Correspondence

Presence or Absence of Cytomegalovirus in Cerebrospinal Fluid from Patients with Guillain-Barré Syndrome?

To the Editor—Steininger et al. [1] reported the presence of cytomegalovirus (CMV) DNA in cerebrospinal fluid (CSF) from patients with Guillain-Barré syndrome (GBS). This observation may have important consequences. In their study, CMV DNA was demonstrated, by polymerase chain reaction (PCR) assay, in CSF from 13 (31%) and in serum from 14 (33%) of 42 patients with GBS. These observations suggest that CMV infection is an important preceding infection in GBS and that serological studies, in which usually <15% of patients are found to be CMV positive, underestimate the frequency of this infection [2]. In addition, serological studies may be biased toward certain types of CMV, as was suggested by Steininger et al. [1]. This would also have implications for further delineating patients with GBS into pathogenic subgroups, since some reports indicate that patients with positive CMV serological test results are younger; have a clinical variant characterized by severe involvement of motor, sensory, and cranial nerves; and a prolonged progressive active phase; and have cross-reactive antibodies to the ganglioside GM2 [3, 4].

The discrepancy between our results and those of Steininger et al. [1] is remarkable, since a method with similar assay characteristics (as determined by quality-control proficiency testing) was used by the 2 reference laboratories. Random errors in our study are unlikely, considering the large number of patients included. Patient selection cannot be excluded, although both study groups were similar with respect to relevant clinical characteristics and frequency of positive CMV IgM serological test results. Steininger et al. [1] tested patients for CMV DNA in CSF and serum only when CMV-specific IgG or IgM antibodies were present, which resulted in selection of 42 of 66 identified patients with GBS. Our patients may have been more severely affected, as indicated by the larger proportion of patients who required ventilation in our group and by our inclusion criterion requiring that patients be unable to walk independently. Furthermore, the time interval between the onset of GBS and lumbar puncture was defined slightly differently in our study. However, the CSF protein content and the observed time intervals were not significantly different between the groups, indicating that the CSF was obtained at about the same time during the acute phase of disease (<2 weeks between first signs of weakness and randomization into the study group), and were unable to walk independently [6]. The patients we studied were comparable to those studied by Steininger et al. [1] with regard to age, frequency of positive CMV IgM serological test results [2], (estimated) time interval to lumbar puncture, and CSF protein level (table 1). Serological evidence of a recent CMV infection was detected in 22 (14%) of 159 patients (table 1). In contrast, we could detect CMV DNA in CSF from only a single patient with GBS. This patient also had serum CMV-specific IgM antibodies.

Table 1. Comparison of baseline and clinical characteristics, cytomegalovirus (CMV) serological test results, and polymerase chain reaction (PCR) results in 2 groups of patients with Guillain-Barré syndrome (GBS).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present study</th>
<th>Steininger et al. [1]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, no.</td>
<td>170</td>
<td>42</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>50 (19.5)</td>
<td>47 (22.7)</td>
</tr>
<tr>
<td>CSF protein level, g/L</td>
<td>1.48</td>
<td>1.72</td>
</tr>
<tr>
<td>Ventilation required, no. (%) of patients</td>
<td>50 (29)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Interval between onset of GBS and lumbar puncture, geometric mean, days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV DNA present in CSF</td>
<td>2.0</td>
<td>3.3</td>
</tr>
<tr>
<td>CMV DNA absent in CSF</td>
<td>4.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Positive CMV IgM serological test result (serum), no. positive/total tested (%)</td>
<td>22/159 (14)</td>
<td>5/42 (12)</td>
</tr>
<tr>
<td>Positive CMV PCR (CSF), no. positive/total tested (%)</td>
<td>1/170 (&lt;1)</td>
<td>13/42 (31)</td>
</tr>
</tbody>
</table>

NOTE. CSF, cerebrospinal fluid.

* Serological results were partially published previously [2].

Potential conflicts of interest: none reported.

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Reply to Kuijf et al.

To the Editor—Kuijf et al. [1] tested cerebrospinal fluid (CSF) samples that were obtained from a large cohort of patients with Guillain-Barré syndrome (GBS) for the presence of cytomegalovirus (CMV) DNA. These patients have been studied in 2 large, multicenter GBS trials that evaluated different therapeutic schemes [2, 3]. In contrast to our study, CMV DNA was detected only in 1 CSF sample in the Kuijf et al. study, despite the use of a comparable assay. This difference in rates of detection of CMV DNA in CSF samples is remarkable and requires explanation, particularly because of its possible implications for the management of patients with GBS.

There exist various possible reasons for the differences in detection rates observed between the studies. The 2 patient cohorts were comparable with respect to the age of the patients, CSF protein level, and rate of positivity for CMV-specific IgM antibodies. Patient selection, however, was significantly different and may have affected the results. The clinical samples tested in our study were collected at different hospitals for routine virological evaluation of the neurological symptoms observed, irrespective of—and often before—the final diagnosis could be established. In contrast, Kuijf et al. studied samples from patients with GBS who participated in large GBS clinical trials at specialized centers [2, 3], after the final diagnosis had been established. In addition, Kuijf et al. mentioned that, in the Dutch study, patients were included at an advanced stage of the disease (when they were unable to walk independently) and were more severely affected.

In our study, patients with GBS were selected according to the parameter of detectable CMV-specific antibodies, because this reliably identifies patients with primary CMV infection [5], as well as those at risk for reactivation of latent infection. As negative controls, we also tested CSF samples from our 23 CMV-seronegative patients with GBS, and all of these samples tested negative for CMV (authors’ unpublished data). In contrast, Kuijf et al. did not differentiate the patients according to seropositivity for CMV IgG antibodies. This may have resulted in testing a considerable number of patients for CMV DNA who had had neither recent nor latent CMV infection and in whom, thus, GBS could not be associated with CMV.

We have also observed that early collection of CSF is essential for the detection of CMV DNA in samples [4]. The mean interval was 1 day longer in Dutch patients with a negative PCR result than in Austrian patients with a positive one. This difference may also have contributed to the observed differences in detection rates. However, it cannot be the only explanation, because the relative risk for a positive PCR result was reduced in our study by 15% for every day between the onset of neurological disease and lumbar puncture.

Finally, Kuijf et al. mentioned that there might be geographical differences in the incidence of CMV-related GBS. Indeed, differences in geographical predominance of GBS variants could be another possible reason for the discrepancies observed, since geographically and demographically variable distributions of CMV genotypes have been described [6, 7]. So far, neither the significance of the CMV genotype infecting patients with GBS nor the geographical differences in the prevalence of coinfections, such as with Campylobacter jejuni, has been evaluated. However, all of these parameters may also have influenced the results.

The role of CMV in the origin of GBS and the actual prevalence of detectable

References

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1472 • JID 2006:193 (15 May) • CORRESPONDENCE