Severe Meningoencephalitis Caused by Human Herpesvirus 6 Type B in an Immunocompetent Woman Treated with Ganciclovir

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(See the article by Isaacson et al. on pages 890–3 and the editorial commentary by Whitley and Lakeman. on pages 894–5)

Human herpesvirus 6 (HHV-6), the causative agent of exanthema subitum in childhood, can also induce meningoencephalitis in immunocompromised individuals. In contrast, HHV-6 encephalitis in immunocompetent patients is rare, and the clinical syndrome not well defined. We report a case of meningoencephalitis caused by HHV-6 type B in an otherwise healthy woman.

The lymphotrophic human herpesvirus 6 (HHV-6), which was first isolated in 1986 in patients with lymphoproliferative disorders or HIV infection, is a ubiquitous agent that infects almost every child [1, 2]. In some cases, primary infection leads to exanthema subitum, which is rarely complicated by meningoencephalitis.

After primary infection, HHV-6 is characterized by life-long latency in PBMCs, salivary glands, and brain tissue [1, 3]. Reactivation of infection occurs occasionally during pharmacological immunosuppression or acquired immunodeficiency and can cause fever, rash, pneumonitis, hepatitis, and, in some cases, encephalitis [4, 5]. In contrast, immunocompetent adults very rarely have HHV-6–induced CNS infection, and the pathogenesis of these cases remains unclear [6–12].

Here, we describe an immunocompetent 21-year-old woman with encephalitis that was probably due to reactivation of HHV-6 infection. In contrast to patients described elsewhere, the clinical course in our patient was characterized by severe psychosis and neuropsychological deficits, with full recovery after 4 months.

Case report. A 21-year-old previously healthy woman who was studying sports and economics, who was not taking medication, and who had no history of drug abuse or recent travel was referred to the Department of Psychiatry at Ludwig-Maximilian-University (Munich) with a psychotic syndrome. Her symptoms included acoustic hallucinations, parathymia, and affective lability. In addition, the patient was disoriented and intermittently agitated. The first symptoms had been observed 3 weeks before admission to the hospital. She was initially treated with haloperidol (5 mg t.i.d.) and amisulpride (400 mg q.d.). Six days after admission, she developed 3 generalized tonic-clonic seizures. Anticonvulsive therapy with carbamazepine (beginning with 200 mg b.i.d.) and clobazam (10 mg t.i.d.) was initiated. Although brain CT findings were normal, analysis of CSF showed pleocytosis (143 cells/µL; 97% lymphocytes, 2% monocytes, and 1% lymphoid cells) with normal protein and glucose levels. Treatment with acyclovir (750 mg t.i.d.) and ceftriaxone (4 g q.d.) was started, and the patient was transferred to the Neurological Department on day 8.

Clinical examination revealed that the patient was awake, agitated, and disoriented and that she seemed to be hallucinating. She showed no neck stiffness. Cranial nerve function, deep tendon reflexes, sensory examination findings, muscle strength, muscle tone, coordination, and fine motor functions were normal, and there were no pathological reflexes. Body temperature and blood leukocyte levels were within the normal range, but the C-reactive protein level was slightly elevated (1.8 mg/dL). Electroencephalography showed an epileptic focus in the right frontal lobe. The findings of an MRI of the brain, which included T2-weighted, diffusion-weighted, and gadolinium-enhanced sequences, were normal.

PCR analysis (using the primers 5′-TGTCCTGGTTGCTGTTCCCGG-3′ and 5′-GTGACTGGATTGCATAACGT-3′, which amplify a target sequence localized in the major capsid antigen) revealed a high HHV-6 type B DNA load in a CSF specimen (110,000 copies/mL) and a serum specimen (297,000 copies/mL). Because specific anti–HHV-6 IgG and IgM antibodies were initially detected in the serum (titers, 1:256 and 1:8, respectively), acute HHV-6–induced CNS infection was assumed, and antiviral therapy was changed from aciclovir to a 13-day course of ganciclovir (375 mg b.i.d.).

