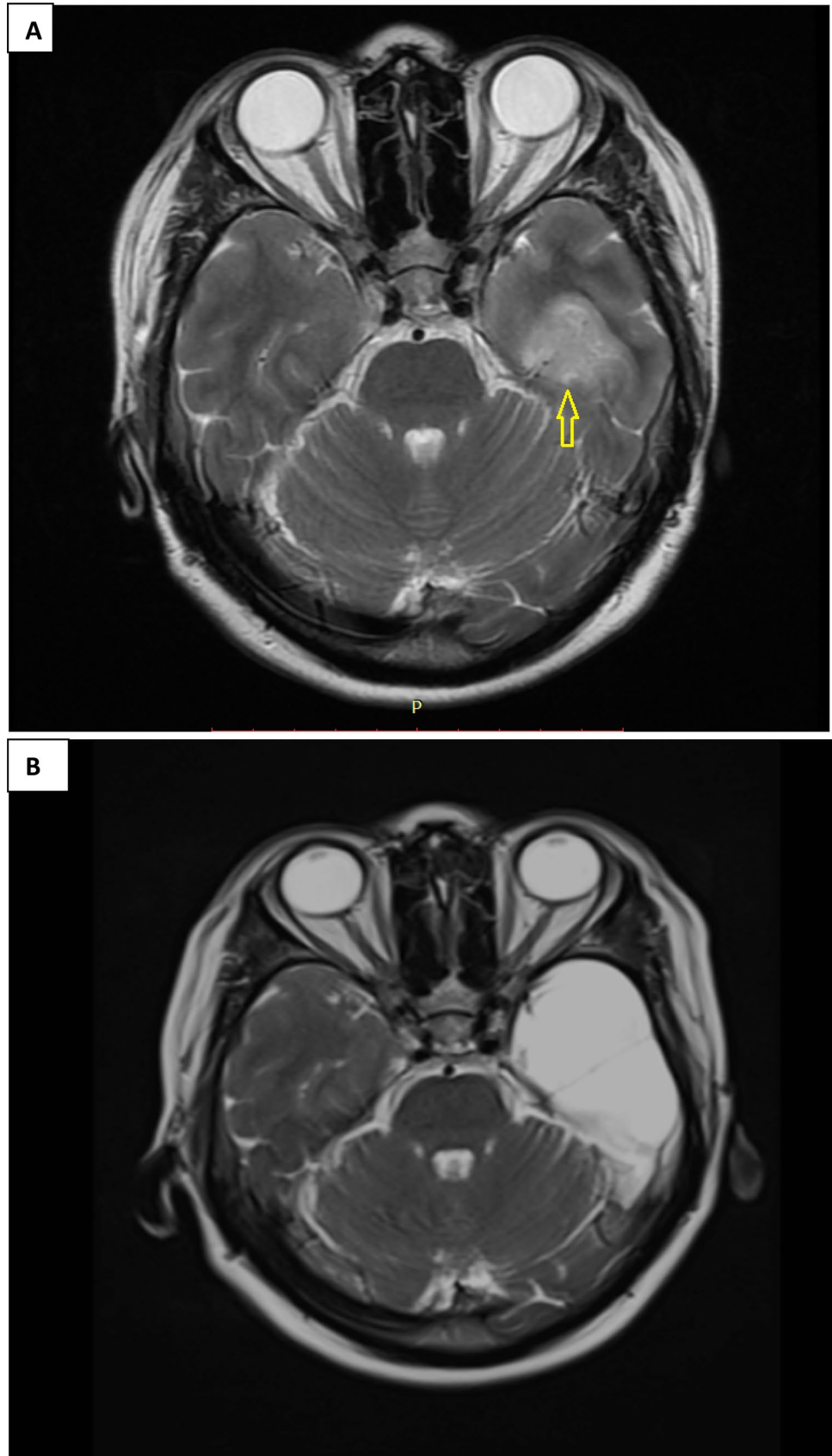
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Fig. 1 Full-sequence contrasted cranial MRI shows a lesion in the left temporal lobe **A**. A follow-up MRI of the patient after surgery **B**



