Atypical Brainstem Encephalitis Caused by Herpes Simplex Virus 2

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Background: Herpes simplex encephalitis is one of the most common and serious sporadic encephalitides of immunocompetent adults. Herpes simplex virus 2 (HSV-2) infections of the central nervous system usually manifest as subacute encephalitis, recurrent meningitis, myelitis, and forms resembling psychiatric syndromes.

Objectives: To report and discuss magnetic resonance imaging (MRI) findings and clinical features in atypical brainstem encephalitis and facial palsy associated with HSV-2.

Setting: Neurology department of a tertiary referral center.

Patient: A 37-year-old woman was admitted to the hospital with fever, diplopia, left hemiparesis, sensory change in the face and limbs, personality changes, frontal dysexecutive syndrome, and a stiff neck. Brain MRI showed multifocal high-signal intensities in the pons, midbrain, and frontal lobe white matter on T2-weighted and fluid-attenuated inversion recovery images. Cerebrospinal fluid (CSF) polymerase chain reaction (PCR) amplification analysis was positive for HSV-2. Acyclovir therapy was started, and the encephalitic symptoms disappeared with a negative conversion of HSV-2 PCR in the CSF. However, after the discontinuation of acyclovir therapy, peripheral facial palsy occurred on the left side. A possible relapse or delayed manifestation of the HSV-2 infection was suspected, and the acyclovir therapy was restarted. A complete remission was achieved 3 days after the treatment. She was discharged without any neurologic sequela.

Conclusions: We describe a patient who developed atypical encephalitis due to HSV-2 and peripheral facial palsy, which could also be related to the HSV-2. This case suggests that HSV-2 should be considered among the possible causes of atypical or brainstem encephalitis and that the PCR amplification method of the CSF can help reveal the possible cause of HSV-2.

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EREPES SIMPLEX encephali- tis (HSE) is one of the most common and serious sporadic encephalitides of immunocompetent adults. It can present at any age and has an estimated incidence of between 1 in 250,000 and 1 in 1 million persons a year.\(^1,2\) Herpes simplex viruses (HSV) are ubiquitous human pathogens; they are widespread in the adult population, with a rate of seropositivity of 60% to 100% for HSV-1 and 10% to 80% for HSV-2.\(^1,2\) In the largest study of HSE to date, HSV-1 or HSV-2 DNA was detected by a nested polymerase chain reaction (PCR) assay in 82 and 6 of 93 patients, respectively, with the assay showing a 95% sensitivity.\(^3\)

The pathologic lesions of classic HSV-1 encephalitis are characteristically located in the temporal lobes. In addition, the orbital surface of the frontal lobe and cingulate gyrus may be involved.\(^1\) A range of clinical presentations of HSV infection of the nervous system, including mild disease courses, relapsing and remitting encephalitis, or unusual neurologic syndromes, sometimes related to specific anatomic locations, has been described.\(^3\) Brainstem encephalitis is caused mainly by HSV-1.\(^4,5\) However, HSV-2 infections in the central nervous system usually manifest as acute meningitis and not infrequently as subacute encephalitis, recurrent meningitis, myelitis, and forms resembling psychiatric syndromes;\(^6\) they rarely involve the brainstem. Herein, we describe a patient who developed atypical encephalitis due to HSV-2 involving mainly the brainstem and peripheral facial palsy caused possibly by a relapse or delayed manifestation of HSV-2 infection.

A 37-year-old woman was admitted to the hospital for diplopia and hypesthesia in the face. She was well until 8 days before admission, when she experienced the onset of fever, headache, nausea, and vomiting. Four days before admission, mild dysarthria, bilateral facial
hypesthesia, and diplopia developed. Gait instability and personality changes, which were characterized by disinhibition, were also noticed. Fever developed on the day of admission. She denied any history of recent infection and other neurologic illnesses. She had a history of genital herpes, which previously had not been treated. Neurologic examination revealed mild frontal executive dysfunctions, bilaterally gaze-evoked nystagmus with small amplitude, diplopia, bilateral facial hypesthesia, dysarthria, left-sided pronator drift, sensory decrease of the bilateral limbs in all modalities, generalized hyperreflexia, bilaterally cerebellar ataxia, a positive Romberg test result, and a stiff neck. The gynecologic examination revealed no evidence of acute or chronic genital lesions. Eye and ear examinations showed no abnormalities.

