Should physicians go out of the way to differentiate between acute hepatitis B and acute exacerbation of chronic hepatitis B?

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Keywords: Hepatitis B; Chronic hepatitis; Antibodies

The article by Lall et al.1 published in Clinical and Molecular Hepatology fuels the discussion on differentiating laboratory markers between acute hepatitis B (AHB) and acute exacerbation of chronic hepatitis B (CHB-AE). This small retrospective study, which included 172 patients with AHB (n=89) or CHB-AE (n=83), had numerous strengths such as relevantly good follow-up, baseline assessment of IgM anti-HBc level, prothrombin time (PT), HBV DNA level, as well as qHBsAg and HBeAg values. The median cut-off ratio of IgM anti-HBc was significantly higher in AHB (30.44) than in CHB-AE (8.63) (P<0.01). The mean PT international normalized ratio (INR) was significantly greater in CHB-AE (1.88±1.24) compared to AHB (1.62±0.17). However, such findings were not new, and they must be taken with caution for several reasons.

In clinical practice, the similarities between AHB and CHB-AE in both clinical and laboratory context make it difficult to distinguish between the two clinical entities.2 Nevertheless, differentiating between the two entities is important, as they have different prognoses and therapeutic strategies.3,4 Most patients with AHB recover spontaneously, and treatment may be required only in a small number of patients who progress to fulminant hepatitis. On the other hand, patients with CHB-AE generally need antiviral therapy, since hepatic decompensation may be developed in patients with cirrhosis, especially.5,6 According to this study, a value of 20.5 for signal cut-off of IgM anti-HBc and 1.27 INR can be used to differentiate between AHB and CHB-AE. The evaluation of IgM anti-HBc levels seems to be an interesting strategy for differentiating the two clinical entities. Likewise, some reports have proposed that IgM anti-HBc levels should be reconsidered to define AHB.7,8 However, the diversity of reference values suggested from various studies is remarkable. These findings make it difficult to establish a standard reference value as the cut-off level.8-12 Unfortunately, as the author mentioned, IgM anti-HBc test was not a quantitative assay but a semiquantitative assay in this study. Therefore, the lack of prospective study about the standardization should physicians go out of the way to differentiate between acute hepatitis B and acute exacerbation of chronic hepatitis B?

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Abbreviations: AHB, acute hepatitis B; ALT, alanine aminotransferase; CHB-AE, acute exacerbation of chronic hepatitis B; HBV, hepatitis B virus; INR, international normalized ratio; PT, prothrombin time

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See Article on Page 187
of quantitative assays and any valid clinical threshold would make the use of this marker quite unreliable. Moreover, the presence of IgM anti-HBc, which is associated with AHB, is necessary but not sufficient to diagnose AHB. IgM anti-HBc can be detected during episodes of CHB-AE. It may be the result of inflammation and liver cell injury during flare-ups of hepatitis, with consequent release of high concentrations of the nucleocapsid protein. These proteins lead to the activation of pre-existing plasma cells which are released into the circulation, and eventually contribute to the secretion of IgM anti-HBc during acute exacerbation. It can also lead to a misdiagnosis of AHB.

In addition, PT is not effective in differentiating between two entities, due to its short half-life and data obtained only at a one-time point. In particular, the proportion of cirrhosis was more than 70% in CHB-AE. PT is affected by the presence of cirrhosis. Therefore, PT seems to have poor sensitivity and specificity to discriminate between two entities.

Among other diagnosis tools, the avidity index of IgG anti-HBc is defined as the strength of IgG binding to antigenic epitopes of hepatitis B virus (HBV). This increases as IgG matures. Therefore, the low avidity index of IgG anti-HBc is an indicator of AHB, and high avidity index refers to CHB-AE. Terkmani et al. reported that an avidity index $≤$3.4 was highly predictive of AHB. A quantitative and kinetics analysis of HBsAg titer is also worth applying. In AHB, HBsAg titer disappears much faster. Various possible serological studies have been performed. A combination study of HBV DNA, HBsAg, and IgM anti-HBc quantification sought to find the best strategy to discriminate between AHB and CHB-AE. Most of the results showed that AHB tends to show high IgM anti-HBc and low serum HBV DNA and HBsAg titer compared to CHB-AE. These findings originate from a vigorous immune response in acute viral infection.

So, do we need to go out of the way to differentiate between AHB and CHB-AE in the era of potent antiviral agents? The KASL clinical practice guidelines for the management of CHB proposed that nucleoside analogues can be initiated in patients with severe AHB (e.g., coagulopathy, severe jaundice, liver failure). Other patients with AHB can be free of the virus without antiviral therapy, and do not progress to chronic illness. In addition, Brahmania et al. reported that alanine aminotransferase (ALT) flares rarely lead to significant decompensation in CHB patients with minimal fibrosis. In this case, it might be prudent to monitor the patients, rather than treating them.

Likewise, in patients with HBeAg-positive or HBeAg-negative CHB, prompt antiviral therapy should be initiated in the case of acute exacerbation, with the elevation of ALT $≥$5–10 times the upper limit of normal, and signs of liver failure such as jaundice, PT prolongation, ascites, or hepatic encephalopathy. Therefore, the indication of antiviral therapy is similar between the two entities. There is no urgent need to establish the criteria and additional strategies for correct classification of AHB or CHB-AE in the era of highly potent and safe antiviral agents.

However, although the amount of clinical interest is low, it would help the physician to understand the natural course of HBV to find the gold standard for better defining and differentiating AHB from CHB-AE. Hopefully, the combination of new biomarkers, such as hepatitis B core-related antigen, HBV RNA, and immunologic markers (cytokine, chemokine profiles), will lead to differential diagnosis between AHB and CHB-AE.

**Conflicts of Interest**

The author has no conflicts of interests to disclose.

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