Clinical, Biochemical, Serological, Ultrasonographic and Histological Evaluation of 300 Asymptomatic HbsAg Positive Individuals

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Summary:

The aim of this study is to know replicative markers of Hepatitis B virus(HBV) as well as evidence of chronic liver disease among asymptomatic HBV carriers. Three hundred consecutive asymptomatic HBsAg positive individuals were evaluated clinically, biochemically, serologically, ultrasonographically and histologically at Combined Military Hospital, Dhaka from January 2001 to June 2002. HBsAg was detected incidentally during routine screening test done for blood donation, foreign mission and courses abroad. They were evaluated after six months of initial detection of HBsAg. Age of the patient ranged from 16 years to 50 years (mean ±SD = 32.44±6.35 years). Two hundred and ninety seven patients (99%) were male and three (1%) were female . HBsAg was found positive in 28 (9.3 %) cases, anti HBe was positive in 257 (85.7%) cases, raised ALT (>45 i.u./L) in 52 (17.33%) cases, prothrombin time more than three seconds of control in 54 (18.0%)cases. Ultrasonography showed coarse hepatic echotexture in 20 (7.62%) cases. Hepatic histology revealed chronic hepatitis in 25 (10.41%) cases and cirrhosis of liver in 4 (1.66%)cases. Hepatocellular carcinoma was not found in any of the cases. Lamivudine therapy was given in 10 (3.33%) patients who had positive HBeAg and ALT more than two times the upper limit of normal.

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Introduction :

Chronic hepatitis B is a common problem in Bangladesh[1]. About 10% of adult and 90% of neonatal or early childhood HBV infection leads to chronicity[2]. Chronic HBV infection may cause chronic hepatitis, cirrhosis of liver and hepatocellular carcinoma[3-5]. Rate of progression to cirrhosis and hepatocellular carcinoma vary according to the immune status and age of the host, stage of infection, geographic and genetic factors. Active viral replication may be found in some of the asymptomatic HBV carriers who may require antiviral or immunomodulatory treatment[6-8]. Reactivation and acute flares may develop during the course of the disease.[9] YMDD motif mutations are also detected in some lamivudine untreated HBV carriers [10]. The aim of this study was to know the clinical, biochemical, serological, ultrasonographic and histological status of asymptomatic HBsAg carriers and evaluate these cases for treatment.

Materials and Method :

Three hundred consecutive asymptomatic HBsAg carriers were evaluated clinically, biochemically, serologically, ultrasonographically and histologically at Gastroenterology Department of Combined Military Hospital, Dhaka, in collaboration with Armed Forces Institute of Pathology and Department of Radiology. Patients were Armed Forces persons and their family members. All of them were asymptomatic. They were detected to have positive HBsAg incidentally during routine screening test for going abroad and blood donation. All the patients were observed for more than six months after initial detection of HBsAg. Detail

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history and clinical examination were done at the entry. Hepatitis B viral profile, serum alanine aminotrasferase (ALT), prothrombin time (PT), albumin, alpha-fetoprotein (AFP) were done in all cases at the entry and during follow up . Polymerase chain reaction (PCR) for HBV DNA was not done due to lack of facility in the above laboratory. Ultrasonography of liver was done in the majority of the patients. Ultrasonography assisted liver biopsy was done at Radiology department. Upper gastrointestinal endoscopy was done in selected cases to see oesophageal and gastric varices. All clinical and laboratory data were recorded in a questionnaire and checklist and then analyzed in computer. Patients were followed up for one year. During follow up two patients showed reactivation of the disease with reversion to positive HBeAg from negative HBeAg. One of the cases with cirrhosis died of bleeding from duodenal ulcer and hepatic encephalopathy during follow up . One patient developed intraperitoneal haematoma during liver biopsy. Haemostasis was secured at laparotomy and he recovered well.

