Correspondence

HBeAg negativity is not equal to the presence of pre core mutations in chronic hepatitis B patients

To the Editor

We read the article published by Atalay et al[1] on "Genotypes of hepatitis B virus in Central Anatolia, Kayseri, Turkey" with interest. They found the predominant genotype D in 110 chronic HBV patients by direct sequencing. They concluded that, firstly, the only genotype found in Turkey is type D; and secondly, the HBeAg negativity of those patients were related to the presence of pre core mutants. However, some issues arose from these conclusions.

First, although genotype D is the prominent genotype in the Middle East countries, however, the circulation of this genotype varies between countries located in this region. Turkey and Iran have shown a unique pattern of distribution, a majority (approximately 100%) of isolates exhibited genotype D. Whereas a different configuration could be seen in other countries in this region.[2-5] On the other hand, there are 2 reports that showed that other HBV genotypes than D and/or recombination patterns could be found in Turkey.[6,7] Further, it should bear in mind that the direct sequencing technique only on a single gene could not be able to find the recombinant forms as well as complex genomic types of HBV.

Second, the authors did not carry out sequencing on the pre core region, thus how they could relate this hypothesis to those patients? The 1896 stop codon mutant is often present in patients with chronic hepatitis, reported to be more common in Asia, Mediterranean basin, The Middle East, and Sub-Sahara. It is more common in genotypes B, C, D and E. The serum of patients with these mutations does not contain HBeAg. However, as shown in **Figure 1**, apart from pre core mutation, HBeAg negativity could be related to the formation of immune complexes, core promoter mutations and low levels of HBeAg in the serum (**Figure 1**). One of the common changes during seroconversion include variants of the basal core promoter (A1762T/G1764A) which may interfere with transcription of the HBeAg precursor, although the effect of such mutations on the synthesis and secretion of HBeAg is not complete, Laras et al[8] found the absence or low levels of pre-C mRNA transcripts in patients who harboured these double mutations.

Also, it should be noted that the production of free HBeAg in chronic HBV patients can and does coexist with anti-HBe production. Therefore, it appears that HBeAg to anti-HBe seroconversion results from

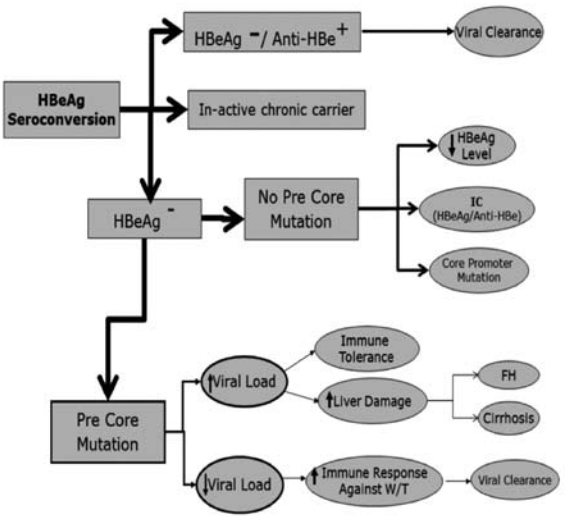

Figure 1 - A schematic presentation of HBeAg negativity in chronic carriers. FH - dulminant hepatitis, IC - immune complex, W/T - wild type

immune responses directed against HBeAg-expressing wild type virus, but this process does not necessarily involve the selection of eAg-minus HBV DNA variants

Taken together, the absence of HBeAg in the sera of HBV chronic carriers does not indicate the presence of pre core mutants entirely. Molecular technique should be applied for the diagnosis of these patients, as in the presence of such mutations, the therapeutic and control of those patients need special management.

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The aim of the study was to determine the genotypes of HBV in Kayseri and not to determine precore mutation of HBV isolates. Of course we do know that HBeAg negativity is not equal to the presence of precore mutation in chronic hepatitis B patients. On the other hand Turkey has a high prevalence of precore-mutant population of HBV[9] and the precore mutation can be detected in 20-95% of HBeAg negative patients in most

areas, but the prevelance is highest in the Mediterranean countries (>85%).[10] The G 1896 A precore mutation was more frequent in the group of patients with genotype D.[11] Because of these reasons in our study we want to represent that our HBV isolates may have precore mutation.We did not claim that our HBV isolates have precore mutation as we did not make sequencing of pre core region of HBV.

The relation between the G 1896 A precore mutation and the HBV genotypes is due to the base paring of the stem loop structure of the encapsidation sequence of pregenome RNA. Nucleotid 1896 (codon 28) present in descending part of the lower stem of pregome RNA pairs with nucleotide 1858 (codon 15) located in the ascending same stem. When the G 1896 A mutation is present, if nucleotide 1858 is composed of the thymine-nitrogen base, there is better stabilization of the lower stem, and the opposite occurs when cytosine is present at position 1858.[12] The geographic variations in prevelance of HBeAg negative chronic hepatitis B appear to be related to the predominant HBV genotype in the region. The G 1896 A stop codon mutant is associated with HBV genotypes B,D,E,C and F featuring a T at position 1858; in these genotypes the G to A mutation at nucleotide 1896 stabilizes the secondary structure of the encapsidation signal loop producing viable mutants. In contrast, in genotype A and some of genotype C and F strains, the presence of C at nucleotide 1858 significantly diminishes the possibility of selection of G 1896 A mutant, because of lower replication fitness.[13]

As a result of these, molecular technique should be applied for the diagnosis of precore mutation of HBV isolates.

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