Obscure clinical implication of occult hepatitis B virus infection by perinatal transmission despite prophylaxis with hepatitis B vaccination and HBIG

Dear Editor:

We are much interested in the article by Shahmoradi *et al.* published in the *Journal of Hepatology* [1]. In the cross-sectional report, the authors investigated the serum samples of 75 children born to hepatitis B surface antigen (HBsAg)-positive mothers. Hepatitis B virus (HBV) DNA could be detected in 21 (28%) out of 75 children previously immunized by a dose of HBIG and three standard injections of hepatitis B vaccines. All were positive for antibody to hepatitis B surface antigen (anti-HBs), while only 5 (24%) were positive for antibody to hepatitis B core antigen (anti-HBc). There are some issues to be addressed.

Almost all babies who acquired HBV infection through perinatal transmission were born to mothers with positive hepatitis B e antigen (HBeAg) [2]. HBeAg can cross the placenta and help establish the infectivity [3]. HBeAg, viral load, and metabolic factors may entangle each other to foster the perinatal transmission [4]. However, this article did not elucidate the association between the risk of occult HBV infection and these three factors.

The relatively higher prevalence of occult HBV infection in this study is not consistent with our findings in Taiwan [5], where the prevalence of occult HBV infection was about 0.1% (3/2954) under the 25-year infant universal vaccination program coverage. One possible explanation is that the polymerase chain reaction used in this report was too sensitive to avoid false positive results [1]. Besides, the detection of HBV DNA in this study might be too early for anti-HBc levels to be measurable [6]. HBV genotyping is another concern. Occult HBV infection in Taiwan is mainly genotype C [5], rather than genotype D as in North of Iran [1]. We also do not know how long the positive HBV DNA status would persist in these cases.

We agree that mother-to-infant transmission is not completely blocked by immunoprophylaxis [7]. Although the emerging escape mutants caused some concern, less infectivity of G145R, recombinant vaccine use, and mutant loss with older age seem to decrease the mutant prevalence in an immunized population over time [8]. In addition to the risk of transmission by blood transfusion, individuals with occult HBV infection are at risk of reactivation when they receive chemotherapy or immunosuppressive therapy [6]. However, whether the clinical outcome of occult HBV infection is significant or not remains unclear since most people with occult HBV infection have a normal liver function.

In conclusion, a long-term follow-up study is mandatory to define the clinical significance of occult HBV infection caused by perinatal transmission if any.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Reply to: "Obscure clinical implication of occult hepatitis B virus infection by perinatal transmission despite prophylaxis with hepatitis B vaccination and HBIG"

To the Editor:

We highly appreciate the valuable comments addressed by Chiang and Ni about our study [1]. The authors highlighted two major points: firstly, the correlation between maternal metabolic and HBV status with the infected children and secondly, the high prevalence of OBI in our study.

Regarding the former, the files of all mothers and infected children showed that only 7 (9.3%) out of 75 mothers were HBeAg

positive. There was no correlation between maternal HBeAg and anti-HBe positive in terms of demography, serology, and viral kinetics (as mentioned in the Results section). Only one out of 76 children was HBsAg positive and was excluded from the study. The metabolic factors were not considered in our survey.

Regarding Ni's comments on the high prevalence of OBI in our study, reports by Alavian *et al.*, revealed the prevalence of HBV in Iran in the range of 1.7% and 2.5% in the general population [2]. However, the prevalence of occult HBV infection in children born to HBV positive mothers was high (28%) in our study.

Different studies have been carried out in South-East Asia after EPI (expanded program on immunization) on HBsAg positive children born to HBsAg positive mothers [3–5]. The surface protein mutants within or outside of "a" determinant were in association with a low frequency. In fact, in most of the studies on EPI, HBV DNA analysis has not been carried out on HBsAg negative cases to address the prevalence of OBI in this high-risk individuals.

On the other hand, in the Mu's study from Taiwan, authors found prevalence of OBI in vaccinated children (without such familial history) to be around 10.9%.

In our opinion, these contradictory results might be related to the technical differences and the levels of sensitivity of the tests (methods for extraction and amplification, etc.), the geographical distribution of HBV infection, and the genotypic nature of the virus (genotype D in Iran, and genotypes B and C from South-East Asia).

We believe that additional studies in large cohorts of patients with long-term clinical and laboratory follow-up are warranted to better understand the biological basis and significance of occult HBV infection and its consequences after HBV vaccination.

Conflict of interest

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