Postoperative Herpes Simplex Virus Encephalitis after Neurosurgery: Case Report and Review of the Literature

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Herpes simplex virus encephalitis is an unusual diagnosis for postoperative sepsis that occurs after a neurosurgical procedure. We describe a patient for whom early diagnosis and aggressive medical and surgical treatment resulted in a good outcome.

Herpes simplex virus (HSV) is the most common cause of sporadic encephalitis throughout the world. Sporadic encephalitis is considered to be the result of reactivation of latent infection with virus located in cranial nerve ganglia or the result of CNS invasion through olfactory pathways. Even with adequate treatment, this infection is associated with a mortality rate of 19%–30% and important neurological aftereffects among survivors [1]. The occurrence of HSV encephalitis after neurosurgery is rare (table 1) [2–7]. All but 2 cases reported in the medical literature had an unfavorable outcome. We report a case that occurred after resection of high-grade oligodendroglioma in which early diagnosis and treatment resulted in a favorable outcome.

Case report. A 28-year-old patient was admitted to Hôpital Sainte Anne (Paris, France) for removal of a right frontocingular oligodendroglioma. The patient’s past medical history was remarkable for a possible episode of viral encephalitis in 1995. At that time, he presented to another hospital with fever, right-side hemiparesis, meningeal syndrome, and mild motor aphasia of sudden onset. MRI revealed 2 cerebral lesions in the left side hemiparesis, meningeal syndrome, and mild motor aphasia of sudden onset. MRI revealed 2 cerebral lesions in the left insula and the right frontocingular area. Lumbar puncture retrieved clear CSF with 977 leukocytes/mL (99% lymphocytes), but the result of PCR for HSV was negative. The patient’s condition improved after 10 days of intravenously administered empirical treatment with thiamphenicol and acyclovir. Findings of stereotactic biopsy of the left insular lesion were inconclusive, and the lesion completely disappeared after a few weeks. Biopsy of the frontocingular lesion revealed an infiltrative low-grade oligodendroglioma. The patient was offered whole-brain radiotherapy and was observed with yearly MRIs.

The patient’s condition was considered to be in remission until October 2000, when MRI revealed an increased tumor volume and appearance of a contrast-enhancement area (figure 1). A partial resection of the tumor that included the contrast-enhancing area was performed. The histological examination of the resected tumor confirmed the presence of an anaplastic oligodendroglioma.

The postoperative course was uneventful until day 7, when the patient presented with a fever (temperature, 39.5°C) that did not affect his general well being (i.e., no anorexia, profound asthenia, impaired mental state, or drowsiness). Findings of a clinical examination, culture of blood and urine samples, and chest radiographs were normal. The following day, another fever spike (temperature, 41°C) and drowsiness prompted the health care workers to perform a lumbar puncture, which disclosed clear, normotensive CSF with 38 leukocytes/mL (28% neutrophils, 30% lymphocytes, and 42% monocytes), a CSF protein level of 0.8 g/L, a normal level of glucose in the CSF, and no organisms found on a smear. A complete blood cell count revealed 17000 leukocytes/mL with a normal differential (66% neutrophils and 26% lymphocytes). Four hours later, the patient experienced rigors, bradycardia, oxygen desaturation, and peripheral hypoperfusion, and he was transferred to the intensive care unit. CT revealed a small hypodense lesion in the right frontocingular area with no mass effect. Postoperative meningitis was suspected, and the patient was treated with cefotaxime and fosfomycin.

On day 9 after the operation, the patient underwent mechanical ventilation after he experienced a convulsive episode caused by coma and respiratory distress. Despite administration of treatment with acetaminophen, external refrigeration, and heavy sedation with thiopenthal, the patient’s temperature remained at >40°C. A new lumbar puncture revealed an increase in the leukocyte count (306 leukocytes/mL) and a CSF protein level of 1.70 g/L. The results of bacterial and fungal cultures of CSF samples obtained during the first lumbar puncture were negative, but the results of CSF PCR for HSV type 1 were positive. The CSF IFN-α level was 37 IU/mL (normal level, <2
IU/mL). Viral serological testing revealed an anti–HSV-IgG level of 48,300 IU/mL and an IgM level of >40 IU/mL, compared with preoperative levels of 10,100 IU/mL for IgG and <40 IU/mL for IgM, which confirmed that previous exposure to HSV and viral reactivation had occurred. Therefore, intravenously administered acyclovir (10 mg/kg q8h) was added to therapy.

