

Case Report

A Fatal Case of Herpes Simplex Encephalitis with Two False-Negative Polymerase Chain Reactions

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Keywords

Herpes simplex virus · Encephalitis · Polymerase chain reaction · False-negative results

Abstract

An 88-year-old man presented with a 1-month history of altered mental status and seizures. His electrographic and imaging findings were suggestive of herpes simplex encephalitis (HSE), for which he was empirically treated with acyclovir. He underwent two lumbar punctures 3 days apart; both cerebrospinal fluid analyses tested negative for herpes simplex virus (HSV) by polymerase chain reaction (PCR). These negative results and his continued deterioration after 9 days of acyclovir therapy prompted treatment with steroids for possible autoimmune encephalitis. Shortly after the change in management, the patient died from cardiac arrest. At autopsy, his brain showed both gross and microscopic evidence of encephalitis and was positive for HSV by immunohistochemistry. This fatal case of HSE emphasizes the limitations of HSV PCR and the importance of clinical suspicion in the diagnosis and management of this disease.

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Introduction

Herpes simplex encephalitis (HSE) is the most common cause of sporadic fatal viral encephalitis [1]. HSE has a mortality rate of approximately 70% in untreated patients and 19% in those treated with acyclovir. Of survivors, more than 50% have moderate to severe neuropsychiatric sequelae [2]. Currently, the diagnosis of herpes simplex virus (HSV) infection relies on cerebrospinal fluid (CSF) abnormalities and confirmation with CSF polymerase chain reaction (PCR) [3, 4]. This test has replaced invasive brain biopsy as the gold standard in the diagnosis of HSE [3–5]. HSV CSF PCR is 98% sensitive and 94% specific [6]. This high sensitivity should theoretically allow exclusion of an HSE diagnosis in patients who test negative [7]. Clinicians may presume that it is reasonable to discontinue acyclovir after a negative CSF PCR result, unaware of the test's limitations [3]. Herein, we present a case of autopsy-proven HSE with two false-negative CSF PCRs to emphasize the importance of clinical suspicion in the diagnosis and management of this disease.

Case Presentation

An 88-year-old Caucasian male presented to an outside hospital with a 1-month history of increasing forgetfulness, paranoia, and a 20-pound weight loss. In the prior week, he had progressed to having slurred speech, bizarre behavior, jerking leg movements, and intermittent lip smacking. On evaluation, he was found to have acute kidney injury with hyperglycemia. His mental status continued to decline, and he became agitated and unintelligible. Brain magnetic resonance imaging (MRI) with contrast demonstrated increased cortical signal intensity in the right temporal lobe with associated diffusion restriction, consistent with cytotoxic edema and highly suggestive of HSE. The patient was empirically started on intravenous acyclovir and transferred to our tertiary referral hospital for further management. Upon arrival, he was found to be unresponsive to verbal and tactile stimuli, with no withdrawal to pain. He also had intermittent lip smacking movements, suggesting seizure activity. Continuous video electroencephalography (EEG) showed diffuse slowing in the delta range (suggesting global cerebral dysfunction) and right-sided periodic discharges that correlated with the patient's rhythmic lip smacking movements. This ultimately progressed to epilepsy partialis continua. Multiple antiepileptic drugs, including levetiracetam, lacosamide, valproic acid, and lorazepam, were used without success. He was eventually intubated for seizure management with a propofol-induced coma in burst suppression. He had undergone a lumbar puncture on arrival and again 3 days later. CSF analyses included a meningitis/encephalitis panel by PCR, which tested negative for HSV-1/2 both times. A computed tomography (CT) scan of the chest, abdomen, and pelvis had already been obtained to evaluate for underlying malignancy, but was only remarkable for aspiration pneumonia, which was appropriately treated with antibiotics. The patient continued to deteriorate and there was talk of palliative care measures. Considering other possible etiologies, it was decided to empirically treat him for probable autoimmune encephalitis. He was administered 1 g of intravenous methylprednisolone daily. The results of the patient's panel of encephalitis autoantibodies only subsequently arrived and were found to be negative. He unfortunately died from cardiac arrest 2 days after having been switched to steroid therapy. At autopsy, his brain showed evidence of necrotizing viral encephalitis, and immunostaining was positive for HSV-1 (Fig. 1) and HSV-2.