All the results were expressed as mean or percentage where indicated. Statistical significance of data was determined by using Pearson's X^2 test. P value of <0.05 was taken as statistically significant. All statistical analyses were done by using the SPSS package (version 10).

Results :

Age of the patients ranged from 16 years to 50 years (mean ± SD=32.44±6.35 years). Two hundred and ninety seven (99%) cases were male and three (1%) were female. Only small number of patients had previous history of jaundice (10#3.33%), hospital admission (12#4.0%), injection (5#1.66%), or transfusion (2#0.66%). Ten patients (3.33%) were health care workers of which four were doctors working in different hospitals. Among the doctors one was surgeon, one anesthetist and remaining two were internists. Hepatomegaly was found in two (0.66%) cases, splenomegaly in three (1.0%) cases and oesophageal varices in 1 (0.33%) case. Spider angioma, gynaecomastia, palmar erythema, testicular atrophy and ascites were not found in any of the cases (Table-I).

Table -I

Base line characteristics of HBV carriers (N=300)

Characteristics	Number	Percentage
Age (Years)		
Range	16-50	
Mean ± SD	32.44±6.35	
Sex		
Male	297	99.00
Female	03	01.00
Previous history of injection	05	01.66
Previous history of blood transfusion	02	00.66
Previous history of jaundice	10	03.33
Previous hospital admission	12	04.00
Contact with jaundice cases	01	00.33
Health care workers	10	03.33
Affected family members of index cases	12	04.00
I.V drug abuse	Nil	Nil
Sexual promiscuity	Nil	Nil
Asymptomatic	300	100.00
Hepatomegaly	02	00.66
Splenomegaly	03	01.0.0
Oesophageal varices	01	00.33

HBeAg was positive in 28 (9.3%) cases which signified replicating stage of the disease. Anti-HBe was positive in 257 (85.7%) cases. Serum ALT level ranged from 13 i.u/L to 379 i.u/L (mean±SD = 39.59 ±41.14 i.u/L). Fifty two (17.33%) cases had ALT above the upper limit of normal (>45 i.u./L). Serum albumin was moderately decreased (30-35 gm/L) in 15 (5.0%) cases. PT was more than three seconds of control in 54 (18.0%) cases. Abnormally coarse echotexture of liver was found in 20 (8.13%) cases. Abnormal hepatic histology was found in 29 (12.07%) cases (Table -II). Abnormally raised serum ALT, PT, decreased serum albumin, coarse hepatic echotexture and abnormal hepatic histology were found more commonly in HBeAg negative cases than HBeAg positive cases. They were statistically significant in cases of raised ALT (P<0.0001), hepatic histology (p <0.0001) and hepatic echotexture (P<0.001). Increased PT (p=0.988) and decreased serum albumin (p=0.184) were not statistically significant between HBeAg positive and HBeAg negative cases . HBeAg and anti HBe both were positive in 5 (1.66%) cases and both were negative in 20 (6.66%) cases. This was statistically significant (P <0.0001). (Table-III). Uitrasonographic echotexture of liver and hepatic histology correlated well and was statistically significant (P<0.0001) (Table - IV) Chronic hepatitis and cirrhosis were found in 22 (9.16%) cases in anti HBe positive patients in comparison to 7 (2.90%) cases in anti HBe negative patients. This was also statistically significant (P <0.05) (Table V).

Table-II

Serological, biochemical, ultrasonographic and histological characteristics of Asymptomatic HBV Carrier (n=300)

Characteristics	Number	Percentage
HBsAg Positive	300	100.00
HBeAg Positive	28	009.30
HBeAg Negative	272	090.70
Anti HBe Positive	257	085.70
Anti HBe Negative	43	014.30
ALT: (l.U./L)		
Range	13-379	
Mean ± SD	39.59±41.14	
S. Albumin: (gm /L)		
Range	30-56	
Mean ± SD	46.34±4.16	
PT : (Sec)		
Range 12-28		
Mean ± SD	14.53±1.78	
AFP (<12.5ng /ml)	300	100.00
USG (N=246)		
Normal echotexture	226	091.86
Coarse echotexture	20	008.13
Hepatic histology (N=240):		
Normal histology	211	087.91
Abnormal histology:	29	012.08
Chronic hepatitis with mild activity	15	006.25
Chronic hepatitis with moderate activity	09	003.75
Chronic hepatitis with severe activity	01	000.41
Cirrhosis of liver	04	01.66

