Original Article

Comparison of histology activity index scores in patients with HBeAg positive and HBeAg negative CHB to see difference in severity of liver injury

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Abstract

The aim of this study is to compare histology activity index (HAI) scores in patients with HBeAg positive and HBeAg negative CHB to see if there is any difference in severity of liver injury between these two types of HBV. We did percutaneous liver biopsies of 77 CHB patients. Serum HBeAg status were assessed in all study subjects. Of them, 37.66% patients (29/77) had HBeAg positive HBV infection, while the rest 62.33% (48/77) had HBeAg negative HBV infection. 22/48 (27.78%) patients with HBeAg negative CHB had mild to moderate CH (HAI score 4-12) and 26/48 (72.22%) patients had minimal CH (HAI score 1-3). In contrast, mild to moderate CH was seen in 19/29(72.23%) patients with HBeAg positive CHB. The study shows there is no correlation between the necro-inflammatory activity in the liver and HBeAg status in the serum in patients with CHB.

Key words: Chronic hepatitis B, HBeAg, histology activity index

Introduction

Hepatitis B virus (HBV) is a double-stranded DNA virus that belongs to the family of hepadnaviruses.[1] HBV infects nearly 350 million people worldwide.[2] The clinical manifestations vary widely with asymptomatic acute viral B hepatitis on one end and hepatocellular carcinoma (HCC) on the other end of the spectrum. There are about 400 million HBV careers worldwide. Of them 75-80% reside in Asia and Western Pacific. HBV is responsible for over 1 million deaths per year globally. It is a major cause of cirrhosis of liver and HCC worldwide.[1] HBV is mainly transmitted by percutaneous and membrane exposure to infected body fluids. HBsAg and HBV DNA by PCR have been identified in most body secretions e.g. blood, saliva, menstrual and vaginal discharges, seminal fluid and serous discharges with the exception of stool.[1] HBV replicates in hepatocytes, but HBV encoded proteins have been identified in other body tissues like testes, stomach, colon, kidney, bone marrow, peripheral mononuclear cells, nerve ganglia and skin, which represent large extra-hepatic reservoir of HBV.[3]

HBV is transmitted from infected mother to neonate in or around the time of birth. 60-90% babies born to HBeAg positive mothers and 15-20% born to HBeAg negative mothers become infected respectively. There is also risk of transmission of HBV if the pregnant mother has acute viral B hepatitis in second or third trimester or within two months of labour. HBV has been detected in breast milk, but it is probably not transmitted through breast milk.[3]

The precore/core region of the HBV genome encodes the nucleocapsid protein (HBcAg) and HBeAg.[4,5] The core open reading frame has two transcripts with heterogeneous[5] ends and two in-phase initiation codons. HBeAg is translated from the precore mRNA producing a precursor polypeptide comprising the precore and the entire core region. The precore polypeptide is translocated into the endoplasmic reticulum by a signal peptide. Cleavage of the amino and carboxy termini results in a secretory protein HBeAg. HBcAg is translated from the pregenomic RNA.

The biological role of HBeAg in the HBV replication cycle is uncertain. Expression of HBeAg is nonessential for virus replication in animal models[6] and in humans.[7] It has been suggested that HBeAg may act as a tolerogen or a target for immune response. In utero exposure to HBeAg can induce immune tolerance in newborn mice.[8] Perinatal transmission of HBV from HBeAg-positive mothers results in chronic HBV infection in the majority of babies.[9] In addition, HBeAg appears to modulate the host's immune respons.[10,13] Precore variants that do not produce HBeAg may be selected because they can evade immune clearance. Mutations in the precore region of the HBV genome have been described.[14,18] It results in HBeAg negative HBV infection.[19,23] The aim of this study is to compare the histological activity in liver due to chronic hepatitis B in patients with HBeAg positive and HBeAg negative CHB to see if there is any difference in severity of liver injury between these two types of HBV.

