HBeAg and Anti HBe Status in Patients with Chronic Hepatitis B Infection

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ABSTRACT

Background: *Data on HBeAg and anti HBe status in patients with chronic hepatitis B infection are not yet available in Indonesia. This study was done to acquire data on HBeAg and anti HBe status in patients with hepatitis B chronic infection.*

Method: *The material of this study was sera, collected from 105 patients with chronic hepatitis B infection from June to November 2007, divided into four groups of hepatoma, liver cirrhosis, chronic hepatitis B and asymptomatic HBsAg carriers. All sera were examined for HBsAg, HbeAg, anti HBe aside from liver function examinations. The sera consisted of 23 sera of patients with hepatoma, 27 with liver cirrhosis, 12 with chronic hepatitis B, and 43 with HBsAg asymptomatic carriers.*

Results: *From 105 samples, only 18.09% samples were in replicative phase, as shown with the positivity of HBeAg and the negativity of anti-HBe. Sera with negative HbeAg and positive anti-HBe were mainly found in liver cirrhosis (70.73%) and least in chronic hepatitis B (50.00%)*

Conclusion: *The high frequency of HBeAg negative and anti-HBe positive in this study might indicate the possible high frequency of pre core mutation. A study using quantitative HBV DNA should be done to confirm it.*

Keywords: *HBeAg, anti HBe, chronic hepatitis B*

INTRODUCTION

The knowledge of HBeAg and anti-HBe system develop from time to time in accordance with the molecular biology knowledge advances of hepatitis B virus. HBeAg was formerly regarded as an indicator of hepatitis B virus replication and was a sign of possible chronic liver disease and transmission. On the other hand, positive anti-HBe was a marker of non-replicative phase, absence of transmission, and good prognosis. However, this understanding has now changed much; positive HBeAg is indeed still an indicator of viral replication and transmission as well as a valuable prognostic tool.[1] Unlike the old understanding, negative HBeAg and positive anti-HBe does not necessarily indicate that the replication of hepatitis B virus is low. In patients with pre core mutant, it was found that HBeAg is negative and anti HBe is positive, but replication still occurs. This is due to the inability of the virus to produce HBeAg, although it is still replicative. Anti-HBe is positive because at the T cells level, HBeAg and HBcAg generate a humoral immune response.[1,2] Until now there has been no study report in Indonesia, which give information about the status of HBeAg and anti HBe in chronic hepatitis B patients, who are grouped according to clinical condition. This data is very important to estimate the number of patients with negative HBeAg and positive anti HBe due to pre core mutation.

This study was conducted to determine the status of HBeAg and anti HBe in patients with liver disease with various clinical forms, ranging from hepatoma, liver cirrhosis, chronic hepatitis B and asymptomatic carrier.

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METHOD

The samples of this study are 105 sera taken from patients seeking treatment at the Biomedika hospital,

showing positive HBsAg from June to November 2007. Diagnosis was done by history taking, physical examination, laboratory examination, ultrasonography, and if necessary, histological examination.

This study used diagnostic criteria that are commonly applied. Laboratory examinations for HBsAg, HBeAg, and anti-HBe were done using artificial imunochromatography made by Acon Lab Inc. USA, which according to the Lau et al study has a fairly good specificity and sensitivity when compared to the ELISA method.[3]

RESULTS

Of the 105 sera collected, 19 (18.09%) showed positive anti-HBe and negative HBeAg. There were as many as 66 (62.86%) patients with negative HBeAg and positive anti-HBe, 23 patients with hepatoma aged 28-59 years old with an average age of 41.08 years old. From table 1, it was found that only 3 (13.04%) of 23 patients with hepatoma were anti-HBe positive and HBeAg negative, while 14 (60.87%) patients showed negative HBeAg and positive anti HBe.

Table 1. HBeAg and anti HBe status in patients with hepatoma due to hepatitis B

HBeAg and anti HBe status	Male	Female	n (%)
HBeAg positive, anti HBe negative	2	1	3 (13.04)
HBeAg negative, anti HBe positive	13	1	14 (60.87)
HBeAg negative, anti HBe negative	4	1	5 (21.73)
HBeAg positive anti HBe positive	1	0	1 (4.35)
Total	**20**	**3**	**23 (100)**

A number of 27 patients with liver cirrhosis comprised 11 female patients and 16 male patients with an average age of 52.68 years old, with the youngest aged 14 years old and the oldest 70 years old. From table 2 it is noted that only 5 (18.52%) from 27 patients with liver cirrhosis were HBeAg positive and anti-HBe negative. On the other hand, liver cirrhosis patients with negative HBeAg and positive anti HBe are as many as 19 (70.37%) patients.

There were 12 patients with chronic hepatitis B, 4 female and 8 male. Patients' ages range from 24 to 43 years old, with an average of 36 years old. From Table 3, it is recognized that only 2 (16.67%) of 12 patients with chronic hepatitis B were HBeAg positive and anti-HBe negative, while 6 (50.00%) patients were HBsAg negative and anti-HBe positive.

