high even at lower titers, so patients with low titers should also be evaluated for scrub typhus. It is known that Weil-Felix test results may be negative during the early stages of the disease because agglutinating antibodies are detectable only during the second week of illness [7]. ELISA, however, when performed with 56 KDa antigen, has 90% sensitivity and specificity, allows detection of IgG and IgM antibodies, and provides positive results within 3–4 days after the onset of illness. However, the availability and the cost of ELISA are major problems in India.

This study report emphasizes the need for increased awareness of rickettsial infections in rural Southern India. Because of current circumstances in India, we suggest that the diagnosis of scrub typhus should be largely based on a high index of suspicion and careful clinical, laboratory, and epidemiological evaluation. Use of empiric treatment should also be considered to reduce the high mortality observed with the disease. Introduction of improved diagnostic methods would allow greater appreciation for the prevalence of the disease.

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Potential conflict of interest. All authors: No conflicts.

Rita Isaac,1 George M. Varghese,2 Elizabeth Mathai,3 Manjula J,4 and Inbakumar Joseph

Departments of 1Rural Unit for Health and Social affairs, 2Medicine, and 3Microbiology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

References


Positive Predictive Value of Epstein-Barr Virus DNA Detection in HIV-Related Primary Central Nervous System Lymphoma

Stu—Epstein-Barr virus (EBV) DNA PCR detection in CSF has been proven to be sensitive and specific for the diagnosis of HIV-related primary CNS lymphoma (PCNSL) [1–6]. In clinical practice, this test has been shown to be useful to achieve a “minimally invasive” diagnosis of PCNSL, in the presence of clinicoradiological findings and thallium 201 single-photon emission tomography findings consistent with PCNSL and no response to antitoxoplasmic treatment [7, 8].

In their recent article, Ivers et al. [9] reported the EBV DNA PCR results for CSF samples obtained from 26 HIV-infected patients with neurological problems. EBV DNA was found in samples from 7 of these 26 patients. Because only 2 of the patients received a diagnosis of PCNSL, the resulting low positive predictive value (PPV) led the authors to conclude that improved standardization may be required for the use of this test in clinical practice.

We would like to discuss 2 important issues that, in our opinion, have not been adequately addressed by Ivers et al. [9]. First, the diagnostic value of a test depends on a number of variables, including the diagnostic standard and the analytical sensitivity of the assay [10]. Nucleic acid amplification protocols may vary significantly between laboratories, because of the use of different nucleic acid extraction techniques, primers, and amplification technology. Assays with high analytical sensitivity may be associated with increased rates of false-positive results—although not necessarily with increased CSF lymphocyte counts—and, thus, with poor diagnostic specificity and a low PPV. It is unfortunate that methodological information was not provided by Ivers et al. [9], making it difficult to compare their results with the results obtained in previous studies.

Second, the positive and negative predictive values of a diagnostic test vary substantially, depending on the prevalence of

Table 1. Diagnoses given to 22 HIV-infected patients whose CSF samples were positive for Epstein-Barr virus DNA.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCNSL</td>
<td></td>
</tr>
<tr>
<td>Histologically proven*</td>
<td>5</td>
</tr>
<tr>
<td>Probable*</td>
<td>7</td>
</tr>
<tr>
<td>Possible*</td>
<td>5</td>
</tr>
<tr>
<td>Lymphomatous meningitis</td>
<td>2</td>
</tr>
<tr>
<td>Other CNS disorder†</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. PCNSL, primary CNS lymphoma.
* Determined by brain biopsy (3 cases) or at postmortem examination (2 cases).
† Defined by abnormalities in brain CT or MRI results that are consistent with PCNSL, lack of response to antitoxoplasmic treatment, and a positive result of thallium 201 single-photon emission tomography (SPECT) examination.
‡ Defined by abnormalities in CT or MRI results that are consistent with PCNSL, lack of response to antitoxoplasmic treatment, and either a negative result of SPECT examination or no performance of SPECT.
§ CNS tuberculosis, HIV encephalitis, or CNS toxoplasmosis (1 case each).
the disease addressed. Although details about the anti-HIV treatment received by patients in the study by Ivers et al. [9] were not given, all of the patients were observed after HAART became available in the Western world. Declines in the incidence and prevalence of PCNSL have been observed since HAART became available and have been more relevant than the declines in incidence and prevalence of other opportunistic CNS disorders [11]. To evaluate the effect of HAART on the PPV of our EBV DNA amplification assays [1, 3], we reviewed the findings of tests performed on CSF samples obtained from 491 HIV-infected patients with neurological problems who were admitted to our clinics between January 1998 and November 2002—in other words, during the same period studied by Ivers et al. [9]. EBV DNA was found in the CSF samples from 22 patients (4.5%) (table 1). When only histologically proven cases of PCNSL and “probable” cases of PCNSL were considered as cases of disease, the PPV was 55%. The PPV increased to 77% when “possible” cases of PCNSL were also included as cases of disease. According to the Bayes formula, the estimated PPV (based on diagnostic specificity and sensitivity of 98% and 97%, respectively [4], and a PCNSL prevalence of 4% [12]) was 67%. The estimated PPV was 90% during 1988–1995 (i.e., before availability of HAART), given a PCNSL prevalence of 16% [4].

Thus, even when the epidemiological changes related to HAART are considered, one would not expect PPVs as low as those reported by Ivers et al. [9]. In this regard, false-positive results due to poor specificity of the assay cannot be excluded. Nevertheless, we believe that it is important to recognize the possible influence of HAART on the clinical significance of diagnostic tests and to interpret the results accordingly.

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Paola Cinque,1 Antonella Cingolani,2 Simona Bossolasco,3 and Andrea Antinori1

1Clinic of Infectious Diseases, San Raffaele Scientific Institute, Milan, and 2Clinic of Infectious Diseases, Catholic University, and 3National Institute for Infectious Diseases “Lazzaro Spallanzani,” IRCCS, Rome, Italy

References


Reply to Cinque et al.

Sr.—We appreciate the letter from Cinque and colleagues [1] that emphasizes the variables that may have been at play in our evaluation of the operational characteristics of PCR for detection of Epstein-Barr virus (EBV) DNA in CSF samples to establish the diagnosis of primary CNS lymphoma in HIV-infected patients [2]. We reported the positive predictive value of EBV DNA PCR to be 29%. A number of factors should be considered when determining the value of any diagnostic test. These factors include the accuracy and precision of the test, the reference standard to which the test is compared, the receiver operating characteristics, and the prevalence of the disease in the population undergoing testing.

Cinque et al. [1] demonstrate a decline in the positive predictive value of EBV DNA PCR in their cohort during the same period as that considered in our study, and they attribute this decline to a decreased prevalence of disease. In our report, we noted that the prevalence of disease in our cohort was low, and we agree that this likely contributes to the low positive predictive value of the test in our study. The changing prevalence of disease over time is sometimes overlooked in the evaluation.

Reprints or correspondence: Dr. Paola Cinque, Clinic of Infectious Diseases, San Raffaele Hospital, Via Stamira d’Arconia, 29, 20127 Milan, Italy (paola.cinque@hsr.it).

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