On day 10 after the operation, a new CT scan of the brain revealed a large right frontal hypodensity with mass effect and disappearance of the basal cisterns (figure 2). An emergency right frontal lobectomy was performed. The brain appeared tense and pale, and thrombosis of cortical veins suggested cerebral circulatory stasis. Histological examination of the resected tumor revealed extensive thrombosis of the cortical veins and capillaries. No pathogen- or cytopathogen-associated effects were noted by histological examination, but the brain sample was in poor condition as a result of diffuse inflammation, destruction of the vessel walls, and postradiotherapy lesions. Treatment with acyclovir was maintained for 3 weeks.

The patient was first apyrexial on day 13 after the operation, and he underwent extubation 3 weeks after the second intervention. A lumbar puncture was performed 6 weeks after the encephalitic episode; the result of PCR of the CSF specimen for HSV was negative, and the CSF IFN-α level was <2 IU/mL. The patient presented for a few weeks with apathy, decreased verbal and motor activity, and marked spasticity. He was transferred to a rehabilitation center. His recovery was complete after 1 year. Follow-up MRI demonstrated progressive reduction of mass effect and contrast-enhancing areas.

**Discussion.** Life-threatening infections that occur after neurosurgical operation are usually bacterial in origin and include meningitis, subdural empyema, and cerebral abscess. Viral encephalitis complicating the early postoperative course is a rare finding (table 1).

There are some interesting features of HSV encephalitis that arise from analysis of cases reported in the literature. The average delay of onset of HSV encephalitis after surgery was 6 days (table 1). The symptoms commonly included high fever and an altered state of consciousness. All patients had received steroids during the postoperative period, but none had previously undergone irradiation. The diagnostic tools used to confirm the diagnoses reflect the evolution of our knowledge during the past 3 decades: brain biopsy and virus cultivation were used for the first 3 cases, and PCR isolation of HSV was used for the recently reported cases. HSV encephalitis had a fatal outcome for 5 of the 7 patients, and there were devastating neurological aftereffects in the 2 survivors.

HSV reactivation in the CNS is explained by 3 possible mechanisms: (1) reactivation of dormant infection with a virus located in the sensory ganglia, especially the trigeminal nerve ganglion; (2) spread of an upper respiratory tract infection through the olfactory nerves; and (3) reactivation of latent CNS infection, a diagnosis that has been supported by identification of HSV DNA in brain tissue specimens obtained from healthy adults [8]. Several circumstances have been incriminated as factors that possibly favor reactivation of a viral infection: receipt of steroids, receipt of radiotherapy, trauma, immunosuppression, and stress. In our patient, diagnosis of HSV encephalitis was hypothesized in 1995, but definitive diagnosis could not be made because examination of histological specimens revealed only nonspecific inflammatory changes, and the result

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**Table 1. Reported cases of postcraniotomy herpes simplex virus (HSV) encephalitis, including the case described in the present report (PR).**

