Clinical Features of Viral Meningitis in Adults: Significant Differences in Cerebrospinal Fluid Findings among Herpes Simplex Virus, Varicella Zoster Virus, and Enterovirus Infections

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Background. In this retrospective study, our objective was to review the epidemiology of viral meningitis and to compare clinical features associated with enterovirus, herpes simplex virus (HSV), and varicella zoster virus (VZV) infections in immunocompetent adults.

Methods. Data on cerebrospinal fluid (CSF) samples submitted to the Trust Virology Laboratory (Sheffield, UK) from April 2004 through April 2007 were reviewed. Notes on immunocompetent adults who were polymerase chain reaction (PCR) positive for enterovirus, HSV type 2, or VZV and who had presented to local clinical departments were scrutinized (4 patients were positive for HSV type 1 and did not meet the inclusion criteria).

Results. A total of 2045 samples were analyzed for viral pathogens during the 3-year period. Of the 109 PCR-positive samples, 38 (35%) were from immunocompetent adults, of whom 22 were infected with enterovirus, 8 were infected with HSV type 2, and 8 were infected with VZV. The median ages were 32 years (range, 16–39 years), 39 years (range, 22–53 years), and 47.5 years (range, 26–80 years), respectively. Rash occurred after the meningitis symptoms in 5 patients infected with VZV (median time from meningitis symptoms to rash, 6 days). Protein levels were significantly higher in CSF samples from patients infected with HSV type 2 (median, 1205 mg/L) and in samples from those infected with VZV (median, 974 mg/L) than in samples from those infected with enterovirus (median, 640 mg/L; P = .001 and P = .01, respectively). White blood cell counts were significantly higher in CSF samples from patients infected with HSV type 2 (median, 240 × 10^3 cells/L) than in samples from those infected with enterovirus (median, 51 × 10^3 cells/L; P = .01).

Conclusions. Enterovirus infection was the most common cause of viral meningitis in immunocompetent adults in this study. White blood cell counts and protein levels were significantly higher in CSF samples from patients infected with HSV type 2 than in samples from patients with enterovirus infection. Zoster rash often occurs after meningitis. PCR testing provides a rapid and specific etiological diagnosis.

The development of PCR has enabled molecular detection of virus genomes and is increasingly being used in routine clinical practice. The high sensitivity of the PCR test has provided an opportunity to study the characteristics of different viral infections. PCR tests should facilitate rapid diagnosis and enable the use of antiviral treatment [1], when appropriate, in patients with meningitis and meningoencephalitis. Acyclovir has been established as an essential early therapy to optimize outcomes of herpes simplex virus (HSV) encephalitis, which is usually a result of HSV type 1 (HSV-1) infection [2, 3]. There are no published data that reveal that acyclovir will modify HSV or varicella zoster virus (VZV) meningitis, but if the drug is to be used, the earlier that it is prescribed, the more likely that it will be beneficial [4, 5].

Since 2004, CSF samples from patients presenting with suspected neurological infections in Sheffield, United Kingdom, have routinely been tested for enterovirus, HSV-2, and VZV by PCR, because these are the most commonly recognized viruses that cause CNS in-
fection in the United Kingdom. Enteroviruses are recognized as the most common identifiable cause of aseptic meningitis [6].

Unlike HSV-1 infection, which usually establishes latency in the trigeminal ganglion, where CNS infection typically results in an encephalitic illness, HSV type 2 (HSV-2) usually establishes latency in the sacral sensory ganglia and typically causes a meningitic illness [7].

Chicken pox (varicella), the primary VZV infection, usually occurs during childhood as a mild-to-moderate disease associated with low mortality [8, 9]. Latency of VZV infection may occur in any dorsal root ganglion. Reactivation of VZV (shingles or herpes zoster) is seldom associated with clinical meningitis, but in 1 study, it was associated with CSF lymphocytic pleocytosis in 40% of patients [10].

The use of molecular diagnostic tests for meningitis provides rapid and accurate differentiation between these infections. The objective of our study was to define the clinical characteristics and laboratory findings associated with enterovirus, HSV, and VZV infections that may help clinicians in defining the probable etiology.

