INCIDENCE AND CLINICAL SIGNIFICANCE OF HBe ANTIGEN AND ANTIBODY IN HBsAg-POSITIVE VARIOUS LIVER DISEASES


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Summary

The HBeAg was detected in 5 of 24 patients with acute type B hepatitis (20.8%), 33 of 95 with chronic hepatitis (34.7%), 6 of 33 with liver cirrhosis (18.2%), and 3 of 39 with hepatocellular carcinoma (7.7%). On the other hand, anti-HBe was found in 4.2% of acute hepatitis, 18.9% of chronic hepatitis, 9.1% of liver cirrhosis, and 12.8% of hepatocellular carcinoma.

We found that an early detection of HBeAg in patients with acute hepatitis is of no prognostic value, but its persistence may provide the earliest evidence of potential chronicity. In chronic liver diseases, HBeAg-positive cases showed remarkable fluctuations of serum transaminase levels, severe histological changes and poor responses to treatment. Many of the HBeAg-positive patients lost their initial positivity of HBeAg within six months or one year and in some cases seroconverted to anti-HBe after acute exacerbation. Follow-up study more than several years revealed that the presence of anti-HBe reflects an inactive stage and a more favorable outcome, whereas persistence of HBeAg may provide an active and continuing hepatocellular damage.

From these results, we believed that serial measurements of HBeAg/anti-HBe system are useful prognostic marker in patients with HBsAg-positive liver disease.

Key Words: HBeAg and anti-HBe, HBsAg-positive liver disease, hepatitis B virus (HBV), asymptomatic carrier.

Introduction

An e-antigen/antibody system (HBeAg and anti-HBe), first described by Magnius and Espmark in 1972, is antigenically and physically distinct from hepatitis B surface antigen (HBsAg). These authors demonstrated that the HBeAg was present in some HBsAg-positive hepatitis sera, mostly from patients on hemodialysis, and anti-HBe was found in HBsAg-positive blood donors. In addition, Nielsen et al. have suggested that the presence of HBeAg in patients with acute viral hepatitis may be a prognostic marker because the most
patients with HBe antigenemia subsequently developed chronic hepatitis or cirrhosis. Many investigators\textsuperscript{3-6} agreed with these observations, but others\textsuperscript{7-9} not. However, evidences have been accumulated to indicate that the HBeAg is closely related to replication with hepatitis B virus (HBV) and is usable as a prognostic marker of HBsAg-positive individuals\textsuperscript{10-29}.

Present study aimed to investigate the clinical significance of HBeAg and anti-HBe in various types of HBsAg-positive liver diseases and to evaluate their prognostic values. Relationships between HBeAg or anti-HBe and clinical laboratory and pathological status in these patients were also examined.

Patients and Methods

One hundred ninety-two patients with HBsAg-positive various liver diseases and 22 asymptomatic HBsAg carriers were subjected to the present study. These patients consisted of 24 cases of acute viral hepatitis, 1 subacute hepatitis, 95 chronic hepatitis including 34 chronic active hepatitis, 33 liver cirrhosis and 39 hepatocellular carcinoma. The diagnosis of these patients were established by clinical, biochemical and histological findings. Several cases have been followed up by serial biochemical and biopsy examinations for more than three years.

Asymptomatic carriers were defined as follows i) a high titer of HBsAg and ii) neither clinical evidence of liver disease nor abnormal liver function tests. Most cases were family members of HBsAg-positive liver disease.

HBsAg was assayed by both immunoelectroosyneresis and reversed passive hemagglutination (RPHA) method, and antigenic titer was expressed as the highest dilution ($2^N$) demonstrating hemagglutination. HBeAg and anti-HBe were detected by the standard immunodiffusion technique of Ouchterlony using a hexagonal arrangement.

Sera were concentrated to about 5 to 10 times of its original volume by addition of 39% polyethylene glycol 6000. The gel was made of 0.9% agarose dissolved in Tris-HCl buffer (0.01M, pH 7.6) containing 0.1M NaCl, 0.02M EDTA, 2% Dextran T-500 and 0.1% sodium azide. Wells, 3 mm in diameter, were cut 3 mm apart (edge to edge). The plate was incubated at room temperature in a humid chamber for 48 hours, and observed after staining by thiazine red. Standard HBeAg and anti-HBe reagents were obtained from HBsAg-positive donor plasma units and gave reactions of complete identity against reference sera kindly provided by Dr. K. Okochi, Kyushu University, Fukuoka, Japan.

Results

The frequency of the HBeAg and anti-HBe among the patients with HBsAg-positive various liver disease and asymptomatic carriers is shown in Table 1.

In 24 patients with acute viral hepatitis type B, five (20.8%) with HBeAg and one (4.2%) with anti-HBe were positive. A striking difference in the frequency of the HBeAg was found between patients with transient HBs-antigenemia and those with persistent antigenemia. The HBeAg was present initially and persisted over 12 months in 4 out of 6 patients (66.7%) with persistent HBs-antigenemia who subsequently developed chronic hepatitis or cirrhosis. Contrastively, only one out of 18 patients (5.6%) with early resolution gave positive HBeAg transiently. Another one case among these 18 patients showed anti-HBe during the convalescent stage of illness, but not in progressive cases.

In 1 patient with subacute hepatitis, neither HBeAg nor anti-HBe was detected.

In 95 patients with chronic hepatitis, HBeAg was positive in 33 (34.7%) and anti-HBe in 18 (18.9%). However, higher percentage of