PCR of CSF was negative for herpes simplex virus 1 and 2,
varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, human herpesvirus types 7 and 8, adenovirus, measles virus, and enterovirus. Infection with tickborne encephalitis virus, Borrelia burgdorferi, and Mycoplasma pneumoniae was ruled out by negative results of serological tests for pathogen-specific IgG and IgM in CSF and serum specimens. Negative results of Treponema pallidum particle agglutination assays of CSF and serum specimens ruled out T. pallidum infection. In addition, all CSF cultures were negative for bacterial and fungal organisms.

Results of extensive tests for detection of an immunocompromising disease were negative. The differential blood cell count, including measurement of lymphocytic subpopulations and quantification of immunoglobulin levels, was within the normal range. Results of ELISA antibody-search tests for HIV-1 and -2 were negative at admission and during follow-up, and there was no evidence of any malignant disease, based on findings of a gynecological examination and CT of the thorax and abdomen.

CSF analysis on hospital day 21 revealed complete remission of the CNS infection: the CSF WBC count had normalized, and there was a sustained decrease in the HHV-6 DNA load (table 1). Brain MRI findings were still normal. Follow-up electroencephalography showed bilateral temporal slowing but no spikes or sharp waves. The psychotic symptoms showed substantial improvement, and the dose of neuroleptic drugs was slowly resolved. At 3.5 months after admission, the only residual memory, apraxia, and aphasia) persisted for weeks but then also slowly resolved. In 88 patients (age range, 42–59 years), the pathogenesis of disease is also unclear. In 2 patients (age, 20 and 85 years), IgG antibodies with a high avidity index were detected, and the authors [7, 12] therefore supposed that encephalitis was due to secondary infection. The third patient (age, 21 years), however, tested negative for both IgG and IgM antibodies, suggesting primary infection. Our patient had quite low IgG and IgM titers (1:256 and 1:8, respectively) on day 13 and at follow-up, which clearly suggests secondary infection. Although the seroprevalence of HHV-6 reaches almost 98% among young children, there seem to be very few cases of primary infection in adults, which leads to severe encephalitis. In addition, data in a few reports (including ours) seem to indicate secondary HHV-6 infections without the presence of any underlying immunocompromising disease. The pathogenesis for such cases is unclear. One possible mechanism is that primary infection with HHV-6 type A is followed by reexposure to HHV-6 type B (or vice versa). Another possibility is that these patients had an immunocompromising disease that had not yet received a diagnosis. We therefore suggest that PCR for detection of HHV-6 should also be performed for immunocompetent adult patients if a viral etiology of meningoencephalitis is probable.

The majority (80%) of immunocompetent patients with HHV-6–induced encephalitis in immunocompetent adults in the literature, and the pathogenesis of this disease remains unclear. A retrospective study reported that PCR detected HHV-6 DNA in 9 of 138 immunocompetent patients with focal encephalitis of unknown etiology [6]. Interestingly, 5 of these 9 patients were <18 years of age, and the ages of 2 patients (13 and 15 months old) were typical of persons with primary HHV-6 infection. Serological assessment had been performed for only 3 patients and for IgG antibodies (results of all tests were positive) but not IgM antibodies. Therefore, the data were insufficient to draw conclusions about the pathogenetic mechanism (i.e., primary vs. secondary infection). Another retrospective study showed specific anti–HHV-6 antibodies in 10 of 50 CSF specimens obtained from immunocompetent patients with meningoencephalitis [13]. Because the age of the patients and the antibody titers were not given or were not available, it is not clear if these cases were due to primary or secondary infection.

In addition to patients described by McCullers et al. [6] and Patnaik and Peter [13], 6 immunocompetent adult patients with encephalitis possibly caused by HHV-6 have been described [7–12]. Because no serological data were given for 3 of these patients, it is uncertain if a viral etiology of meningoencephalitis is probable.