METHODS

CSF samples from patients hospitalized at Sheffield Teaching Hospitals National Health Service Foundation Trust are routinely sent to Sheffield Virology Services. The teaching hospital serves a local population of ∼515,000 persons and a regional population of ∼1.27 million persons. Standard operating procedures during the study period included PCR analysis for HSV-1, HSV-2, VZV, and enterovirus from CSF samples from all patients with suspected infection, as evidenced by information on the request form or by a CSF WBC count >1 cell/cm². In addition, all submitted CSF samples underwent PCR testing for HSV-1, HSV-2, and VZV, irrespective of clinical information or WBC count, if the patient was aged <1 year, was immunocompromised, or was admitted to the infectious diseases or intensive care unit. PCR for Epstein-Barr virus and cytomegalovirus was also performed for all immunocompromised patients or if specifically requested. Positive PCR results over 3 years (from April 2004 through April 2007) were identified from laboratory records. The total numbers of samples submitted for analysis and the total numbers of samples positive for any virus were recorded.

The notes on immunocompetent adult patients who were hospitalized at the Sheffield Teaching Hospitals and who had positive results of PCR for enterovirus, HSV, or VZV were reviewed as part of a service evaluation, with the consent of the admitting consultant. Patients were considered to be immunocompetent if there was no evidence of immunocompromise attributable to disease or immunosuppressive drugs. Clinical and laboratory data were collected in accordance with the standard format. The notes on the other patients whose samples were sent for PCR testing were not reviewed individually.

Statistical analysis was performed with use of SPSS (SPSS). The Mann-Whitney U test was used to assess differences in CSF findings and C-reactive protein levels between patients with enterovirus infection and those with HSV-2 or VZV infection. P < .05 was considered to be statistically significant.

RESULTS

Epidemiology

Data on all CSF samples. During the 3-year period of study, 2045 CSF samples were tested by PCR for viruses. Of these, 109 samples (5.3%) tested positive (table 1). Thirty-eight (35%) of the positive samples were obtained from immunocompetent adult patients, of whom 22 were infected with enterovirus, 8 were infected with HSV-2, and 8 were infected with VZV. Four patients who had samples that were PCR positive for HSV-1 did not meet the inclusion criteria and were not included in further analysis.

Data on immunocompetent adults with enterovirus, HSV-2, or VZV infection. All of the reviewed patients underwent lumbar puncture on the first day of hospitalization. The demographic details and clinical findings are summarized in table 2. The mean maximum temperature for all 3 groups is shown in table 2. In all cases, the temperature returned to normal within 48 h after hospital admission. Two of the 22 patients with enterovirus infection and 3 of the 8 patients with VZV infection had no temperature recorded at hospital admission. All 8 patients with HSV-2 infection had a fever at the time of hospital admission.

Two patients with enterovirus infection had a rash. Of the patients with HSV-2 infection, none had a rash at the time of the neurological illness. 2 had a history of recent genital herpes, and 1 had a history of HSV-2 meningitis. Of the patients with VZV infection, 3 (age, >70 years) had ophthalmic zoster, 4 (age, <50 years) had thoracic zoster, and 1 (age, 26 years) did not have a rash. In 5 of the 7 patients in this series, the

Table 1. Positive results of viral PCR of CSF samples.

<table>
<thead>
<tr>
<th>Virus</th>
<th>No. of patients with positive PCR results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥16 years of age</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>24</td>
</tr>
<tr>
<td>Herpes simplex virus type 1</td>
<td>4</td>
</tr>
<tr>
<td>Herpes simplex virus type 2</td>
<td>10</td>
</tr>
<tr>
<td>Varicella zoster virus</td>
<td>10</td>
</tr>
<tr>
<td>Mumps</td>
<td>4</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>7</td>
</tr>
<tr>
<td>Human herpes virus 6</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 2. Demographic characteristics and clinical findings for immunocompetent adults with enterovirus, herpes simplex virus type 2 (HSV-2), or varicella zoster virus (VZV) infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients with enterovirus infection (n = 22)</th>
<th>Patients with HSV-2 infection (n = 8)</th>
<th>Patients with VZV infection (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>32 (16–39)</td>
<td>39 (22–53)</td>
<td>47.5 (26–80)</td>
</tr>
<tr>
<td>Female sex</td>
<td>9 (41)</td>
<td>7 (88)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Duration of symptoms before presentation, median days (range)</td>
<td>2 (0–7)</td>
<td>2 (1–7)</td>
<td>4 (2–7)</td>
</tr>
<tr>
<td>Duration of hospitalization, median days (range)</td>
<td>4 (2–8)</td>
<td>6.5 (4–17)</td>
<td>8 (2–69)</td>
</tr>
<tr>
<td>Symptoms and signs at hospital admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22 (100)</td>
<td>8 (100)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>20 (91)</td>
<td>8 (100)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>17 (77)</td>
<td>8 (100)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>18 (82)</td>
<td>5 (63)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Temperature, mean °C ± SD</td>
<td>37.8 ± 0.8</td>
<td>37.8 ± 0.6</td>
<td>37.3 ± 1.0</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>7 (88)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients, unless otherwise indicated.

