Brain stem encephalitis caused by primary herpes simplex 2 infection in a young woman


A 27 year old woman developed a vesicular genital rash and cerebellar dysfunction with progressive neurological deterioration suggesting brain stem encephalitis. Respiratory support was required. Magnetic resonance imaging (MRI) of the brain on day 7 showed signal hyperintensity in the central medulla and ventral pons, typical of acute inflammation. The course was severe and occurred. MRI on day 33 showed a haemorrhagic area in the medulla. Treatment with aciclovir/valaciclovir eventually led to gradual recovery. Herpes simplex virus 2 (HSV-2) DNA was detected in CSF on days 11 and 14. HSV-2 was also detected in vesicle fluid from the genital rash. Serum was initially negative for HSV-1 and HSV-2 antibodies, but convalescent samples showed seroconversion to HSV-2, indicating primary infection. Intrathecal synthesis of oligoclonal IgG bands specific for HSV was identified in the CSF. It is important to differentiate HSV-2 from HSV-1, and primary from initial or reactivated infection, so that prolonged aciclovir treatment followed by prophylaxis is instituted to prevent the high likelihood of symptomatic relapse in primary HSV-2 infection.
It was restarted on day 20 when renal function had returned to normal. On day 25 it was discontinued (after 15 days of treatment), as a third CSF sample taken on day 20 had been tested for HSV-1 and HSV-2 DNA and found to be negative, although the pleocytosis persisted (table 1).

On day 27, vesicles appeared on the patient’s left foot and HSV-2 was cultured from vesicle fluid. Concomitantly, the patient developed worsening upper limb, truncal, and head ataxia, and the new symptom of vertigo. At this point, a fourth CSF sample was taken which still showed a lymphocytic pleocytosis, but was negative for HSV DNA (table 1).

Valaciclovir (500 mg twice daily orally) was started on day 27, as treatment for the relapse of disease. Oral valaciclovir was used as an alternative to intravenous aciclovir because of difficulty with venous access. Repeat brain MRI on day 33 showed haemorrhagic transformation within the original area of hyperintensity in the medulla. From day 60 valaciclovir was discontinued and prophylactic oral aciclovir (400 mg once daily) was given for the next six months. After a period of rehabilitation the patient was finally discharged four months after admission, walking with a rollator frame, with some residual diplopia and dizziness.

The results of laboratory tests on CSF and serum are shown in table 1. Four lumbar punctures were done during the patient’s admission and on each occasion her serum was also examined. HSV-2 DNA was found in the first two CSF samples but not in the third or fourth. Oligoclonal IgG bands specific for HSV were detected in the third and fourth CSF samples but were absent from serum. Testing of sequential serum samples showed seroconversion to HSV-2 antibody in the absence of HSV-1 antibodies, indicating a primary infection.

**DISCUSSION**

In this case report we describe a primary HSV-2 infection in an immunocompetent adult which caused a brain stem encephalitis. Primary HSV-2 infection was indicated by seroconversion to HSV-2 antibodies in the absence of antibodies to HSV-1. There was unequivocal evidence of HSV-2 encephalitis as there was both viral invasion of the CNS and an HSV specific intrathecal antibody response. Furthermore, the MRI findings showed a lesion localised to the brain stem which accounted for the patient’s neurological signs and symptoms.

Encephalitis limited to the brain stem is a rare presentation of herpes simplex encephalitis—although cranial nerve signs

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**Table 1  Summary of laboratory tests**

<table>
<thead>
<tr>
<th>Time after onset of rash (days)</th>
<th>CSF</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cell count (cells/µl)</td>
<td>Glucose: CSF/plasma (mmol/l)</td>
</tr>
<tr>
<td></td>
<td>White Red Total protein (g/l)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>220 30 2.0</td>
<td>4.8/8.1 Pos</td>
</tr>
<tr>
<td>11</td>
<td>344 1800 1.0</td>
<td>4.1/6.8 Pos</td>
</tr>
<tr>
<td>14</td>
<td>75 1000 0.25</td>
<td>4.0/7.1 Neg</td>
</tr>
<tr>
<td>20</td>
<td>38 150 0.4</td>
<td>3.3/5.2 Neg</td>
</tr>
<tr>
<td>27</td>
<td>41 69</td>
<td></td>
</tr>
</tbody>
</table>

1 All white cell counts were predominantly lymphocytes.
2 Negative for HSV-1, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus DNA.
3 After isoelectric focusing, specificity confirmed by antigen mediated blot to HSV antigen [pooled HSV-1 and HSV-2] as previously described.
4 Confirmed by immunoblot to HSV-2 antigen.

CSF, cerebrospinal fluid; EIA, enzyme immunoassay; HSV, herpes simplex virus.
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are noted in 32% of cases of herpes simplex encephalitis, this is more often the result of raised intracranial pressure than of direct viral invasion of the brain stem. Also, herpes simplex virus brain stem encephalitis confirmed by MRI or necropsy histology usually shows involvement of cerebral cortex. Most reports of herpesvirus brain stem encephalitis do not distinguish between HSV-1 and HSV-2. Indeed, there are only two previous reports of HSV-2 brain stem encephalitis, and neither of these reports addressed the possibility of primary HSV-2 infection (that is, seroconversion to HSV-2 in the absence of HSV-1 antibodies), as the appropriate serological tests were not done.

The more severe the primary HSV-2 infection the more likely and frequent are recurrent episodes of disease. In view of this, thorough treatment of encephalitis caused by primary HSV-2 infection is essential. The well established and universally accepted treatment for herpes simplex encephalitis occurring outside the newborn period (normally caused by HSV-1) is intravenous aciclovir (10 mg/kg every eight hours) for 10 to 14 days. In our adult case of primary HSV-2 infection, the recommended dose of intravenous aciclovir was given for 10 days followed by a further course of five days. Notwithstanding the apparently successful clearance of HSV from the CSF, the patient developed further vesicles on her left foot from which HSV-2 was cultured, her neurological disease relapsed, and repeat MRI of her brain showed haemorrhage in the medulla. Upon immediate treatment with valaciclovir, the vesicles resolved and the neurological symptoms improved markedly. She subsequently made a gradual recovery but was maintained on aciclovir prophylaxis to prevent further episodes of disease.

In this context, it is of interest to consider the latest recommendations for the management of neonatal herpes simplex infections, the majority of which are primary HSV-2 infections. The use of high dose intravenous aciclovir (20 mg/kg every eight hours) for 21 days has been shown to reduce morbidity and mortality, and prophylactic aciclovir is under clinical investigation to improve the outcome of those who survive neonatal herpes simplex virus disease. Thus prolonged high dose intravenous aciclovir followed by oral aciclovir prophylaxis may be justified to prevent relapse and recurrence where primary HSV-2 infection in an adult is accompanied by encephalitis.

Conclusions

We report a case of HSV-2 brain stem encephalitis in an immunocompetent adult in which the only factors predisposing to severe disease were primary HSV-2 infection and female sex. As far as we are aware this is the first time that brain stem encephalitis has been documented as a result of primary HSV-2 infection. Given the decreasing prevalence of HSV-1 infection in the United Kingdom, primary HSV-2 infection is likely to be an increasing problem in adults. Recognition of neurological disease caused by primary HSV-2 infection is important not only to predict severity, but also as an indication for prolonged aciclovir treatment and prophylaxis.

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