Exacerbation of Herpes Simplex Encephalitis after Successful Treatment with Acyclovir

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Herpes simplex encephalitis (HSE) in children sometimes exacerbates after successful treatment; yet the frequency, etiology, and clinical features of exacerbation remain unclear. We report data for 27 children with HSE confirmed by polymerase chain reaction (PCR) analysis; all were successfully treated with acyclovir, but 7 (26%) had a relapse of encephalitic illness. In 2 of those 7, serial examination with a PCR assay showed that herpes simplex virus (HSV) DNA reappeared temporarily in the cerebrospinal fluid (CSF). For 5 of the 7 patients, a second course of acyclovir therapy was effective. Coxsackievirus A9 was isolated from CSF of 1 case patient during subsequent exacerbation. The total dose during initial acyclovir therapy was significantly lower in the relapse group than in the control group (P = .027). In conclusion, exacerbation of HSE in children may be more common than previously recognized. It is suggested that the replication of HSV or another viral pathogen caused a second encephalitic illness (HSE) in some cases.

Antiviral agents such as acyclovir are effective in treating patients with herpes simplex encephalitis (HSE) [1–3]. Despite this therapeutic advance, HSE is still difficult to manage; the associated mortality and morbidity are still high, and occasionally patients relapse after completing antiviral therapy [2, 4–8]. The precise etiology of the relapsing HSE and the frequency of relapses remain unclear. Better understanding of the mechanisms for the recurrence might permit treatments that are more effective. Previous studies have suggested that relapsing HSE might be due to reactivation of the herpes simplex virus (HSV) [4–6] or immune-mediated encephalopathy [1, 7, 8]. We report data for 27 children with HSE who were successfully treated with acyclovir, of whom 7 (26%) later relapsed.

Methods

Twenty-seven children aged 3 months to 16 years who had HSE between September 1982 and December 1996 were enrolled in this study. HSE was diagnosed by the detection of HSV DNA in the CSF with a PCR assay. The diagnosis was supported by clinical and serological findings. Neonates with HSV infection were excluded. CSF samples were obtained from each patient during and after the antiviral therapy and were used for the qualitative PCR assay. CSF samples from 14 patients were available for the quantitative real-time PCR assay during the acute phase of the first encephalitic illness.

A qualitative PCR assay and Southern blot hybridization were performed as described elsewhere [9, 10]. A real-time quantitative PCR assay with a fluorogenic probe was performed by use of a TaqMan PCR kit (PE Applied Biosystems, Foster City, CA), as described elsewhere [11]. The PCR primers for this assay are in the UL30 gene encoding the viral DNA polymerase of HSV type 1 [12]. The upstream and downstream primer sequences were 5'-ACATCATCAACTTGACTGG-3' and 5'-CTCAGGTCTTCTCTTGTC-3', respectively. A fluorogenic probe consisted of an oligonucleotide sequence located between the PCR primers (5'-ATGTTGAACATCGACATGTACGG-3'), a 5'-reporter dye, and a 3'-quencher dye.

The data were analyzed by means of the χ² test, Fisher's exact test, and Student’s t test. P < .05 was considered significant.

Results

Frequency and etiology of relapsing HSE. Of 27 patients with PCR-proven HSE, 7 (26%) had apparent relapses of encephalitic illness after successful completion of acyclovir therapy, with fever, altered consciousness, convulsions, meningeal irritation, and re-elevated WBC counts and CSF protein concentrations (table 1). Patient 3 was diagnosed with idiopathic thrombocytopenic purpura; the prednisone dosage was tapered (0.9 mg/kg/d) at the onset of HSE. All the patients received a second course of acyclovir therapy (30–45 mg/kg/d) for 10–21 days, and 5 children (patients 2–6) showed clinical improvement. One patient (patient 3) had a second relapse, which was treated with oral acyclovir (45 mg/kg/d) for an additional 14 days.
Each CSF sample from 6 patients (patients 1–6) was negative for HSV PCR before recurrence of HSE. Serial examination with the qualitative PCR assay showed that HSV DNA reappeared temporarily in the CSF in patients 5 and 6 (on days 13 and 6 of the relapse, respectively); however, the assay for HSV DNA was negative in the other 5 case patients. In patient 7 a subsequent exacerbation was diagnosed as viral meningitis in the acute phase. Coxsackievirus was isolated from the CSF on day 3 of meningitis, and then the illness worsened to an encephalitic state.