Table 3. Laboratory results for patients with enterovirus, herpes simplex type 2 (HSV-2), or varicella zoster virus (VZV) infection.

<table>
<thead>
<tr>
<th>Laboratory result</th>
<th>Patients with enterovirus infection (n = 22)</th>
<th>Patients with HSV-2 infection (n = 8)</th>
<th>Patients with VZV infection (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count, ×10⁶ leukocytes/L⁶</td>
<td>51 (0–1298)</td>
<td>240 (180–2200)</td>
<td>207 (6–450)</td>
</tr>
<tr>
<td>Lymphocyte percentage⁶</td>
<td>91 (5–100)</td>
<td>100 (80–100)</td>
<td>100 (90–100)</td>
</tr>
<tr>
<td>Protein level, mg/L⁶</td>
<td>640 (100–875)</td>
<td>1205 (611–3704)</td>
<td>974 (581–2616)</td>
</tr>
<tr>
<td>CSF:serum glucose ratio</td>
<td>0.6 (0.26–0.76)</td>
<td>0.48 (0.47–0.67)</td>
<td>0.55 (0.4–0.73)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count, ×10⁶ leukocytes/L⁶</td>
<td>6.6 (3.6–12.2)</td>
<td>7.9 (5.5–13.9)</td>
<td>7.7 (5.6–15.6)</td>
</tr>
<tr>
<td>C-reactive protein level, mg/L¹</td>
<td>15 (2.1–112.3)</td>
<td>4.6 (2–28)</td>
<td>6.2 (2.2–22.9)</td>
</tr>
</tbody>
</table>

NOTE. Data are median value (range).

a P<.01 for the comparison between patients with enterovirus and patients with HSV-2 by 2-tailed Mann-Whitney U test.
b Data are for 15 patients with enterovirus infection and 7 patients with VZV infection.
c P<.001 for the comparison between patients with enterovirus infection and patients with HSV-2 infection, and P<.01 for the comparison between patients with enterovirus infection and patients with VZV infection, by 2-tailed Mann-Whitney U test.
d Data are for 16 patients with enterovirus infection and 6 patients with VZV infection.
e Data are for 21 patients with enterovirus infection and 7 patients with HSV-2 infection.
f Data are for 7 patients with HSV-2 infection.

rash appeared 3–8 days (median, 6 days) after the onset of CNS symptoms.

All patients with enterovirus or HSV-2 infection had a history of subacute onset of severe frontal or retro-orbital headache, sometimes radiating to the occipital region and to the back of the neck. Systemic flu-like symptoms before hospital admission in patients with enterovirus infection included sore throat and myalgia (in 8 patients), malaise (4), diarrhea (3), and abdominal discomfort (2). Systemic symptoms were not recorded for any patients with HSV-2 infection. Patients with VZV infection had prior symptoms recorded, including myalgia (in 2 patients), diarrhea (1), and scalp tenderness (1).

Two patients (age, >70 years) with VZV infection had symptoms at hospital admission, including confusion, memory impairment, and visual hallucinations, which may be suggestive of meningoencephalitis.

A positive epidemiological history was recorded for 5 patients. All of these patients had enterovirus infection and had contact with a family member with similar symptoms or confirmed enteroviral infection or recently traveled to a foreign country (within <1 week before hospital admission).