Methods

Patients with chronic HBV infection (HBsAg positive for at least 6 months) attending hepatology OPDs in BSMMU, Dhaka, Bangladesh between March 2008 and December 2008 were studied prospectively. Written informed consent

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was obtained from each patient. The patients had to be negative for anti-HCV antibody and positive for serum HBV DNA (>1 × 105 copies/ml) using a DNA hybridization assay (Digene Hydrid Capture^2 system; Digene Corporation, Gaithersburg, Maryland, USA); they were enrolled irrespective of their HBeAg status and liver enzyme levels. Patients with clinical evidence of liver cirrhosis were excluded.

All patients underwent percutaneous liver biopsy. Biopsies were done using trucut biopsy needle under local anaesthesia. The present study was carried out at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from March 2008 to December 2008, to evaluate the histopathological changes in liver biopsies in HBsAg-positive chronic hepatitis patients. The aim of this study was to see the relationship between serum HBeAg status, and liver histology for the proper diagnosis and management of chronic hepatitis B patients. Out of seventy seven patients 29 patients were HBeAg positive and 48 case were HBeAg negative. Liver tissue were examined histologically to evaluate the features of chronic hepatitis and the intensity of necroinflammatory activity and fibrosis were scored by Knodell scoring system.

Results

Results are presented in a tabulated and figure forms. A total of 77 patients were studied. Results show that in HBeAg positive CHB HAI score (i.e. necro-inflammatory score) was between 1-3 in 10/29 patients, between 4-8 in 17/29patients, between 9-12 in 2/29 patients and no patients had score between 13-18. In HBeAg negative CHB, these figures are 26/48, 17/48, 5/48 respectively.

34.48% HBeAg CHB patients included in this study had minimal chronic hepatitis, 58.62% had mild chronic hepatitis and 6.89% had moderate chronic hepatitis. In HBeAg negative CHB patients, these figures were 54.16%, 50%, 35.41% and 10.41% respectively.

There was no histological diagnosis of marked chronic hepatitis in any group.

Table-I: Distribution of seventy-seven patients in different groups according to the degree of necroinflammatory activity

Groups	Number of patients	Percentage
Group I (minimal chronic hepatitis)	36	46.75%
Group II (mild chronic hepatitis)	34	44.15%
Group III (moderate chronic hepatitis)	07	9.10%
Total	77	100%

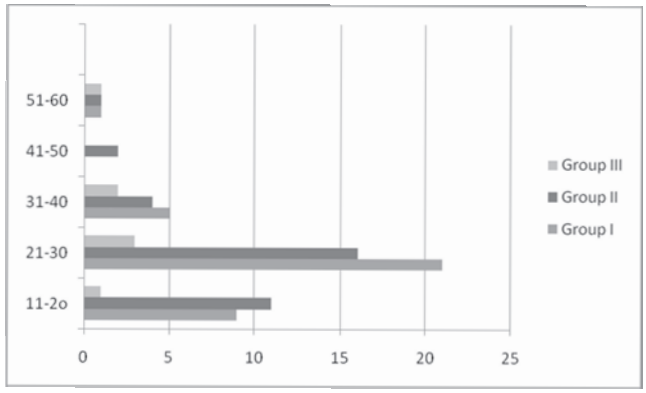

Figure-1. Showing age distribution in different groups

Table-II: Serum HBeAg status in the study subjects (n=77)

Serum HBeAg	Group I		Group II		Group III	
	No	%	No	%	No	%
Positive	10	27.77	17	50	2	28.57
Negative	26	72.22	17	50	5	71.42
Total	36	100	34	100	7	100

Table-III: Correlation of HAI score (excluding fibrosis) and diagnosis in chronic hepatitis

HAI	Diagnosis
1 - 3	Minimal
4 - 8	Mild
9 - 12	Moderate
13 - 18	Severe

Table-IV: HAI (excluding fibrosis): grades

Component	Scores
Peri -portal necrosis with or without bridging necrosis	0-10
Intra -lobular degeneration and focal necrosis	0-4
Portal inflammation	0-4

