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Retrospective analysis of hepatitis B virus chronic infection in 247 patients: clinical stages, response to treatment and poor prognostic factors

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ABSTRACT

Background: Chronic hepatitis B is a major cause of cirrhosis, and the natural history of the disease has several clinical stages that should be thoroughly understood for the implementation of proper treatment. Nonetheless, curing the disease with antiviral treatment remains a challenge.

Aims: To describe the clinical course, response to treatment, and poor prognostic factors in 247 hepatitis B virus chronic infection patients treated in a tertiary hospital in Brazil.

Methods: This was a retrospective and observational study, by analyzing the medical records of HBV infected patients between January 2000 and January 2015.

Results: Most patients were male (67.2%) and 74.1% were HBeAg negative. Approximately 41% had cirrhosis and 8.5% were hepatitis C virus coinfected. The viral load was negative after two years on lamivudine, entecavir and tenofovir in 86%, 90.6%, and 92.9% of the patients, respectively. The five-year resistance rates for lamivudine, adefovir, entecavir, and tenofovir were 57.5%, 51.8%, 1.9%, and 0%, respectively. The overall seroconversion rates were 31.2% for HBeAg and 9.4% for HBsAg. Hepatocellular carcinoma was diagnosed in 9.7% of patients, liver transplantation was performed in 9.7%, and overall mortality was 10.5%. Elevations of serum alanine aminotransferase ($p = 0.0059$) and viral load ($p < 0.0001$) were associated with progression to liver cirrhosis. High viral load was associated with progression to hepatocellular carcinoma ($p < 0.0001$). Significant risk factors associated with death were elevated alanine aminotransferase ($p = 0.0039$), liver cirrhosis ($p < 0.0001$), high viral load ($p = 0.007$), and hepatocellular carcinoma ($p = 0.0008$). HBeAg positive status was not associated with worse outcomes, and treatment may have been largely responsible.

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Conclusions: Elevations of viral load and serum alanine aminotransferase may select patients with worse prognosis, especially progression to cirrhosis and hepatocellular carcinoma, which were strongly association with death.

Introduction

Hepatitis B virus (HBV) affects over 240 million people worldwide, with 780,000 deaths each year from complications of the disease.[1] In Brazil, 7.4% of the population have been exposed to the virus and about 0.37% have chronic disease.[2]

The stages of the disease must be understood to define the need for treatment. The natural prognosis of the infection depends on several aspects, such as geographic location, age at primary infection, viral genotype, host immune system, association with alcoholism, steatosis, and coinfections such as hepatitis C, hepatitis D and HIV.[3,4]

The first stage of the infection is the immunotolerant phase, in which individuals are positive for HBeAg, the antigen associated with viral replication, and there is absence of hepatocellular aggression. Subsequently, the patient experiences a reactive phase, during which inflammation is present and liver enzymes are elevated in attempt to eliminate the HBe antigen. Anti-HBe antibody appears and the patient enters the dormant stage of the disease, when viral replication is minimal or absent. At this point, HBsAg can be negative and anti-HBs positive, the patient can progress to healing; or the virus may become active again, even in the absence of HBeAg, setting the stage of HBeAg negative chronic hepatitis B (CHB).[3,5]

The disease is slowly progressive. The virus binds to hepatocyte DNA, causing inflammation and fibrosis, which may progress to liver cirrhosis (LC) and its complications, especially hepatocellular carcinoma (HCC), a major cause of death in this group of patients.[6] Treatment slows the progression of the disease, decreasing morbidity and mortality. However, despite advances in antiviral therapy, a cure for hepatitis B remains challenging, since the drugs can eliminate the virus from the blood, but not from the hepatocytes.[7,8]

Few publications have detailed all factors associated with the disease in a population. The objectives of this study were to describe (1) the clinical and laboratory features of chronic hepatitis B virus infection in patients seen in a tertiary hospital, (2) the response to treatment and development of virological resistance, and (3) to analyze the factors that influence progression to LC, HCC, and death.

Methods

This was an observational and retrospective study conducted by reviewing the medical records of patients treated at the Liver Unit of the Hospital de Clínicas-UNICAMP between January 2000 and January 2015. This study was approved by the local ethics committee (21589513.7.0000.5404).

Inclusion criteria: HBsAg positive patients aged between 16 and 81 years, who were followed at the clinic for more than six months. **Exclusion criteria:** patients with incomplete data related to the studied variables and HIV coinfected patients, as they are not treated in our center.

Clinical and laboratory classification

The parameters analyzed were gender, hepatitis B virus serology, liver histology, alanine aminotransferase (ALT), hepatitis B viral load (VL), presence of nephropathy, and coinfection with hepatitis C virus (HCV). Poor prognosis factors were progression to LC, HCC, and death.

Patients were classified into two main groups: HBeAg positive (HBeAg+) and negative (HBeAg−), according to the initial HBeAg status.

In addition, patients were classified according to the developmental stages of hepatitis B virus chronic infection. HBeAg+ patients with repeatedly normal liver enzymes were classified as immunotolerant. HBeAg+ patients with abnormal liver enzymes and/or evidence of significant histological changes were classified as having HBeAg+ CHB. HBeAg− patients with VL less than 2000 IU/mL or without evidence of significant histological changes were classified as inactive carriers. HBeAg− patients with VL greater than 2000 IU/mL or with evidence of significant histological changes were classified as having HBeAg− CHB. Histological changes were considered significant in patients who had inflammatory activity $\geq$2 and/or fibrosis $\geq$2 in the METAVIR classification.[9]

Liver biopsy was performed when necessary for a definitive diagnosis or to assess indications for treatment. All biopsies were performed with a Tru-Cut 14G needle guided by ultrasound. The material was fixed in 10% formaldehyde and analyzed by an experienced pathologist using the METAVIR classification.[9]

The laboratory kits of serology, ALT dosage, and VL varied during the study period. The limits of detection and normal values were established according to the kit used by our laboratory.

LC was diagnosed according to the following criteria: liver histology showing grade 4 fibrosis, according to the METAVIR classification,[9] or liver ultrasonography suggestive of cirrhosis, as well as evidence of portal hypertension on endoscopy or Doppler. Abdominal ultrasound examinations were performed with a Powervision 6000 SSA-370A C8612580 series (Toshiba) apparatus, using a 5 MHz linear convex transducer. HCC diagnosis was established by biopsy or through three-phase imaging examination, with increased uptake by affected tissue in the arterial phase and rapid contrast wash-out in the portal and equilibrium phases. Patients were