Discussion

HSV CSF PCR has become the gold standard in the diagnosis of HSE [3]. Despite its high sensitivity and specificity, there have been reports of HSE in patients with negative CSF PCR [3, 7–9]. The Infectious Disease Society of America guidelines suggest repeating an HSV PCR after 3–7 days if clinical suspicion is high [10], as the test is known to yield false-negative results early in the course of the disease [11]. Other causes of false-negative CSF PCR results include testing late in the disease [12], low viral levels in the CSF (due to most of the viral replication occurring within the brain with only a small quantity being released into the CSF) [3], the sensitivity of the assay (although high, it is not 100%) [13], and possible neutralization of HSV by antibodies [14]. In our case, the patient's clinical syndrome had already been present for approximately 1 month, so we suspect that the lateness of his testing may have been the cause for his negative CSF PCR results. He may also have had low viral levels in the CSF. This is supported by his autopsy findings, which showed that his infection appeared to be restricted to the interior brain parenchyma, without superficial cortical or leptomeningeal involvement.

Other tests can help support a diagnosis of HSE. Our patient's MRI showed the classic medial temporal lobe T2-weighted and fluid-attenuated inversion recovery hyperintensities (Fig. 2a). Such neuroimaging abnormalities are strongly associated with a positive CSF PCR assay [15]. MRI findings consistent with HSE have been reported in 86% of patients with HSV-positive PCR results obtained after 48 h from symptom onset [16]. Others have reported 100% sensitivity and specificity of HSE-associated MRI abnormalities within the 3–10 day period after symptom onset, with an overall sensitivity of approximately 80% for both CT and MRI [17].

EEG can also serve as an adjunct in diagnosing HSE. Periodic sharp waves are the most specific EEG finding for patients with HSE [18]. When used alone, the specificity of EEG remains low in the diagnosis of HSE; however, it can be helpful when the PCR is negative in patients with a high clinical probability [16]. In our case, the patient's EEG revealed right-sided periodic discharges (Fig. 2b) that correlated with his rhythmic lip smacking movements, which progressed into difficult-to-control epilepsy partialis continua. Electrographic seizures and periodic epileptiform discharges are associated with poor outcome (e.g., severe disability, vegetative state, or death) in patients with central nervous system infections [19].

Empiric treatment with acyclovir is recommended in all patients with suspected encephalitis [10]. Starting this antiviral treatment as early as possible is the most significant factor affecting the outcome of a patient with HSE [20]. We suspect that the lack of therapeutic response to acyclovir in our case was attributable to a delay in antiviral treatment due to the patient presenting so late in the course of the disease.

Conclusions

CSF PCR for HSV has revolutionized the way we diagnose HSE. With a high sensitivity and specificity, HSV PCR results guide the management of HSE. However, it is important to consider the limitations of this test when HSE is highly suspected. Clinical management in these cases should be conducted by clinical suspicion.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare no conflict of interest.