Results of testing of CSF samples are shown in table 3. Two patients with confirmed enterovirus infection had a CSF WBC count ≤1 × 10⁶ cells/L. Of note, the median CSF leukocyte...
count was significantly higher in patients with HSV-2 infection than in patients with enterovirus infection ($P<.01$), and CSF protein levels were significantly higher in both patients with HSV-2 infection and patients with VZV infection than in patients with enterovirus infection ($P<.001$ and $P<.01$, respectively). Both of the patients with VZV meningoencephalitis had CSF WBC counts and protein levels that were lower than the median values in the group with VZV infection. The median CSF:plasma glucose ratio was not available for all patients with enterovirus infection, but of note, the median ratio was $<0.5$ in the 8 patients with HSV-2 infection (table 3).

Figures 1 and 2 show the CSF WBC count and protein levels, respectively, for the 3 groups. Figure 3 shows the percentage of lymphocytes in CSF in relation to the duration of symptoms in patients with enterovirus infection (data for 15 patients were available from records). The percentage of lymphocytes was 80%–100% in all patients who had symptoms of meningitis for $>48$ h.

Table 3 shows the C-reactive protein levels in the patients at hospital admission, and figure 4 shows a comparison of the C-reactive protein levels among the different patients groups. Two patients, both with enterovirus infection, had a C-reactive protein level $>50$ mg/L.

**Management and Duration of Hospitalization**

The median durations of hospitalization for the 3 groups are shown in table 2. Four patients for whom there was clinical uncertainty with regard to the cause of meningitis received antibiotics (cefotaxime). Intravenous acyclovir was administered to 5 patients with HSV-2 meningitis because of persisting symptoms after the PCR result was available. The median duration of hospitalization was 7 days for those who received acyclovir, compared with 6 days for those who did not receive the drug. The median duration of hospitalization was 21 days for the 4 patients with VZV infection who received intravenous acyclovir, compared with 5 days for the 2 who received oral valacyclovir and 2 days for the 2 who were not treated with antivirals. The median duration of hospitalization was 4 days (range, 2–10 days) for the 5 patients with VZV infection who were $<50$ years of age, compared with 23 days (range, 18–69 days) for the 3 patients with VZV infection who were $>70$ years of age.

**DISCUSSION**

A common bedside clinical challenge is whether a case of meningitis has a viral or bacterial etiology, because this will define the treatment. The threshold is usually set low, so that in cases
of doubt, antibiotics are prescribed, as was the case for 4 patients in this study. The use of PCR in routine clinical practice allows for a rapid diagnosis and assists in clinical decision making, particularly regarding the potential use of antiviral therapy. Routine PCR testing over recent years allowed this review of the epidemiology of viral CNS infections in a UK city with a population of ~515,000 persons but also provided an opportunity to compare the clinical and laboratory features of viral meningitis of differing etiologies.

Over the 3-year study period, 5.3% of samples (from both adults and children) that were sent for analysis were reported as PCR positive, most commonly for enterovirus. Because of the diversity of the patients whose CSF samples had been sent for testing, the detailed comparative analysis was restricted to a defined group of immunocompetent adults with enterovirus, HSV-2, or VZV infection, which we found to be the most common viral etiologies.

Most patients with enterovirus or HSV-2 infection presented before the fourth decade of life, and interestingly, 5 of the 8 patients presenting with VZV meningitis were <50 years of age, although VZV reactivation more commonly occurs in older adults [11]. Although the numbers were small, it was notable that 7 (87.5%) of the 8 patients with HSV-2 meningitis were female; this finding was similar to those in other studies in which 9 (69%) of 13 and 11 (79%) of 14 patients with HSV-2 meningitis were female [12, 13]. This observation may be explained by the fact that women are more susceptible to HSV-2 infection than are men, in the context of genital infection [14].