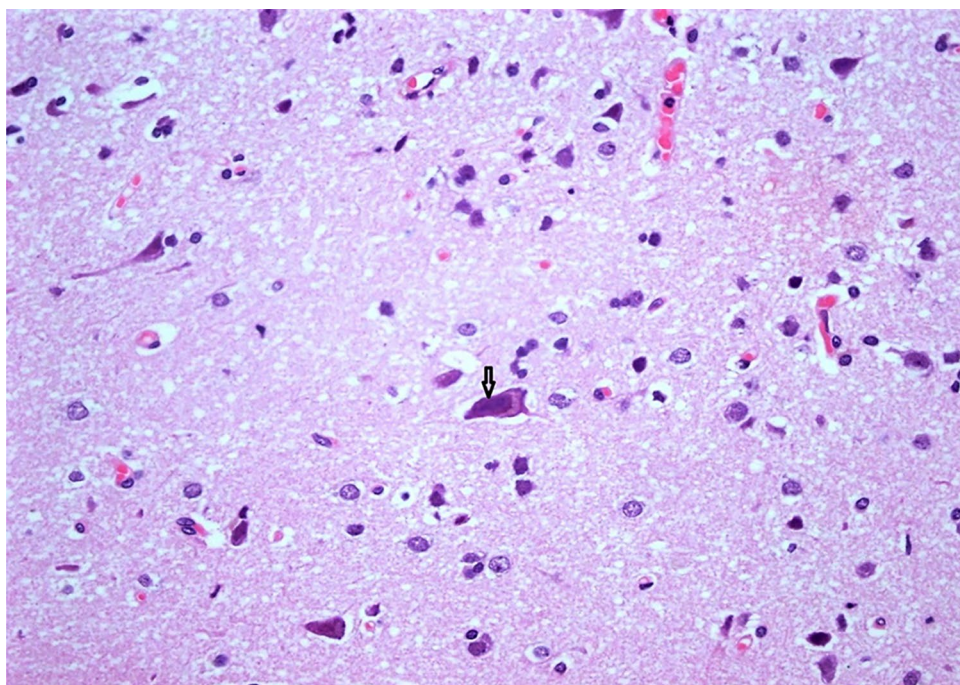
clear in appearance with no leukocyte or erythrocyte seen under microscopy. CSF analyses showed no cells/ μL , normal glucose level (49 mg/dL; simultaneous serum glucose: 80 mg/dL), and mild increase in protein level (67 mg/dL). Gram staining did not reveal any leukocytes or microorganisms. CSF was sent out for analysis with multiplex PCR FTD Neuro 9 panel (Fast Track Diagnostics Luxembourg; herpes simplex virus 1 and 2, adenovirus, varicella zoster virus, enterovirus, cytomegalovirus, parechovirus, parvovirus b19, human herpes virus type 6, 7) and PCR for *Mycobacterium tuberculosis*. A full-sequence contrasted cranial MRI taken later showed a lesion in the left temporal lobe (Fig. 1A). Radiological interpretation was compatible with a glioma. For this reason as well as non-progressive, stable nature of clinical presentation despite 9 days of duration, HSE was not on top of differential diagnoses anymore. Consequently, consulting physicians attributed all the complaints to a tumor involving left temporal lobe. She was then transferred to neurosurgery ward for further follow-up, and methylprednisolone 4×5 mg per day was administered in this clinic. As her complaints regressed, she was discharged from the neurosurgery clinic 4 days later with a scheduled operation. However, 40 days after discharge her complaints progressed and dysphasia developed before the scheduled operation took place. Upon this development, she was re-admitted and the tumor was removed from the left temporal lobe. She was discharged from the hospital 6 days after the operation with almost all her complaints regressed. The pathology report was disclosed 47 days after the operation (92 days

after the first presentation to the emergency service). The excised temporal lobe tumor showed diffuse encephalitic findings with neuronal and glial cellular damage characterized by perivascular lymphocytic infiltration and presence of microglial nodules in meningeal and brain parenchymal areas. Intranuclear inclusion bodies compatible with viral infection were observed in few neuronal cells (Fig. 2). There was no tumor tissue.

CSF culture for bacterial pathogens including tuberculosis were negative. Autoimmune encephalitis panel testing for Anti-Hu, Anti-Yo, Anti-Ri, Anti-amphiphysin, Anti-Tr, Anti-PCA-2, Anti-Ma, Anti-CV2.1, and Anti-ANNA-3 antibodies in CSF were all negative. To the surprise of physicians taking care of the patient, CSF PCR for HSV-1 from initial LP was found out to be positive. This result was overlooked due to presumptive tumor diagnosis.