Cerebrospinal fluid (CSF) examination revealed an elevated opening pressure (21 cm H$_2$O), a white blood cell count of 29 cells/µL (polymorphonuclear leukocytes, 3 cells/µL; lymphocytes, 11 cells/µL; monocytes, 15 cells/µL), no red blood cells, and a slightly elevated protein level (0.054 g/dL) (Table 1). The CSF PCR was performed in our infection laboratory as previously described. The presence on an ethidium bromide–stained gel of PCR products of the expected size (518, 524, and 589 base pairs corresponding to HSV-1 and HSV-2, Epstein-Barr virus [EBV], and cytomegalovirus [CMV], respectively) attested to the specificity of the PCR assay. Although the CMV-amplified product was accurately identified by its molecular weight, HSV and EBV, which led to PCR products of similar sizes, needed further characterization. The specific Smal and BamHI patterns of these amplified PCR products clearly distinguished HSV from EBV. In addition, this restriction analysis permitted an unambiguous discrimination between HSV-1 and HSV-2 genomes by comparing sizes. The PCR methods for searching for enterovirus were performed as previously described. Results of a PCR test of the CSF were positive for HSV-2, which was confirmed by direct sequencing. The PCRs for other viral pathogens, such as CMV, EBV, and enterovirus, revealed no abnormalities. Electroencephalography results were normal. Magnetic resonance imaging (MRI) of the brain (Figure 1) showed multifocal high-signal intensities in the pons, midbrain, subcortical white matter of the frontal lobe, and external capsule on fluid-attenuated inversion recovery imaging. The main lesion was situated in the brainstem. However, there was no involvement of the medial temporal lobes.

Intravenous administration of acyclovir, 30 mg/kg, was started on the third hospital day (HD). Her encephalitic symptoms disappeared in 10 days. Follow-up PCR of the CSF on the seventh HD revealed negative conversion for HSV-2. However, mild lymphocytic pleocytosis, with a blood cell count ranging from 24 cells/µL to 202 cells/µL, remained in follow-up CSF examinations and protein values were normal (Table 1). Intermittent fever, a slightly stiff neck, and mild headache persisted during acyclovir therapy. Other neurologic symptoms improved completely by the 27th HD.

**Table 1.** Summary of CSF Findings and Clinical Courses*

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>CSF (Cells/µL)/Glucose (mg/dL)</th>
<th>HSV-2 PCR Test Result</th>
<th>Time of Acyclovir Administration</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>29 (10% PMN, 34% L, 56% O)/0.054/67</td>
<td>Positive</td>
<td>ND</td>
<td>Initial</td>
</tr>
<tr>
<td>7th</td>
<td>202 (100% L)/0.049/78</td>
<td>Negative</td>
<td>5 Days</td>
<td>Acyclovir therapy was started on the 3rd HD</td>
</tr>
<tr>
<td>14th</td>
<td>24 (100% L)/0.047/69</td>
<td>ND</td>
<td>12 Days</td>
<td>Encephalitic symptoms disappeared on the 12th HD</td>
</tr>
<tr>
<td>24th</td>
<td>27 (100% L)/0.049/72</td>
<td>ND</td>
<td>22 Days</td>
<td>Acyclovir therapy was discontinued on the 27th HD</td>
</tr>
<tr>
<td>28th</td>
<td>152 (100% L)/0.050/68</td>
<td>Negative</td>
<td>Restarted, first</td>
<td>Acute peripheral facial palsy developed on the 28th HD</td>
</tr>
<tr>
<td>40th</td>
<td>15 (100% L)/0.039/69</td>
<td>Negative</td>
<td>12 Days</td>
<td>Facial palsy disappeared on the 31st HD and acyclovir therapy was discontinued on the 42nd HD</td>
</tr>
</tbody>
</table>

*CSF indicates cerebrospinal fluid; HSV-2, herpes simplex virus 2; PCR, polymerase chain reaction; PMNs, polymorphonuclear lymphocytes; L, lymphocytes; O, other cells; ND, not done; and HD, hospital day.

