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CLINICAL CHALLENGE

Chronic hepatitis B and fatty liver: Issues in clinical management

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Summary With an increasing incidence of non-alcoholic fatty livers, the existence of concomitant hepatitis B and fatty liver is becoming more common in clinical practice. In clinical practice, the concomitant existence of hepatitis B and fatty livers raises practical issues in clinical management. It becomes more difficult for the clinician to decide on the mode of treatment in the case of elevated Alanine aminotransferase (ALT) and in deciding potential causes, whether they are related to chronic hepatitis B or to non-alcoholic steatohepatitis (NASH). With evolving changes in the practice and knowledge of non-alcoholic fatty liver disease and chronic hepatitis B, clinical judgment on the predominant disease becomes essential for their coexistence. This short review is aimed at reviewing the evidence available on the frequency of the two diseases existing concomitantly, possible ways of differentiating the two, the prognosis, outcomes of treatment and a possible common pathway.

Introduction

Hepatitis B is prevalent in almost all countries of the world, with a higher prevalence in countries with a low standard of living [1,2]. The prevalence of hepatitis B is approximately 0.5% in the United States and 10% in African countries. The prevalence of hepatitis B has decreased with the increase of vaccinations [3]; on the contrary, the prevalence of non-alcoholic fatty liver disease (NAFLD) has increased in recent decades [4], and the prevalence of NAFLD varies between 20 to 51%, depending on the modality used for diagnosis and the study population [4—6].

A high prevalence of NAFLD has resulted in the increased coexistence of NAFLD with hepatitis B patients in the endemic population.

Chronic hepatitis B is defined as the persistence of HBsAg (surface antigen) in the serum for more than six months. Fatty liver or non-alcoholic fatty liver disease (NAFLD) is defined as the presence of intrahepatic steatosis; other causes of steatosis have been excluded. Ultrasonography of

Abbreviations: ALT, Alanine aminotransferase; CHB, chronic hepatitis B; AASLD, American association for study of liver disease; APASL, Asia-pacific association for study of liver; EASL, European association for study of liver; HCC, hepatocellular carcinoma; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; miRNA, microRNA; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

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the liver is commonly used for diagnosing fatty liver. Ultrasonography can detect fatty liver by increased echogenicity of more than 20% fat in the liver with an accuracy of 90% [7]. Non-alcoholic steatohepatitis (NASH) is defined as the presence of inflammation in association with fatty liver.

A dilemma exists on the coexistence of the two entities and subsequent clinical management. This review addresses the prevalence, patient outcomes and possible ways to differentiate the predominant disease when the two coexist.

Prevalence of NAFLD and concomitant hepatitis B

Irrespective of the geographical region, fatty livers are increasing in prevalence. As reflected by liver transplant recipients, more patients with fatty liver disease are undergoing transplantation than those with hepatitis B [8,9]. The concomitant existence of the two disease entities is interesting; however, the determining the prevalence of fatty livers has been limited by the methodology used for diagnosing a fatty liver.

In a study of the Hong Kong population, 891 chronic hepatitis B patients were compared with 922 controls. The prevalence of NAFLD in patients with hepatitis B was 13.5% compared to the controls, where the prevalence was 28.3%. In this study, the diagnosis of NAFLD was based on MRI assessment of intrahepatic triglycerides [10].

In the Western population, Bondini et al. [11] found that biopsy-proven NAFLD was observed in 19% of the patients with chronic hepatitis B. In this study, 64 patients had liver biopsy data and the predominant population was of Asian descent. In a study by Thomopoulus et al., the prevalence of biopsy-proven NAFLD was 19% in a cohort of 234 patients with chronic hepatitis B [12].

Taking these studies into consideration, it can be reasonably concluded that the prevalence of a fatty liver in hepatitis B patients is approximately one in five, which is similar to the general population.

Raised alanine aminotransferase in patients with hepatitis B and fatty liver

A raised ALT level is often observed in patients with hepatitis B in clinical practice, however both hepatitis B and NASH can cause a raised ALT level.

Treating patients with hepatitis B where the indication does not exist carries the risk of inducing viral resistance and increases the cost of treatment. Yet, under-treating hepatitis B when there is inflammation in the liver carries the risk of progressive liver fibrosis and inflammation.

In a study of patients with both a fatty liver and hepatitis B by Spradling, 1090 patients were followed-up over a period of 7.7 years [13]. They found that a raised ALT level was attributed to the fatty liver in 27% of patients, and in patients with a low HBV DNA the most common causes for a raised ALT level was fatty liver or alcohol consumption.

Similarly, in a study by Demir K et al., they found that NASH was the cause for a raised ALT level in patients that were HBeAg negative, and had low HBV DNA chronic hepatitis B, where low HBV DNA was defined as < 2000 IU/mL [14].

The American association for the study of liver disease (AASLD), and the Asia pacific association for the study of the liver (APASL) guidelines recommend treatment of hepatitis if the ALT is more than two times the upper limit of normal, while the European association for the study of the liver (EASL) recommends treatment if the ALT is more than the upper limit of normal.

Hepatitis B HBeAg negative treatment should be considered if the HBV DNA is more than 2000 IU/mL, and more than 20,000 IU/mL if HBeAg positive [15—17]. However, the guidelines do not mention the clinical condition when the raised ALT can be due to other causes, or in the case of concomitant diseases. The guidelines only provide guidance to clinicians when the raised ALT is attributed to hepatitis B.

In patients with both a fatty liver and hepatitis B the clinical assessment is important for finding the cause of a raised ALT level. The cause can be a fatty liver in patients with low HBV DNA.

Fatty liver in hepatitis B and its clinical outcomes

Many cross-sectional studies have been conducted to examine the impact of the both hepatitis B and fatty liver on the liver and the clinical impact.

In his study from Taiwan, Lin et al. reported hepatitis B and fatty liver had a synergistic effect. Fatty liver was defined based on an ultrasound in a cohort of 5406 patients and liver disease was defined by an ALT more than 40 IU/mL. This was a cross-sectional, observational study [18]. However, in a larger study of a general population of 33,439 patients from Taiwan in 2013, where hepatitis B was observed in 3,642 patients, the authors concluded an inverse relation between the hepatitis B virus and fatty liver disease. In this study, there was a smaller prevalence of hepatitis B (38.9%) patients than those without hepatitis B (44.5%) in patients with a fatty liver ($P < 0.001$), and patients with a fatty liver had a smaller prevalence of hepatitis B at 11.9% versus 10.7% ($P < 0.001$). However, the ALT was higher in the fatty liver group.

Similar findings were noted by Wong et al. in a study of 1013 patients in a Hong Kong population, where the presence of hepatitis B was associated with a smaller prevalence of fatty liver [9].

In a study by Bondini et al. on biopsy-proven NASH in 64 patients, they found that metabolic factors were related to superimposed NASH in patients with chronic hepatitis B [11].

In a meta-analysis by Machado et al. of 17 studies and 4100 patients with hepatitis B and hepatic steatosis [19], they came to the conclusion that the presence of hepatic steatosis was associated with metabolic factors and had no association with transaminase levels.

Based on the conclusion of the meta-analysis, it can be reasonably concluded that metabolic factors determine the hepatic steatosis in patients with concomitant hepatitis B.

Differentiating between chronic hepatitis B and NASH

When the ALT level is increased for a period of time in patients with hepatitis B, medications need to be started