Quantification of HSV DNA in patients with HSE. We estimated the virus load in the CSF of 14 patients with HSE by means of a quantitative PCR assay in the acute phase of their first illness. All 4 patients in the relapse group were under the detection limit. Only 3 of 10 patients in the control group were positive (10^{2.1}, 10^{2.5}, and 10^{3.3} copies/mL, respectively, of CSF).

Factors responsible for relapsing HSE. The relapse group (patients 1, 2, and 4–6) and nonrelapse group (control patients) were compared (table 2) with regard to age, sex, initial acyclovir therapy for HSE, and mortality and morbidity. Two cases (patient 3, who received prednisone, and patient 7, in whom coxsackievirus caused the second encephalitic illness) were excluded from the analysis. The duration of acyclovir therapy was significantly shorter for patients in the relapse group than for those in the control group (P = .044). In addition, the total dose was significantly lower during initial therapy in the relapse group than in the control group (P = .027).

Discussion

In our study of 27 HSE patients, 7 children (26%) had an exacerbation of clinical manifestations and laboratory values after successful treatment with acyclovir. The frequency of relapsing HSE remains unclear. Sköldenberg et al. [2] reported that 2 of 53 patients with HSE relapsed, and Whitley et al. [3] found that 4 of 56 patients (aged 18–53 years) relapsed. Their populations were mainly adult. Findings for our series suggest that a relapse of HSE might be more common in children than in adults.

In this study we used qualitative PCR to examine CSF samples from patients who relapsed and found that HSV DNA reappeared in 2 of 7 case patients. We cannot explain why HSV DNA was not detected in the CSF in the other 4 patients who relapsed. It may be possible that a very small amount of the viral genome leaked into the CSF because of localized replication of the virus in the brain.

The total acyclovir dose in the initial therapy was also significantly lower in our relapse group than in the nonrelapse group, and 5 relapse patients responded well to a second course of acyclovir therapy. These findings suggest that regrowth or reactivation of HSV caused the relapse in 5 of our 7 case patients. If the replication of HSV is the primary cause of relapse, a higher dose of acyclovir for >2 weeks might be effective in preventing relapse.

By using the quantitative PCR assay, we estimated the virus load in the CSF in order to determine whether the virus load in the acute phase is associated with relapse. Although the number of patients was limited, our results showed that relapse

Table 1. Data from case patients whose herpes simplex encephalitis relapsed after successful treatment with acyclov.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, sex</th>
<th>Onset day of relapse</th>
<th>Initial symptom(s)</th>
<th>Protein, mg/dL</th>
<th>WBCs/µL</th>
<th>Protein, mg/dL</th>
<th>WBCs/µL</th>
<th>CSF analysis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 y, M</td>
<td>10</td>
<td>Altered consciousness</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>25</td>
<td>Negative PCR</td>
<td>Moderate sequelae</td>
</tr>
<tr>
<td>2</td>
<td>3 y, F</td>
<td>9</td>
<td>Altered consciousness</td>
<td>38</td>
<td>55</td>
<td>81</td>
<td>104</td>
<td>Negative PCR</td>
<td>Moderate sequelae</td>
</tr>
<tr>
<td>3</td>
<td>12 y, F</td>
<td>2, 78</td>
<td>Vomiting, headache</td>
<td>2</td>
<td>46</td>
<td>NA</td>
<td>55</td>
<td>Negative PCR</td>
<td>Recovery</td>
</tr>
<tr>
<td>4</td>
<td>16 y, M</td>
<td>1</td>
<td>Altered consciousness</td>
<td>78</td>
<td>35</td>
<td>76</td>
<td>34</td>
<td>Negative PCR</td>
<td>Mild sequelae</td>
</tr>
<tr>
<td>5</td>
<td>3 mo, M</td>
<td>14</td>
<td>Convulsions</td>
<td>10</td>
<td>40</td>
<td>43</td>
<td>88</td>
<td>Positive PCR</td>
<td>Severe sequelae</td>
</tr>
<tr>
<td>6</td>
<td>5 y, F</td>
<td>4</td>
<td>Convulsions</td>
<td>26</td>
<td>50</td>
<td>45</td>
<td>54</td>
<td>Positive PCR</td>
<td>Moderate sequelae</td>
</tr>
<tr>
<td>7</td>
<td>4 y, M</td>
<td>18</td>
<td>Fever</td>
<td>1</td>
<td>15</td>
<td>43</td>
<td>73</td>
<td>Coxsackievirus A9</td>
<td>Moderate sequelae</td>
</tr>
</tbody>
</table>

