Correspondence

Detection of Immunoglobulin M Antibody to Hepatitis A Virus in Patients without Acute Hepatitis A: The Usefulness of Specific Immunoglobulin G Avidity

Sir—The presence of IgM antibody to hepatitis A virus (HAV) is considered to be the gold standard for acute hepatitis A diagnosis. Castrodale et al. [1] report the presence of IgM antibody to HAV in persons who do not have illness meeting the case definition for acute hepatitis A in Alaska. This observation was previously published by the Centers for Disease Control and Prevention [2], along with similar cases reported from Connecticut and local health departments. Both reports suggest that test results positive for anti-HAV IgM are more likely to be false positive in older persons without typical symptoms of hepatitis. The authors recommend restricting serological testing to patients with clinical or epidemiological indication. However, because some cases of hepatitis A are asymptomatic, HAV IgM can be found without clinical symptoms or biological abnormalities [3]. In addition, authors underline that nontargeted anti-HAV IgM testing is widespread; when a clinician has to deal with a test result positive for anti-HAV IgM, the biologist cannot simply tell him, “you shouldn’t have tested IgM!”

Immune cells may become activated during viral infections or immune diseases; thus, IgM antibodies directed against specific viral antigens can be detected because of nonspecific polyclonal activation of memory cells resulting from a previous infection with an unrelated agent [4–6]. As members of the National Reference Centre for HAV (Villejuif, France) and because of the widespread use of nontargeted IgM testing, we often have to deal with such diagnosis problems. HAV infection can be confirmed by HAV RNA detection in blood samples and stool specimens, but its detection can be transitory [7].

Therefore, we developed an avidity test for HAV IgG antibodies [8]. Avidity testing has proved to be useful in a number of viral infections in immunocompetent patients; the normal humoral response includes maturation from low to high levels of avidity antibodies, which are maintained for life. We found that patients with a history of prior infection had avidity indexes of >70% (mean ± SD, 86% ± 10%), whereas the mean avidity index ± SD among patients with acute HAV infections was 36% ± 16% (P < .001). Of anti-HAV IgM–positive serum samples that were obtained from 60 patients and that were provided by a routine laboratory, 16 (27%) had an avidity index >70% and were not accompanied by HAV viremia. These 16 patients with immune reactivation were significantly older (mean years ± SD, 50 ± 16) than the other patients (mean years ± SD, 26 ± 14), a finding that is confirmed by Castrodale et al. [1]. This first study prompted establishment of the following interpretation rules: values ≤50% are interpreted as corresponding to a recent infection, and values >70% are interpreted as a past infection. Results ranging from 50% to 70% are to be interpreted as a gray zone of the avidity assay, because a protracted course of recent HAV infection is possible, as demonstrated by the HAV RNA positivity in some of these cases.

From January 2004 to August 2005, one hundred forty-three anti-HAV IgM–positive serum samples were prospectively analyzed for HAV viremia and anti-HAV IgG avidity (table 1). Patients with no viremia and an avidity index >70% comprise 23 of 143 patients, meaning that 16% of the anti-HAV IgM–positive serum samples sent to the Reference Centre corresponded to immune reactivations.

Five patients (4 men and 1 woman; mean age ± SD, 25.7 ± 16 years) had test results positive for viremia, despite having avidity indexes >70%. All 5 patients had protracted courses of HAV infection. In 2 of the patients, this protracted course could be linked to coinfection with HIV-1.

Testing of persons with no clinical symptoms of acute viral hepatitis certainly lowers the predictive value of the anti-HAV IgM test. However, many viral infections or immune diseases may cause hepatitis, and in some of these cases, anti-HAV IgM may be detected because of polyclonal activation of the immune system. The observation presented by Castrodale et al. [1] corresponds to a well-known diagnosis challenge in virology that can be solved by avidity assays.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

Table 1. Hepatitis A viremia and avidity results for 143 patients with anti–hepatitis A virus IgM.

<table>
<thead>
<tr>
<th>Avidity index</th>
<th>No. of patients with viremia</th>
<th>No. of patients without viremia</th>
<th>Age, mean years ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50%</td>
<td>88</td>
<td>8</td>
<td>27.2 ± 16.2</td>
</tr>
<tr>
<td>50%–70%</td>
<td>17</td>
<td>2</td>
<td>17.6 ± 13.6</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>5</td>
<td>23</td>
<td>48.3 ± 23.4</td>
</tr>
</tbody>
</table>

References


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Clinical Infectious Diseases 2006; 42:887–8

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Where Is the Humility for the Limitations of Research?

Str—We read with interest the article by Paz-Bailey et al. [1] regarding changes in the etiology of sexually transmitted infections (STIs) in Botswana between 1993 and 2000. Paz-Bailey and colleagues compare the prevalence of STIs in their own study from 2002 with data from an unpublished study from 1993. These analyses provide important information about STIs in sub-Saharan Africa and indicate a decrease in the prevalence of several bacterial STIs and trichomoniasis. However, Schmid et al. [2] use these findings rather indiscriminately in an editorial commentary.

In Botswana, there has been no systematic population-based STI surveillance, and the prevalence of specific organisms in the general population remains unknown. We appreciate the authors’ effort to use the limited existing data to discuss changes in the STI epidemiology. However, the editorial’s conclusions regarding the “evidence” of changes in STI prevalence are surprisingly certain and lack sound statistical evidence. For example, the authors claim, “The decreased prevalences of gonorrhea (68.1%), chlamydial infection (55.0%), and trichomoniasis (65.4%) in the cross-sectional surveys of persons practicing family planning between 1993 and 2002 were considerable” [2, p. 1313]. Using decimals to accurately describe changes in STI prevalences on the basis of data with obvious inherent uncertainties is both simplistic and misleading.

If we limit analysis to samples obtained from patients practicing family planning, the number studied is small (102 patients in 1993 and 277 patients in 2002). To assess time trends is difficult, and it is doubtful that the 2 populations studied are representative and comparable. The studies were conducted with different methodologies, by different researchers and assistants, in different types of clinics, in different towns, and at different times. Paz-Bailey and colleagues do an honest effort to adjust for different sensitivities and specificities in the diagnostic tests used. However, their calculations are based on the exact prevalences found; 95% CIs are absent in both the article and the commentary. Simple arithmetic shows that the prevalence of trichomoniasis in patients practicing family planning in 1993 was 16.7% (range, 9.5%–23.9%), overlapping with a prevalence of 6.8% (range, 3.5%–10.1%) in 2002. Researchers in the field know that there are more uncertainties to a study than the diagnostic tests. For Schmid and colleagues to conclude that the prevalence of trichomoniasis is decreased by 65.4% is a striking lack of humility regarding the limitations of research.

In the population of 1.7 million in Botswana, there were 180,000 registered STI-related outpatient consultations in 2000 [3]. Among these consultations, urethral and vaginal discharge and genital ulcer syndromes were the most common presentations, for which all patients are provided treatment with at least ceftriaxone plus penicillin or doxycycline. In addition, a high number of patients with positive rapid plasma reagin results receiving antenatal care have been treated with penicillin. It would be surprising if widespread treatment with multiple antibiotics for more than 1 decade did not lead to changes in the etiology of STI syndromes.

There is a need for epidemiological knowledge to develop adapted STI management methods and treatment regimens in the developing world. But to talk about evidence and to use decimal points when the existing information is based on limited existing data is to undervalue the research, the researchers, and the readers.

Acknowledgments


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Clinical Infectious Diseases 2006; 42:888–9

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