The pattern of meningitic symptoms at presentation was similar regardless of the etiology, and all patients had a lumbar puncture performed within 24 h after hospital admission, in-
indicating a clinically significant illness. However, patients with enterovirus infection often had systemic flu-like symptoms unrelated to meningitis that were recorded in the notes. These observations, however, are subject to the limitations of a retrospective study. The epidemiological history was often a helpful pointer in the context of enteroviral infection: 23% of patients with such infection had a relevant history. HSV-2 meningitis may occur as part of a primary infection or as a result of reactivation. In primary disease, cutaneous lesions may occur concurrently, but this is not usually the case in recurrent infection [14]. We did not have any serological data from patients in this study to establish whether these were primary infections. However, none of the patients in this study had clinically evident genital lesions recorded at the time of hospital admission, but 2 patients had a history of genital herpes, and 1 had a history of HSV-2 meningitis. Future prospective studies should include serological analysis. Seven patients with VZV meningitis developed a characteristic herpes zoster rash, although in 5 patients, this occurred after presentation with meningitis (mean time from onset of meningitis to development of rash, 5.6 days). One patient (age, 26 years) never developed a rash, and the etiological diagnosis would never have been made on the basis of clinical findings alone. In 1 study, VZV DNA was detected in CSF samples from 21 patients, ~50% of whom had no coincidental rash [15].

Harrison’s Principles of Internal Medicine states that, in viral meningitis, “The typical profile is a lymphocytic pleocytosis (25–500 cells/μL), a normal or slightly elevated protein concentration (0.2–0.8 g/L [20–80 mg/dL]), a normal glucose concentration, and a normal or mildly elevated opening pressure (100–350 mm H$_2$O)” [16, p. 2477]. We noted that patients with HSV-2 or VZV infection had significantly higher protein levels in CSF than did those with enterovirus infection, as shown in figure 2. In addition, patients with HSV-2 infection had significantly higher WBC counts in CSF than did patients with enterovirus infection (figure 1). Protein levels >1000 mg/L have been considered to be unusual in viral meningitis, but in our series, the median protein levels were 1205 mg/L in patients with HSV-2 infection and 974 mg/L in patients with VZV infection (table 3). An etiology that must always be considered in the differential diagnosis of lymphocytic meningitis is tuberculosis, and of note, the median CSF:plasma glucose ratio was <0.5 in patients with HSV-2 infection; a low ratio is another feature of tuberculosis meningitis. However, the clinical history is usually longer for patients with tuberculosis and is usually associated with clinical progression, whereas in our series, all patients with viral meningitis of any etiology had a normal temperature by 48 h after hospital admission.

It has been acknowledged that the progression of WBCs in CSF from polymorphs to lymphocytes may evolve during the first 48 h of CNS infection [17]; a progression from polymorphs to lymphocytes was observed in the patients with enterovirus...
infection (figure 3), whereas most WBCs in CSF were lymphocytes during initial lumbar puncture in patients with other infections, regardless of the duration of symptoms. Measurement of C-reactive protein levels can be helpful in distinguishing between bacterial and viral infections [18], and a previous study of meningitis noted that C-reactive protein levels seldom exceeded 50 mg/L in patients with viral infection (M.W.M., personal observation); in the current series, C-reactive protein levels were increased to >50 mg/L in only 3 patients, all of whom had enterovirus infection (table 3 and figure 4).

The duration of hospitalization was shorter for patients with enterovirus infection (median duration, 4 days) than for patients with HSV-2 or VZV infection. For patients with HSV-2 infection, the duration of hospitalization was similar regardless of whether the patient had received intravenous acyclovir. However, in our series, duration of hospitalization was longer for patients with VZV meningitis who received intravenous acyclovir. However, in our series, duration of hospitalization was longer for patients with VZV meningitis who received intravenous acyclovir than for those who did not, but 3 of these 4 patients were >70 years of age. It is not possible to be certain from this retrospective review whether the longer duration of hospitalization for those who received intravenous acyclovir reflected more severe disease in those patients or other comorbidities in an older group.

In summary, it is well recognized that meningitis is more commonly associated with a viral etiology than a bacterial etiology. This retrospective review of data over a 3-year period has revealed the characteristic pattern of infection and CSF findings in enterovirus, HSV-2, and VZV infections. Of particular interest were the relatively high CSF protein levels often seen in patients with HSV-2 or VZV infection; these levels were significantly higher than those seen in patients with enteroviral infection. Limiting factors of our study are the retrospective nature and the relatively small numbers; despite these limitations, the findings are statistically significant.

A positive diagnosis by PCR is clinically valuable for optimizing therapy and management. The role of intravenous acyclovir is well established in the treatment of HSV encephalitis, but prospective controlled studies are needed to determine its value in the treatment of HSV meningitis.

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References