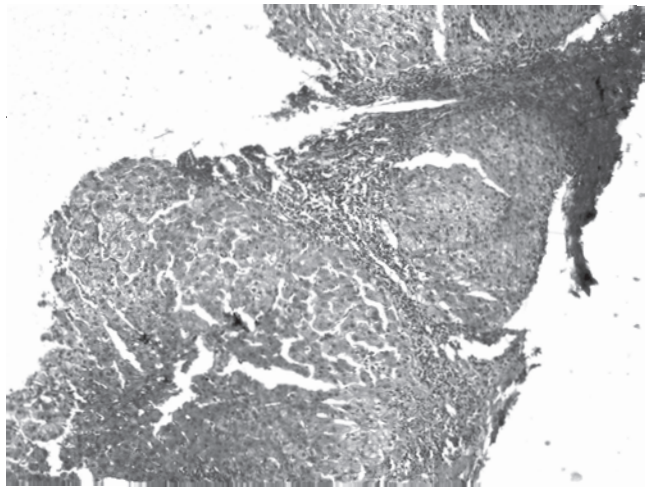

Figure-2: *Marked piecemeal necrosis with bridging necrosis and marked portal inflammation (Case No. 27,H&E × 100)*

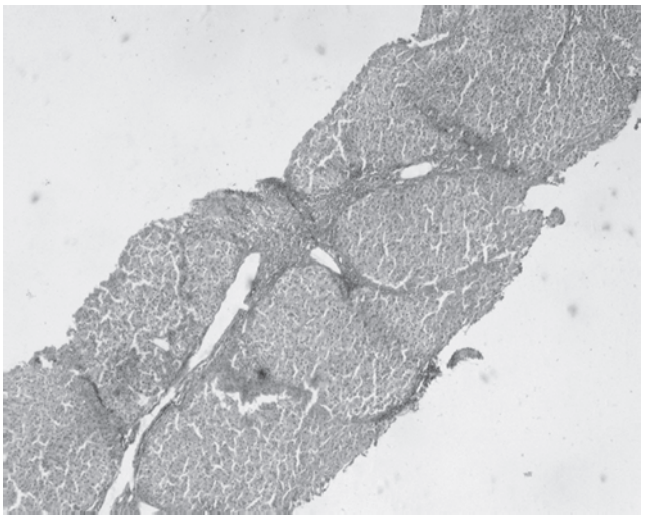

Figure-3: *Moderate piecemeal necrosis with bridging necrosis and bridging fibrosis (Case No. 77, H&E × 100)*

Discussion

Our study reveals that patients with HBeAg negative CHB tend to develop more severe necro-inflammation and fibrosis in the liver compared to those who are HBeAg positive.

In 2004, an Indian study involving 60 patients conducted by a group from GB Pant Hospital, New Delhi demonstrated statistically significant difference in liver fibrosis between HBeAg positive and HBeAg negative patients, with fibrosis score being higher in HBeAg negative CHB. Although these patients also had higher HAI score than those infected with HBeAg positive HBV, the difference was not statistically significant.[24]

A Korean study in 2004 also yielded similar results. The study included chronic HBV infected 85 young, male patients and demonstrated lower fibrosis score in those HBeAg positive HBV infection than those who had HBeAg negative HBV infection. Here also the correlation was not significant statistically in case of HAI score.[25]

A Turkish study in 2003, that included 354 CHB patients revealed significant difference between necro-inflammatory activity and HBeAg negative CHB infection and HBeAg positive CHB. However the difference in fibrosis was not significant.[26]

In one of the study carried out at hepatology department of BSMMU, Dhaka with 80 CHB patients, it was seen that 7.69% patients with HBeAg positive CHB had minimal chronic hepatitis, 69.23% had mild chronic hepatitis, 19.23% had moderate chronic hepatitis 3.85% had severe chronic hepatitis. In case of HBeAg negative CHB these figures were 10.71%, 53.57%, 25% and 10.71% respectively. That study showed that patients with HBeAg negative CHB tend to develop moderate to severe chronic hepatitis more.[27]

In conclusion our study shows that there is no correlation between necro-inflammation and serum HBeAg status in patients with chronic hepatitis B infection. Our finding is not consistent with similar studies carried out elsewhere including those of Bangladesh. Since there is no significant correlation among serum HBeAg and liver histology of CHB, assessment of liver enzymes, histopathology and viral load all together are recommended to select the patients who need treatment.

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