<table>
<thead>
<tr>
<th>Report</th>
<th>Patient age, years</th>
<th>Primary lesion</th>
<th>Time to onset, daysa</th>
<th>Clinical features</th>
<th>Diagnostic testb</th>
<th>Antiviral treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2]</td>
<td>11</td>
<td>Pituitary adenoma</td>
<td>8</td>
<td>Fever (temp., 40°C), seizures, coma</td>
<td>Acyclophlic intranuclear inclusion bodies</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>[2]</td>
<td>41</td>
<td>Pituitary adenoma</td>
<td>4</td>
<td>Fever (temp., 38°C)</td>
<td>Virus isolation from CSF specimen</td>
<td>Idoxuridine</td>
<td>Death</td>
</tr>
<tr>
<td>[3]</td>
<td>65</td>
<td>Temporal astrocytoma</td>
<td>NS</td>
<td>NS</td>
<td>Acyclophlic intranuclear inclusion bodies</td>
<td>NS</td>
<td>Death</td>
</tr>
<tr>
<td>[4]</td>
<td>64</td>
<td>Craniopharyngioma</td>
<td>8</td>
<td>Confusion, blindness</td>
<td>CSF PCR</td>
<td>Acyclovir</td>
<td>Survival, blindness</td>
</tr>
<tr>
<td>[5]</td>
<td>78</td>
<td>Parasagittal meningioma</td>
<td>10</td>
<td>Fever (temp., 38.3°C), hemiparesis, aphasia, coma</td>
<td>CSF PCR</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>[7]</td>
<td>28</td>
<td>Glioblastoma</td>
<td>1.5</td>
<td>Fever (temp., 41°C), convulsions, coma</td>
<td>Type 1 inclusion bodies, presence of IFN in the CSF, serologically proved reactivation of HSV infection</td>
<td>None</td>
<td>Death</td>
</tr>
<tr>
<td>PR</td>
<td>28</td>
<td>Oligodendroglioma</td>
<td>7</td>
<td>Fever (temp., 40°C)</td>
<td>CSF PCR</td>
<td>Acyclovir</td>
<td>Full recovery</td>
</tr>
</tbody>
</table>

**NOTE.** NS, not specified; temp., temperature.

a Time from craniotomy to onset of HSV encephalitis.
b Only the second case from [2] had virus isolation that permitted definitive diagnosis of HSV encephalitis. For the other cases, including our own, diagnosis is only indicative.
Figure 1. CT scan of the brain showing the initial lesion. Anatomopathological examination confirmed the presence of an anaplastic oligodendroglioma.

of PCR for HSV was negative. Only 1 of the previously described patients had a documented history of HSV encephalitis; this was certified by identification of chronic viral encephalitis, suggesting the possible persistence of viral infection in a latent state.

Diagnosis of postoperative herpes simplex encephalitis is difficult because its clinical features can mimic other, more common postoperative complications. High fever, impairment of consciousness, and seizures are the most common clinical symptoms, but these symptoms are not specific. Quick exclusion of other causes of elevated temperature and a high index of suspicion for patients with a previous history of encephalitis are necessary to make the diagnosis. The advent of PCR identification of HSV DNA has simplified the diagnosis, because this method is fast and has a sensitivity and specificity of >90% for diagnosis of HSV meningoencephalitis [9–12]. In our patient, the diagnosis of HSV encephalitis was indicated by the PCR result, as well as an elevated CSF IFN-α level and the findings of CSF serological testing. IFN-α is produced by lymphocytes as part of the humoral immune response within the CNS, and this production precedes the antiviral antibody response. MRI typically demonstrates high-intensity signals in the temporal region, but the findings may be normal early in the course of infection and are impossible to interpret in the context of postoperative neurosurgery [1].

For our patient, absence of the cytopathogen-associated effect noted during histological examination may be explained by the poor condition of the resected brain tissue specimen. Also, it should be noted that the specimen did not contain any part of the limbic system, which is the main location of HSV in the CNS. In the 2 surviving patients described elsewhere [4, 6], a cytopathogen-associated effect was not reported, which may reflect the necessity of examining large specimens for identification of this feature.

In our patient, early awareness of a possible HSV infection (because of the patient’s past medical history) resulted in prompt administration of antiviral therapy with acyclovir; this, in association with aggressive medical and surgical management of intracranial hypertension, resulted in a favorable clinical result. Previously, survivals were reported only for the 2 patients who were treated with acyclovir [4, 6]. In these 2 patients, there were neurological aftereffects. In our opinion, the good evolution of our patient’s condition was related to the early introduction of acyclovir therapy. Acyclovir should
be prescribed immediately after the diagnosis of HSV encephalitis has been considered, and a CSF sample should be obtained. Given the severe outcome associated with this kind of postoperative complication, prophylactic therapy with acyclovir should be considered for neurosurgery patients with a previous history of encephalitis [8].

Postneurosurgery HSV encephalitis is a rare but severe complication. It should be suspected in cases of unexplained postoperative high fever associated with an altered state of consciousness, especially in patients with a previous history of encephalitis. A bacterial origin first has to be excluded by examination of a CSF specimen, but PCR for HSV should also be performed to exclude HSV encephalitis.

References