Dengue in Patients with Central Nervous System Manifestations, Brazil

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We investigated the prevalence of dengue in patients with suspected viral meningitis/meningoencephalitis in a dengue-endemic area. Cerebrospinal fluid analysis showed positive results and a 6.74× greater likelihood of identifying positive fluid in patients who died. Our findings support testing patients with neurologic manifestations for the virus in dengue-endemic areas.

Dengue is the most prevalent arboviral infection in humans (1). Since the reintroduction of dengue virus (DENV) into Brazil in the 1980s, >60% of the reported dengue cases in this region of the Western Hemisphere have occurred there (2). As the disease has become more common, unusual clinical signs, some of which involve the central nervous system, have been observed in dengue patients (2–4). We therefore assessed prevalence of dengue neurologic cases from Ceará State, Brazil, a region where dengue is endemic.

The Study

We enrolled 183 patients with suspected viral meningitis/meningoencephalitis admitted to São José Hospital of Infectious Disease and 26 deceased patients with suspected fatal meningitis who had been sent to the city coroner’s office. A diagnosis of dengue meningitis was suspected when a patient had fever and symptoms of irritation of the meninges, such as headache and neck stiffness; a diagnosis of dengue meningoencephalitis was established when the patient showed signs of focal involvement of the central nervous system (CNS). A diagnosis of dengue was confirmed with a DENV-positive CSF result by reverse transcription PCR (RT-PCR), nonstructural protein (NS) 1, or IgM against DENV (3,4).

Samples were analyzed by using RT-PCR, ELISA for NS1, and IgM monoclonal antibody and a rapid immunochromatography test for IgG (3–5). Viral RNA for the nested RT-PCR was extracted from 140 μL of the CSF samples by using the QIAamp Viral RNA Mini Kit (QIAGEN, Valencia, CA, USA), following the manufacturer’s protocol, and stored at −80°C until tested. The RT-PCR for DENV was performed on 209 CSF samples, as described (5).

The NS1Ag Pan-E Dengue Early ELISA kit (Panbio Diagnostics, Brisbane, Queensland, Australia) was used to detect the dengue NS1 in 209 CSF specimens in accordance with the manufacturers’ instructions (4). The Dengue IgM Capture ELISA (Panbio Diagnostics) was performed on 209 CSF samples, according to the manufacturer’s instructions.

Conclusions

DENV as a causal agent for meningitis has been rarely reported, although some cases have been described in the...
The presence of DENV NS1 antigen (NS1Ag) has been associated with virus replication and viremia with the risk for development of DHF (12). The NS1Ag was detected in 4 of the fatal cases reported here, but because none fulfilled the World Health Organization criteria for DHF, they were considered to have been cases of severe dengue because the patients died (1) (Table 1). Detection of dengue IgM in CSF has shown a high specificity (97%) for diagnosing neurologic dengue and might be associated with the neurovirulence of DENV and its ability to cause encephalitis (13). Prior to the 1996 publication of findings
by Lum et al., involvement of the CNS in dengue infection had been thought to be secondary to vasculitis only; direct involvement of the brain by DENV was thought to be unlikely (14). The literature has reported detection of DENV in the brain and CSF by PCR and virus isolation and detection of NS1 and dengue IgM, providing strong evidence that DENV has neurovirulent properties (3,4,11,13–15). Meningeal lesions, neuronal damage, and evidence of DENV in CSF by RT-PCR and ELISA (NS1/ IgM) found in this study are consistent with CNS infection (Table 1).

The prevalence of CNS involvement in patients with dengue infection seems to vary with severity of dengue cases (11). Mortality rates also vary among studies; the reported rate of neurologic dengue was found to be 3.7% (2/54) in a study in Jamaica (7). In another study conducted in Vietnam, no patients with the neurologic form of dengue died (3); our study found a mortality rate of 1.9% (4/209). However, the proportional positivity was higher for the group of patients who died (4/27, 14.8%) than for those who recovered (4/182, 2.2%) (Table 2). The relative risk for identifying DENV-positive CSF in patients who died was 6.74× greater than that for patients who recovered (95% CI 1.79×–25.38×; p<0.0109). No patients had DHF or a concurrent condition to predict deterioration to death, thus suggesting that patients with meningitis/meningoencephalitis and DENV-positive CSF may have higher risk for development of severe forms of dengue infection.

The high risk for death among patients with dengue meningitis/meningoencephalitis in this study supports the need for increased surveillance. Dengue should be suspected in patients with neurologic manifestations in dengue-endemic areas, and appropriate treatment should be given to prevent death.

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Table 2. Risk for death among patients with meningitis/meningoencephalitis with DENV+ versus DENV– cerebrospinal fluid test results, Brazil, 2005–2008*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DENV+</th>
<th>DENV–</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (14.8)</td>
<td>23 (85.2)</td>
<td>27 (100)</td>
</tr>
<tr>
<td>Recovery</td>
<td>4 (2.2)</td>
<td>178 (97.8)</td>
<td>182 (100)</td>
</tr>
</tbody>
</table>

*Values are no. (%) patients. Relative risk 6.74 (95% CI 1.79–25.38); p<0.0109. DENV, dengue virus; –, negative; +, positive.

References


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