Discussion. To our knowledge, there are only a few reports of HHV-6–induced encephalitis in immunocompetent adults in the literature, and the pathogenesis of this disease remains unclear. A retrospective study reported that PCR detected HHV-6 DNA in 9 of 138 immunocompetent patients with focal encephalitis of unknown etiology [6]. Interestingly, 5 of these 9 patients were <18 years of age, and the ages of 2 patients (13 and 15 months old) were typical of persons with primary HHV-6 infection. Serological assessment had been performed for only 3 patients and for IgG antibodies (results of all tests were positive) but not IgM antibodies. Therefore, the data were insufficient to draw conclusions about the pathogenetic mechanism (i.e., primary vs. secondary infection). Another retrospective study showed specific anti–HHV-6 antibodies in 10 of 50 CSF specimens obtained from immunocompetent patients with meningoencephalitis [13]. Because the age of the patients and the antibody titers were not given or were not available, it is not clear if these cases were due to primary or secondary infection.

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Table 1. Results of laboratory analysis of CSF and serum specimens obtained from a 21-year-old woman with meningoencephalitis due to human herpesvirus 6 (HHV-6).

<table>
<thead>
<tr>
<th>Variable</th>
<th>6</th>
<th>8</th>
<th>13</th>
<th>21</th>
<th>39</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count, cells/µL</td>
<td>143</td>
<td>161</td>
<td>98</td>
<td>2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Lymphocyte %</td>
<td>ND</td>
<td>97</td>
<td>94</td>
<td>ND</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Protein level, mg/dL</td>
<td>23</td>
<td>34</td>
<td>29</td>
<td>24</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td>61</td>
<td>60</td>
<td>53</td>
<td>54</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>HHV-6 load, copies/mL</td>
<td>ND</td>
<td>ND</td>
<td>110,000</td>
<td>ND</td>
<td>25,500</td>
<td>9250</td>
</tr>
<tr>
<td>Serum finding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td>ND</td>
<td>90</td>
<td>88</td>
<td>70</td>
<td>89</td>
<td>101</td>
</tr>
<tr>
<td>HHV-6 load, copies/mL</td>
<td>ND</td>
<td>ND</td>
<td>297,000</td>
<td>ND</td>
<td>120,000</td>
<td>ND</td>
</tr>
<tr>
<td>HHV-6 IgG titer</td>
<td>ND</td>
<td>ND</td>
<td>1:256</td>
<td>1:128</td>
<td>1:128</td>
<td>ND</td>
</tr>
<tr>
<td>HHV-6 IgM titer</td>
<td>ND</td>
<td>ND</td>
<td>1:8</td>
<td>1:8</td>
<td>Negative</td>
<td>ND</td>
</tr>
</tbody>
</table>

NOTE. ND, not determined.
pletely normal in some cases. Whether this possibly correlates with a weaker inflammation process and a better outcome is not currently known.

Ganciclovir and foscarnet proved to be more effective than aciclovir for some immunosuppressed patients with HHV-6–induced encephalitis [14, 15]. In most of the reported cases involving immunocompetent patients, the specific treatment regimen was not given or was not available; 2 patients were treated with aciclovir (one received 500 mg t.i.d. for 10 days), 1 patient was initially treated with aciclovir (10 mg/kg t.i.d. for 5 days) and was later treated with cidofovir (5 mg/kg q.d. for 1 day) and ganciclovir (5 mg/kg b.i.d. for 15 days). Of the 12 patients for whom data were available, 6 recovered without any sequelae, 3 had moderate neurological impairment (i.e., memory loss and developmental delay), 1 had severe persistent seizure disorder, and 2 died.

Our patient was first treated with aciclovir for 13 days (until HHV-6 etiology was confirmed) and then with ganciclovir for another 13 days. Putative treatment success was documented on the basis of remission of CSF pleocytosis, a significant decrease in serum and CSF virus loads, and, most importantly, good clinical outcome. Retrospectively, it is not possible to clearly differentiate which of the 2 antiviral agents was effective in our case, and even though clinical remission was not seen until ganciclovir therapy was started, this of course is no proof that the outcome was influenced by the antiviral treatment.

Acknowledgments

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References