**Figure 1.** A, Fluid-attenuated inversion recovery magnetic resonance imaging shows multifocal hyperintensities in the pons with swelling. B, Additional lesions are shown in external capsule and frontal white matter.
Atypical presentations have been reported in 20% of HSE patients in a large series confirmed by PCR amplification of viral DNA from the CSF.18 Widespread use of the CSF PCR amplification method might improve recognition of mild or atypical cases of HSE with excellent sensitivity and specificity. Our case presents several interesting occurrences. First, although HSV-2 has rarely been reported to cause brainstem encephalitis, the HSV-2 encephalitis in our patient involved mainly the brainstem. There has been just one previous case reported by a group of Japanese investigators.19 In the Japanese study, the MRI results of the patient were normal, and the diagnosis of brainstem HSE was made on the basis of the clinical symptoms and a CSF PCR test result positive for HSV-2. In our patient, MRI of the brain showed atypical findings for HSE owing to HSV-2: bilateral involvement of the pons, midbrain, and white matter of frontal lobe. The frontal dysexecutive syndrome and personality change could be explained by the involvement of frontal lobe white matter and the sensory symptoms, diplopia, and increased deep tendon reflexes by the bilateral involvement of the pons and midbrain.

Second, the clinical course of our patient was mild compared with the usual course of HSE, which is usually devastating. The initially positive CSF PCR test result in our patient was converted to negative in 10 days with acyclovir therapy, and neurologic symptoms and signs resolved completely while the patient was undergoing acyclovir therapy, except for the remaining CSF pleocytosis and a mild headache.

Third, peripheral facial palsy developed after the discontinuation of acyclovir therapy. In addition, MRI of the internal auditory canal showed a mildly enlarged facial nerve with gadolinium–diethylenetriamine penta-acetic acid enhancement, consistent with the findings of facial neuritis. The clinical usefulness of internal auditory canal MRI in facial neuritis has been reported previously.20,21 This occurrence raises the questions of the possibility of the causative role of HSV-2. At this time we can only speculate that a relapse or a delayed manifestation of HSV-2 infection may have been the possible cause of the facial palsy, because we were not able to clarify the probable mechanism; at the onset of the facial palsy, the CSF PCR test result was negative for HSV, and a salivary fluid PCR was not performed. However, the immediate response to the prednisone and acyclovir suggests an inflammatory mechanism.

Herpes simplex virus infection has long been postulated as a cause of peripheral facial palsy. However, a direct relationship between HSV-1 reactivation and peripheral facial palsy has been demonstrated in only a few cases. Some authors22-25 have reported viral DNAs for HSV-1 in endoneurial fluid, muscle, saliva, and geniculate ganglion in patients with peripheral facial palsy and experimental models. Recently, Kohler et al26 investigated CSF abnormalities in 265 patients with acute peripheral facial palsy, using antibody responses in the CSF. In their series, 35 of the 265 patients had nonidiopathic causes of facial palsy: herpes zoster (n = 17), Lyme disease (n = 8), human immunodeficiency virus infection (n = 8), sarcoidosis (n = 1), and HSV-1 (n = 1). In the assessment of acute-onset cases, clinical presentation is the most important clue as to a specific cause, and a CSF analysis may provide additional information early in the disease. The validity of this relationship between HSV-1 and facial nerve palsy is difficult to prove, because it is impossible to definitively confirm an etiologic mechanism involving the facial nerve since a biopsy cannot be performed without causing permanent nerve damage. The indirect diagnosis of HSV-1 relapse by serologic tests is itself problematic because there are no specific elevations of antibodies in HSV-1 reactivation.27,28 However, using the PCR amplification method, Murakami et al27 found HSV-1 DNA in 79% of the patients with Bell palsy and 89% with Ramsay-Hunt syndrome. They suggested that facial palsy with a CSF PCR test result negative for HSV-1 might have been caused in part by etiologic agents other than HSV-1, such as HSV-2 or herpes zoster virus.

Finally, another distinctive feature of this case report is that we used the PCR amplification method to detect viral DNA in the CSF. The PCR amplification method has been suggested as the gold standard for diagnosing HSE.16,18 In previous literature on brainstem HSE, mainly caused by HSV-1, diagnoses were made by the serum and CSF viral antibody testing.19 However, PCR-proven brain-
stem encephalitis is rare. The clinical profiles and salient features of the herpetic brainstem encephalitis, proven by CSF PCR, are summarized in Table 2.

Herein, we describe a patient who developed atypical encephalitis due to HSV-2 and peripheral facial palsy, which could also be related to HSV-2. This case suggests that HSV-2 should be considered among the causes of atypical or brainstem encephalitis and that the PCR amplification method of the CSF can help reveal the possible cause.

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