Long Term Follow-Up of a Large Cohort of Inactive HBsAg (+)/HBeAg (-)/ anti-HBe (+) Carriers in Greece

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Abstract

Aim. To investigate the long-term outcome and the risk of progression to chronic hepatitis B in inactive hepatitis B surface antigen carriers. Material and methods. A total of 307 HBsAg (+)/HBeAg (-)/antiHBe (+) subjects with initially normal alanine aminotransferase (ALT) levels and undetectable/low serum HBVDNA with hybridization assay and later with PCR (<105 copies/ml), were followed-up every 6 months for a period of 3 to 21 years (7.45±3.75 years). Results. 234 out of the 307 HBsAg (+) patients (76.2%) had persistently normal ALT and undetectable/low (< 105 copies/ml) HBVDNA during follow-up. In 73 patients (23.8%), a reactivation of the disease with elevated ALT and positive HBVDNA (>105 copies/ml) was recorded during the follow up. Thirty-five out of 73 patients underwent liver biopsy, while 22 of them received treatment. Twenty-four patients (7.8%) lost HBsAg after a mean of 7.4±3.6 years. Regarding the complications of chronic hepatitis B, only one patient developed compensated cirrhosis and no one developed HCC. Conclusions. Our results show that in almost 24% of inactive chronic hepatitis B carriers reactivation of the disease may occur even after many years. However the risk of liver-related complications is very low in these subjects.

Key words
Chronic hepatitis B – HBVDNA - inactive carrier

Introduction

Hepatitis B virus (HBV) infects more than 350 million people worldwide and is a leading cause of chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma (HCC) (1-2).

Chronic HBV infection is a dynamic process with replicative and non-replicative phases (3-4). The presence of circulating HBeAg and high levels of serum HBVDNA but only minimal inflammation in the liver and normal ALT levels identifies the early immunotolerant phase of active virus replication. This phase is followed by an active phase of inflammation - the immune-clearance phase - which is associated with a marked decrease in serum levels of HBVDNA and increased ALT levels, reflecting the effort of the host to eliminate the virus. The late non-replicative phase follows seroconversion from HBeAg to anti-HBe, accompanied by cessation of HBV replication and biochemical and histological remission of liver disease. This phase of chronic HBV infection may last for a lifetime and is also referred to as the inactive HBsAg carrier state. Inactive carriers usually do not have progressive disease, do not develop complications and have a good long-term prognosis. However there can be exceptions if they develop reactivation of the disease. This can occur spontaneously or can be induced by immunosuppression. During reactivation, marked ALT increases and rising of HBV DNA levels are noted, which occasionally can lead to severe liver disease (3-8).

The natural history of the chronic carrier state is not completely understood. The aim of the present study was to investigate the long-term outcome and the risk of progression to chronic hepatitis in inactive HBsAg(+)/HBeAg (-) carriers.

Material and methods

We retrospectively analyzed 307 Caucasian subjects (193 men, 114 women, mean age 45.65±11.37 years) fulfilling the criteria for an inactive HBsAg (+) carrier state who were referred for evaluation to our department between January 1980 and December 1998. The inclusion criteria were:
- the presence in serum of HBsAg for > 6 months and HBeAg-negative /anti-HBe-positive;
- serum HBVDNA undetectable with hybridization assay or <105 copies/ml with polymerase chain reaction (PCR) assay;
- persistently normal serum ALT/AST levels, measured three times within a 12 month period;
- anti-δ(-), anti-HCV (-) HIV (-);
- exclusion of other causes of chronic liver disease, including alcohol abuse.

The study was approved by the Ethics Committee of Hippokration General Hospital of Thessaloniki.

At initial evaluation and during follow-up the following tests were carried out:
- thorough medical history and physical examination;
- laboratory tests every 6 months: complete blood counts with platelets, serum ALT, AST, γ-GT, bilirubin, albumin, alkaline phosphatase and prothrombin time;
- screening for HCC - α-feto protein and liver ultrasound every 12 months;
- markers of HBV infection, including HBsAg, anti-HBs, HBeAg, anti-Hbe, anti-HBc determined in the serum of all patients every 12 months, using standard procedures (ABBOTT assay kits);
- serum HBVDNA quantification performed by the hybridization technique that uses radioisotopic systems (Genostics Abbott Laboratories, Chicago, IL) up to 1996 and thereafter in all patients by PCR (AmpliCor HBV MONITOR, Roche Diagnostics Systems) every 12 months and every 6 months in case of elevated ALT levels. The sensitivity of the hybridization technique was 5x10^4 copies/ml, while the sensitivity of the PCR assay was 400 copies/ml;
- anti-δ and anti-HCV assessed again during acute flares of hepatitis, so that these flares could be differentiated from superinfection with other hepatotropic viruses;
- a percutaneous liver biopsy was recommended to patients with disease reactivation. Liver histology was graded and staged according to current international recommendations (9-10).

Results

In the majority of subjects (243/307, 79.15%) the possible source of HBV infection was unknown, 76 (24.75%) reported a probable intrafamiliar route of transmission and the remaining 3 (0.97%) reported transmission through blood transfusion.

