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Editorial

HBsAg carriers with normal ALT levels: Healthy carriers or true patients?

Claudio Puoti

It is well documented that many HBsAg-positive / HBeAg-negative patients show normal alanine aminotransferase (ALT) levels. However, two different scenarios have been proven to exist: inactive Hepatitis B Virus (HBV) carriers (previously defined as "healthy" HBV carriers) and patients with chronic hepatitis B (CHB) with transient virological and biochemical remission. These subsets of patients share HBsAg positivity and normal ALT levels; however, progression of disease, outcome, HBV DNA levels, severity of liver damage, requirement for liver biopsy and antiviral treatment significantly differ between the two patient populations.

Thus, among HBsAg-positive / HBeAg-negative subjects with normal liver biochemistry, it is important and sometimes difficult to distinguish the '*true inactive HBV carriers*' from patients with '*active CHB*' in whom phases of spontaneous remission have occurred. The former have a good prognosis with a low risk of complications, while the latter patient population have active liver disease with a high risk of progression to liver cirrhosis and/or hepatocellular carcinoma (HCC). Therefore, prolonged biochemical and virological follow-up are mandatory for diagnosis and decision to treat.

The term '*chronic hepatitis B*' refers to a chronic necroinflammatory disease of the liver caused by persistent HBV infection [1]. The term 'necroinflammatory' describes the presence of death of periportal hepatocytes (periportal necrosis) with or without disruption of the limiting plate by inflammatory cells, intralobular necrosis, portal or intralobular inflammation, and formation of bridges between vascular structures (the so-called bridging necrosis). Chronic hepatitis B can be subdivided into HbeAg positive and HBeAg-negative chronic hepatitis B [1,2]. These two forms may have different natural histories and different response rates to antiviral treatment, although both may progress to more severe liver damage [3], such as, liver cirrhosis [4] or HCC [5].

The second subset is called the *'inactive HBsAg carrier state'*. It means a persistent HBV infection of the liver but without continual significant necroinflammatory disease. It is characterized by very low or undetectable serum HBV DNA levels and normal serum aminotransferases [1]. It has been shown that histologically significant liver damage is rare in these patients, particularly when HBV DNA is lower than 2000 IU/ml, and thus a liver biopsy is not indicated in these subjects [4]. Even among HBeAg-negative carriers with serum HBV DNA between 2000 and 20,000 IU/ml, histologically significant liver disease is also rare [6]. Thus, these subjects should be followed up closely, but biopsy and treatment are not currently indicated.

As mentioned above, it is sometimes difficult to distinguish true inactive HBV carriers from patients with active HBeAg-negative CHB in whom phases of spontaneous remission may have occurred [1]. The former patients have a good prognosis with a very low risk of complications, while the latter have active liver disease with a high risk of progression to advanced hepatic fibrosis, cirrhosis and subsequent complications such as decompensated cirrhosis and HCC [3-6]. Thus, a minimum follow-up of 1 year with ALT levels every 3–4 months and periodical measurements of serum HBV DNA levels are required before classifying a patient as an inactive HBV carrier [1]. ALT levels should remain consistently within the normal range, and HBV DNA should be below 2000 IU/ml [7]. Thereafter, the inactive HBV carrier with undetectable or very low HBV DNA levels should be followed up with ALT determinations every 6 months after the first year and periodical measurement of HBV DNA levels [6] for the rest of their lifetime. This follow-up policy usually allows detection of fluctuations of activity in patients with true HBeAg-negative CHB [8].

It is important to underline that some inactive carriers may have HBV DNA levels greater than 2000 IU/ml (usually below 20,000 IU/ml), despite their persistently normal ALT levels [1,6,9]. In these carriers the follow-up should be much more condensed, with ALT determinations every 3 months and HBV DNA measurements every 6–12 months for at least 3 years [1]. After these 3 years, these patients should be followed up for life like all inactive chronic HBV carriers [6]. After all, the inactive HBV carrier state confers a favourable long-term outcome with a very low risk of cirrhosis or HCC in the majority of patients [1,10,11]. Patients with high baseline viremia levels have higher risk of subsequent reactivation. A liver biopsy should be recommended if ALT levels become abnormal and HBV DNA increases above 20,000 IU/ml. Non-invasive evaluation of liver fibrosis [12] may be useful, although these non-invasive tools, such as transient elastography, need further evaluation [6].

HBsAg clearance and seroconversion to anti-HBs antibody may occur spontaneously only in 1–3% of cases per year, usually after several years with persistently undetectable HBV DNA [7].

On the other hand, progression to HBeAg-negative CHB may also occur [10].

Although the optimal definition of persistently normal ALT (PNALT) levels has not been established, the fluctuating nature of chronic HBV infection reasonably justifies serial ALT determinations. These should be done with a minimum of four to five tests 3–4 months apart within the first year of presentation, before determining whether an HBeAg-negative patient truly has PNALT. An initial follow-up of at least 1 year is supported by the finding of mild histological lesions in HBeAg-negative patients with true PNALT during the first year [6]. The risk of developing abnormal ALT levels in HBeAg-negative patients with a normal baseline ALT have been reported to be higher during the first year (15–20%) and decline after 3 years of follow-up, therefore frequent monitoring during the first 1–3 years is critical [6,10].

Antiviral treatment of inactive HBsAg subjects is not indicated [1]. Patients should be considered for treatment only when they have HBV DNA levels above 2000 IU/ml, serum ALT levels above the upper limit of normal and severity of liver damage assessed by liver biopsy showing moderate to severe active necroinflammation and/or at least moderate fibrosis[1,2].

Competing Interests
None declared
Author Details
CLAUDIO PUOTI, MD, Chief, Dept. of Internal Medicine and Liver Unit, Marino General Hospital, Marino, Rome, Italy
CORRESSPONDENCE: CLAUDIO PUOTI, Chief, Dept. of Internal Medicine and Liver Unit, Marino General Hospital, Viale XXIV Maggio, 00047, Marino, Rome, Italy.
Email: puoti@epatologia.org

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