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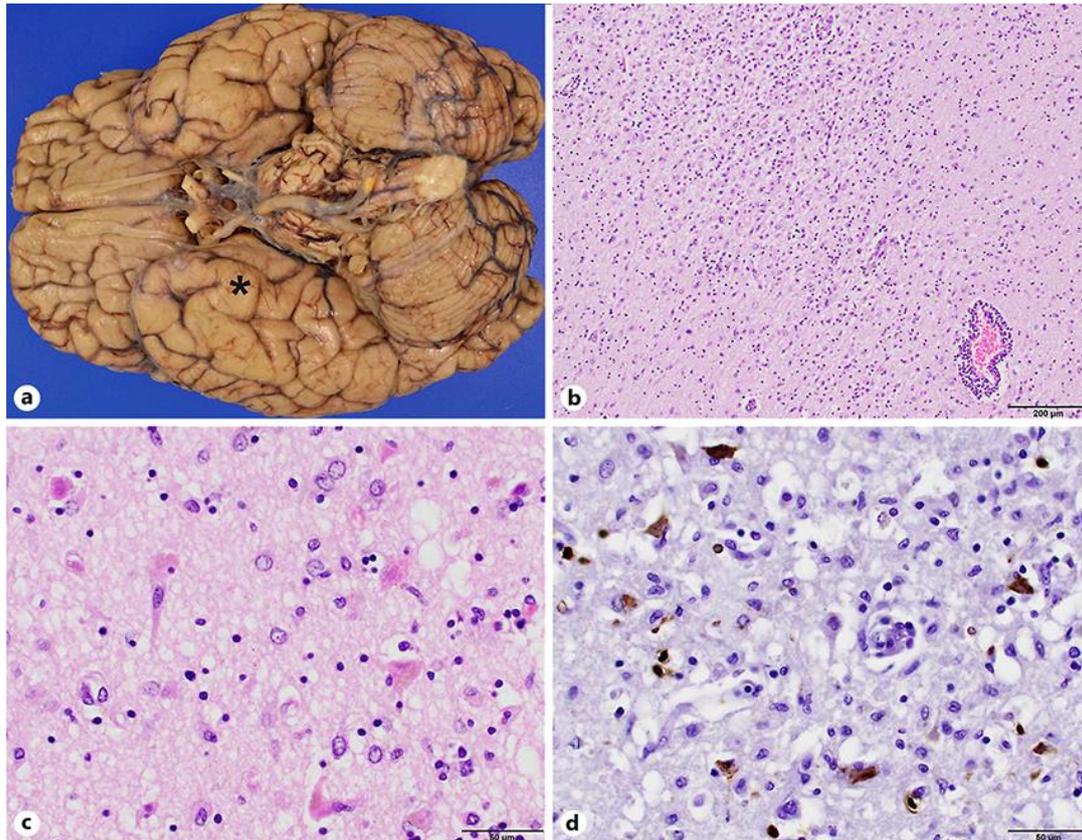


Fig. 1. **a** The brain at autopsy was grossly unremarkable except for slight atrophy in the right temporal lobe cortex (asterisk). **b, c** Photomicrographs of hematoxylin and eosin-stained brain parenchyma from hippocampus and temporal lobe at $\times 100$ (**b**) and $\times 400$ (**c**) original magnification demonstrating subacute necrosis and mixed perivascular lymphocytic infiltrate. **d** Immunohistochemical staining for herpes simplex virus 1 at $\times 400$ original magnification highlights neurons, glia, and macrophages positively. Overall, these findings are consistent with necrotizing viral encephalitis, more specifically herpes simplex encephalitis.

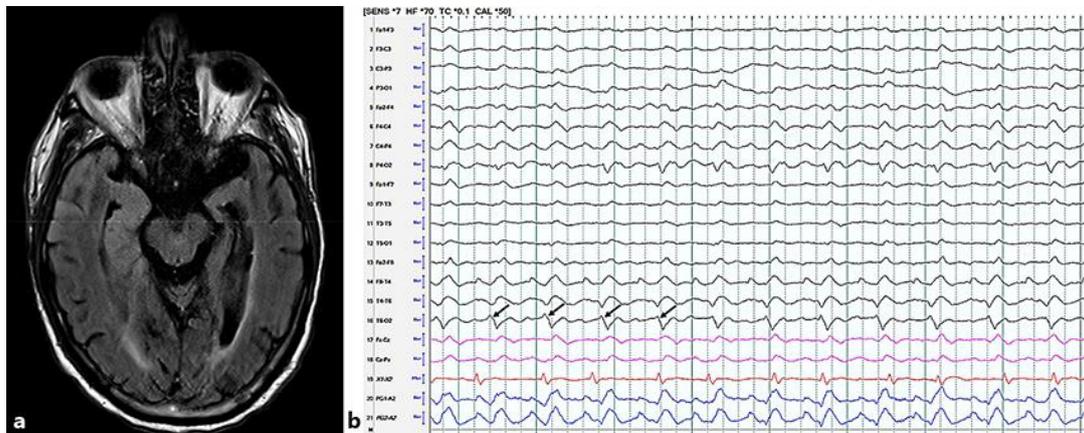


Fig. 2. **a** Magnetic resonance imaging-fluid-attenuated inversion recovery, axial image; hyperintense signal involving the medial and anterior lateral right temporal lobe. **b** A 10-s interval of electroencephalography displayed using a longitudinal bipolar montage at a sensitivity of 7 mV with a time constant of 0.1 s and high-frequency filter of 70 Hz, demonstrating 40–50 mV 1.5 Hz right temporal lateralized periodic discharges (black arrows) with superimposed rhythmic delta activity.