NOTE. NA, not available.

a Onset day of relapse was counted from completion of the first course of acyclovir therapy.

b Change in CSF values between recovery phase of initial encephalitis and acute phase of relapse are shown.

c PCR assay was qualitative for herpes simplex virus DNA.

d Positive culture.

Table 2. Clinical characteristics of patients with relapsing herpes simplex encephalitis and control patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Relapse cases (n = 5)</th>
<th>Controls (n = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean ± SD</td>
<td>5 ± 6</td>
<td>4.2 ± 3.8</td>
<td>.373</td>
</tr>
<tr>
<td>Sex (males : females)</td>
<td>3 : 2</td>
<td>14 : 6</td>
<td>.833</td>
</tr>
<tr>
<td>Glasgow coma scale score</td>
<td>5.8 ± 2.3</td>
<td>6.3 ± 2.5</td>
<td>.405</td>
</tr>
<tr>
<td>Acyclovir therapy</td>
<td>Initial day of disease</td>
<td>3.4 ± 2.2</td>
<td>± 4.4 ± 1.8</td>
</tr>
<tr>
<td>Duration of therapy, d</td>
<td>11 ± 2.8</td>
<td>14.8 ± 3.5</td>
<td>.044</td>
</tr>
<tr>
<td>Daily dose, mg/kg</td>
<td>26.2 ± 5.8</td>
<td>30.8 ± 5.5</td>
<td>.142</td>
</tr>
<tr>
<td>Total dose, mg/kg</td>
<td>285 ± 92.0</td>
<td>462 ± 149</td>
<td>.027</td>
</tr>
<tr>
<td>Moderate to severe morbidity or death, no. (%) of patients</td>
<td>4 (80)</td>
<td>13 (65)</td>
<td>.413</td>
</tr>
</tbody>
</table>

a Assessed on admission for first encephalitic illness.

b Initial day of disease was counted from onset of initial encephalitis.
patients did not have a higher virus load in the acute phase. Combined with the fact that the Glasgow coma scale score for the 2 groups did not differ significantly, these results suggest that subsequent exacerbation is not related to the severity of the acute phase.

The precise pathogenesis of relapsing HSE remains unclear; a direct viral-invasion mechanism, immune-mediated encephalopathy, or other neurological complications are possible causes. The positivity of biopsy-specimen cultures [4], the positivity of CSF for HSV DNA during the acute phase of the relapse [5–7], and the clinical benefit of a second course of antiviral therapy [6] all support the first mechanism. In most case patients, the relapses occur within 2 weeks after completion of acyclovir therapy, suggesting that the relapse of HSE is related to reactivation of HSV. All the patients described here, except patient 7, relapsed within 14 days after completion of the initial course of acyclovir therapy.

Another mechanism for relapsing HSE is infectious pathogens other than HSV. In patient 7, coxsackievirus was isolated from the CSF on day 3 of the disease, whereas PCR for HSV was negative. It is suggested that coxsackievirus infection may cause the subsequent episode of HSE. Impairment of the blood-brain barrier in HSE patients is likely to develop during the first 2 months of the disease and diminishes thereafter [13]. Therefore, in the convalescent phase of HSE, patients are probably prone to other CNS infections. It is important to consider the possibility of pathogens other than HSV when a relapse occurs.

Acknowledgment

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References