In light of these findings, the primary diagnosis of the patient was re-evaluated and the patient was diagnosed with temporal lobe encephalitis caused by HSV-1. After a repeat MRI and LP, intravenous acyclovir (10 mg/kg three times daily) was administered starting on day 92 of initial presentation for three weeks. In this second CSF analyses, cell count was 4 cells/ μL , glucose was 59 mg/dL (serum glucose: 118 mg/dL), and protein was 61 mg/dL, but PCR for HSV-1 was negative. Follow-up MRI revealed no pathological findings other than surgical excision on temporal lobe (Fig. 1B). Electroencephalography analysis remained unremarkable. At one year follow-up after the operation, she was in good general condition with only mild memory loss.

Fig. 2 Diffuse encephalitis findings and intranuclear inclusion bodies compatible with viral infection on histopathology



Discussion

The clinical presentation of HSE can differ among patients. Fever and encephalopathy should raise the suspicion of HSE. However, these clinical signs and symptoms are not specific because a wide range of diseases including brain tumors may mimic HSE (Whitley and Kimberlin 2005; Whitley et al. 1989). In a study, reviewing 432 encephalitis patients who underwent temporal lobe biopsy for presumed HSE, 195 patients (45%) had HSE, 95 patients (22%) had other identifiable etiologies, five (1.2%) had cancer, and 143 (33%) remained idiopathic (Whitley et al. 1989). In our case, HSE was overlooked, because all the signs and symptoms were attributed to brain tumor. The opposite can also happen. Giglio et al. reported a case where initial presumptive diagnosis of HSE was later found to be lymphoma (Giglio et al. 2002). In our case, the patient received appropriate antiviral treatment almost 90 days later than she should have been administered empirically. In fact, duration of disease before the onset of effective antiviral therapy was an independent factor affecting prognosis (McGrath et al. 1997) (Raschilas et al. 2002). Delays may occur either between start of symptoms and presentation to a hospital (before-hospital) or between admission and start of antiviral treatment (in-hospital). It has been shown that poor prognosis is related to delays in the diagnosis and treatment of HSE and delays over 2 days was found to be strongly associated with poor outcomes (McGrath et al. 1997; Raschilas et al. 2002). To the best of our knowledge, this patient is the first to have no significant neuropsychiatric sequelae, despite delay in acyclovir treatment for almost 90 days. Additionally, in our study published in 2014, 69% of HSE survivors ended up with sequelae despite acyclovir treatment. Although majority of patients (73%) resulted in favorable outcome, 19% of patients had severe sequelae. Furthermore, poor prognosis was shown to be associated with duration of disease before start of acyclovir and extent of the brain involvement on MRI at admission (Sili et al. 2014).

In a study conducted in France, the reason for the delay in initiation of acyclovir is that the physician attributed mental status changes at presentation to other causes such as alcoholism and underlying diseases. Furthermore, on admission, the absence of fever and CSF white cell count $< 10/\text{mm}^3$ were commonly found in patients with delayed treatment (Poissy et al. 2009). In our case, she had no fever and no leukocyte in CSF on hospital admission and all complaints were attributed to brain tumor. The patient underwent brain operation 45 days after the initial presentation. Interestingly, the key complaints regressed after surgery. Our interpretation is that the infected tissue was removed by surgery.

Although acyclovir is known to be effective in the treatment of HSE, severe neuronal damage cannot be reversed.

Neurological damage is known to be mediated by both viral factors and immune system. Though the host immune system causes tissue damage, it is also important for controlling viral spread and replication. In the current case, corticosteroid was given for tumor and continued until surgery. On the other hand, corticosteroids have strong anti-inflammatory and immunomodulatory effects that can theoretically facilitate viral replication. Therefore, differing views on their use in HSE is not surprising. In a retrospective analysis of patients with HSE, older age, lower Glasgow coma score, and lack of corticosteroid administration were found to be important independent predictors of poor outcome (Kamei et al. 2005). However, routine use of corticosteroids in HSE treatment was not recommended in the guidelines until its effectiveness is shown in randomized, placebo-controlled trials (Solomon et al. 2012).

The effects of corticosteroid administration and acyclovir treatment in an animal model of HSE were published (Thompson et al. 2000) (Meyding-Lamade et al. 2003). The data showed that the HSV viral load of brain tissue in both acyclovir and corticosteroid treated animals is similar to that of the brain tissue of animals treated with acyclovir alone. These studies also demonstrated that corticosteroids do not inhibit the antiviral effect of acyclovir and can reduce the extent of HSE infection.

In conclusion, although HSE has high mortality and morbidity if acyclovir treatment is delayed, our patient lived with minimal sequelae despite receiving appropriate treatment with a delay of 90 days. Steroid administration may have limited the tissue damage caused by inflammation in our case. HSE should always be within the differential diagnosis of temporal lobe tumors.

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