Table 2. HBeAg and anti-HBe status in liver cirrhosis due to hepatitis B

HBeAg and anti HBe status	Male	Female	n (%)
HBeAg positive; anti HBe negative	3	2	5 (18.52)
HBeAg negative; anti HBe positive	11	8	19 (70.37)
HBeAg negative; anti HBe negative	2	1	3 (11.11)
HBeAg positive; anti HBe positive	0	0	0 (0)
Total	**16**	**11**	**27 (100)**

Table 3. HBeAg and anti HBe status in chronic hepatitis B patients

HBeAg and anti HBe status	Male	Female	n (%)
HBeAg positive; anti HBe negative	2	0	2 (16.67)
HBeAg negative; anti HBe positive	4	2	6 (50.00)
HBeAg negative; anti HBe negative	2	2	4 (33.33)
HBeAg positive; anti HBe positive	-	-	-
Total	**8**	**4**	**12 (100)**

Patients with asymptomatic HBsAg carrier were as many as 43 patients, with an age range of 18-55 years old and an average of 36.14 years old. From table 4, it can be seen that the positive HBeAg and negative anti-HBe were found in 9 (20.93%) patients, and negative HBsAg and positive anti-HBe in 27 (62.79%) patients.

Table 4. HBe Ag and anti-HBe status in asymptomatic HBsAg carrier

HBeAg and anti HBe status	Male	Female	Total
HBeAg positive; anti HBe negative	6	3	9 (20.93%)
HBeAg negative; anti HBe positive	23	4	27 (62.79%)
HBeAg negative; anti HBe negative	4	2	6 (13.95%)
HBeAg positive; anti HBe positive	1	-	1 (2.33%)
Total	**34**	**9**	**43 (100)**

DISCUSSION

There are 4 phases of disease progression in chronic hepatitis B, i.e. imunotolerant phase, imunoclearance phase, inactive carrier state, and reactivation phases. In the imunotolerant phase, there is practically no immune response against hepatitis B virus particles so there is no cytolysis of infected liver cells and no symptoms.[4,5]

In the imunoclearance phase, the levels of transaminases are increased, and the body begins to

Table 5. HBeAg and anti HBe status in patients with chronic hepatitis B infection

Diagnosis	Hepatoma	Liver cirrhosis	Chronic hepatitis B	Asymptomatic carrier	Total
HBeAg positive; anti HBe negative	13.04%	18.52%	16.67%	20.93%	18.09%
HBeAg negative; anti HBe positive	60.87%	70.37%	50.00%	62.79%	62.86%

produce an immune response against hepatitis B, which will change the positive HBeAg to negative and anti-HBe to positive. In this phase, clinical symptoms appear and transaminases increase at various levels, ranging from asymptomatic to severe clinical symptoms that can occur repeatedly. Acute exacerbations called flares can occur here. When flares happens repeatedly, liver cirrhosis will quickly develop.[6,7] After imunoclearance phase progresses, the patient entered the inactive carrier state in which there is practically no clinical symptoms, usually normal transaminase, negative HBeAg and positive anti HBe.[8] However, in some patients, although HBeAg negative and anti HBe positive, hepatitis B virus replication has not stopped. These patients suffer from hepatitis B infection with mutant pre core, a virus that has undergone mutation that it is not capable of making HBeAg but anti-HBe is still formed by the host because at the level of T cell immunologic response against the HBcAg and HBeAg is the same.[1] In patients with wild type HBV, HBeAg seroconversion to anti HBe is a good marker and the likelihood for cirrhosis and hepatoma to occur is small.[9,10] In patients with mutant pre core HBV infection, due to the persistence of disease activity and yet high number of virus particles, cirrhosis and hepatoma are more common.

In this study of 105 samples, only 18.09% of the replicative phases were recognized from positive HBeAg and negative anti-HBe. Ijoma et al reported that there were 8.6% of patients with positive HBeAg, while from Yap et al a high yield of 43.3% patients with HBeAg positive and anti-HBe negative was obtained.[11,12] In this study, there were 62.86% cases showing HBeAg negative and anti-HBe positive. This condition was formerly called non-replicative phase, but in fact there are 2 possibilities of this situation, that are: (1) Wild-type hepatitis B infection which have undergone seroconversion called inactive carrier state which theoretically has a good prognosis[7,9]; and (2) The patient is included in chronic hepatitis B HBeAg negative who has hepatitis B virus infection with pre core mutant. Pre core mutant is unable to produce HBeAg but can cause a response in the form of anti-HBe positive. Both conditions can be distinguished by examining the level of HBV DNA.

In this study, it is noted that the highest cases with HBeAg positive and anti-HBe negative were in asymptomatic carrier (20.93%) and the lowest in hepatoma (13.04%). This is consistent with Rapicetta et al who obtained asymptomatic carrier cases as many as 87.6%.[13] As for the HBeAg negative and anti-HBe positive group, most cases were in liver cirrhosis (70.37%) and least in chronic hepatitis B (50.00%). With the high cases of HBeAg negative and anti HBe positive, the incidence of pre core mutation was also estimated high. To determine this, further investigation is needed regarding the quantitative HBV DNA.

CONCLUSION

From the high frequency of HBeAg negative and anti HBe positive cases in this study, it can be estimated that the incidence of pre core mutation was also high. Therefore we need further study that uses quantitative HBV DNA to verify this.

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