The duration of follow-up was 7.45±3.75 years (3-21 years). At the end of the follow-up patients were divided in two groups according to ALT and HBVDNA levels:
- in 234 out of the 307 patients (76.2 %) included in the study (136 men - 98 women, mean age 43.5±11.21 years), who were followed-up for a mean of 7.25±3.32 years, serum HBVDNA was undetectable (210 patients), or detectable in low titers (<10^5 copies/ml - in 24 patients). Liver function tests remained normal throughout the follow-up period. In some cases minor elevations in ALT levels were observed, which however were <1.5 x ULN (Fig.1).
- the remaining 73 patients (23.8 %) (57 men - 16 women, mean age 44.8±10.87 years), who were followed-up for a mean 8.12±3.96 years, exhibited a reactivation of the disease 7.25±3.32 years after their initial evaluation, with persistently elevated serum ALT levels (> x 1.5 ULN) and a progressive increase in serum HBVDNA levels >10^5 copies/ml (median serum HBVDNA level 1.2 X 10^6 copies/ml) (Fig.2).

Concerning possible predictors for disease progression to chronic hepatitis, it was found that age was not a predictor of progression (p=0.7), whereas male sex was significantly correlated with disease reactivation (p<0.001).

Thirty-five of the 73 subjects with disease reactivation underwent liver biopsy: liver histologic lesions were minimal (Hepatitis Activity Index, HAI 1-3) in two patients, mild (HAI 4-8) in 23 patients, moderate (HAI 9-12) in four patients and severe (HAI 13-18) in the remaining 6 subjects. The majority of the patients (25 out of 35) had a fibrosis score 2-3, 8 had fibrosis 0-1, one had a fibrosis score 4 and one patient had cirrhosis.

Antiviral treatment was recommended in all patients of this group who had a HAI>4, however finally only 22 agreed to undergo therapy.

Anti-δ and anti-HCV, assessed during flares of hepatitis, were negative in all cases. Furthermore, no other cause for ALT elevation, such as drug or alcohol use, was detected.

All patients remained HBeAg (-)/anti-HBe (+) throughout the follow-up period.
Inactive HBsAg (+)/ HBeAg (-)/ anti-HBe (+) carriers

Regarding the complications of chronic hepatitis B, only one patient developed compensated cirrhosis and no one developed HCC.

Twenty-four out of the 307 HBV carriers of the original cohort (7.81%) lost HBsAg after 3 to 17 years of follow-up (mean 7.4±3.6 yrs), two of them after interferon treatment. In another two of these patients HBV DNA remained positive in low titers despite the loss of HBsAg.

Discussion

There has been not much data in the literature on the natural course of chronic hepatitis B virus infection in asymptomatic carriers. In the present study we investigated the long-term outcome and the risk of liver-related complications in a large cohort of inactive HBV carriers, who were followed-up in our department for a long period of time.

Our data indicate that inactive HBV carriers have in most cases a good prognosis. In the present study HBV DNA remained undetectable or below 10^5 copies/ml during follow-up in 76.2% of the subjects. This high percentage of HBV DNA negativity could be explained by the fact that a hybridization technique with low sensitivity (5x10^4 copies/ml) was used during years 1980-1996. However even the “undetectable” HBV DNA was in all cases not higher than 5x10^4 copies/ml, which meets the criteria of the inactive HBV carrier. Exacerbation of the disease - with persistently elevated ALT levels and HBV DNA >10^5 copies/ml - was observed in 23.8% of the subjects included in the study, after a long period of follow-up (7.25±3.32 years). It has been reported (17) that as many as 20-30% of acute exacerbations occurring during the inactive HBsAg carrier state may be caused by superinfection with other hepatotropic viruses. However in our study superinfection with HDV or HCV was not detected in any of the subjects with disease reactivation.

Liver histologic lesions were mild in the majority of subjects with disease reactivation who underwent liver biopsy.

Interferon treatment was highly recommended in all patients with disease reactivation - with the exception of those with minimal histological lesions, but finally only 22 of them agreed to receive treatment.

Concerning progression of the disease, only one patient developed compensated cirrhosis, while no one developed hepatocellular carcinoma.

Our findings are in line with most of the data available in the literature.

Villeneuve et al (13) studied the outcomes of 317 asymptomatic HBsAg (+) carriers from the Montreal area after 16 years of follow-up. The results of their study indicated that the majority of carriers remained asymptomatic and that the occurrence of hepatitis B related deaths and HCC was low. In addition the annual negativation rate for HBsAg was 0.7%.

In a recently published study, Martinot-Peignoux et al (12) investigated serum hepatitis B virus DNA levels and liver histology in inactive HBsAg carriers. They showed that when serum HBV DNA is measured with a sensitive PCR method, 98% of the carriers have levels below 10^5 HBV copies/ml. During follow-up (for 3.2±2.6 years) serum HBV DNA titers remained unchanged and serum ALT levels remained within the limit of normal in 96% of the patients. These results support the recommendations of the National Institutes of Health research workshop (14) defining a level of HBV DNA below 10^5 copies/ml to classify inactive HBsAg carriers.

Manno et al (15) studied the natural history of 296 asymptomatic HBV carriers over a very long period of time and concluded that Italian inactive HBsAg carriers did not develop clinically significant liver disease, hepatocellular cancer or other liver-related morbidity or mortality at a higher rate than uninfected controls.

Other studies (17-18) also showed that the vast majority of inactive HBsAg carriers have sustained biochemical remission and very low risk of cirrhosis or HCC. In addition, in longitudinal studies approximately 20% of inactive HBsAg carriers may undergo spontaneous reactivation of hepatitis B with reappearance of biochemical activity and high levels of HBV DNA (17-19).

Conclusion

One can not ignore the fact that reactivation of the disease may occur even after many years and therefore HBV carriers should be followed-up for life, although cirrhosis and hepatocellular carcinoma are extremely rare in this group of patients.

References