Table-III

Relationship Between HBeAg positivity and serum ALT, Anti-HBe, hepatic ultrasonography and histology (N=300)

Characteristics	HBeAg +VE (N=28) no %	HBeAg -VE (N=272) no %	P value
ALT: (i. u/L)			<.0001
≤ 45	13 (4.33)	235 (78.33)	
≥ 45	15(5.0)	37(12.33)	
PT: (Control =12 sec)			0.988
≤ 15	22(7.33)	224 (74.66)	
≥ 15	06(2.0)	48 (16.0)	
Serum Albumin: (gm/L)			0.184
>35	25(8.33)	260(86.66)	
30-35	03(l.0)	12(4.0)	
< 30	Nil	Nil	
Anti HBe +VE	05(l.66)	252(84.0)	<.0001
Anti HBe -VE	23 (7.66)	20(6.66)	
Hepatic Histology (N=240)			<.0001
Normal Histology	08 (3.33)	203(84.58)	
Abnormal histology:	06 (2.5)	23(9.58)	
Chronic hepatitis with mild activity	01(0.41)	14(5.83)	
Chronic hepatitis with moderate activity	03(1.25)	06(2.50)	
Chronic hepatitis with severe activity	01(0.41)	-	
Cirrhosis of liver	01 (0.41)	03(1.25)	
USG (N= 246)			<.001
Normal hepatic echotexture	14 (5.69)	212(88.33)	
Coarse hepatic echotexture	01(0.40)	19 (7.72)	

Table-IV

Relationship Between Hepatic Histology and Ultrasonographic Findings (N=240)

Hepatic Histology	Normal echotexture number (%)	Coarse echotexture number (%)	P value
Normal	200(83.33)	11(4.58)	
Chronic hepatitis with mild activity	13(5.41)	02(0.82)	
Chronic hepatitis with moderate activity	06(2.5)	03(1.25)	<.0001
Chronic hepatitis with severe activity	01(0.41)	-	
Cirrhosis of liver	01(0.41)	03(1.25)	

Table-V

Relationship Between Hepatic Histology and anti-HBe (N=240)

Hepatic Histology	Anti HBe +VE Number (%)	Anti HBe -VE Number (%)	P value
Normal	188(78.33)	23(9.58)	
Abnormal histology (Chronic hepatitis and cirrhosis)	22(9.16)	07(2.90)	<0.05

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Discussion :

Chronic hepatitis B is the leading cause of chronic liver disease throughout the world. Its prevalence is highest in Asia-paciffic region, China and Africa. HBsAg positive carriers are also very high in these areas. It is not clearly known about the status of hepatic inflammation and replication of the virus among the chronic HBV carriers.

In this study active viral replication (HBeAg positive) was found in 28 (9.3 %) cases, anti HBe positive in 257(85.7%) cases, chronic hepatitis in 25 (10.41%) cases and cirrhosis in four (1.66%) cases. Mukhopadhya A et al showed HBeAg positive in 6.5% and anti HBe in 75% of HBV carriers. Mean age of patients was 29.5±8.0 years and mean ALT was 34.9±23.3 U/L in his series[11]. In this series mean age of patients was 32.44±6.35 and mean ALT was 39.59±41.14 i.u./L. These findings were comparable in both these studies. Evidence of chronic hepatitis and replicating viral markers were found in 53.8% and 44% of cases in a study done by Puri P et al[12]. These findings were not comparable to the findings (10.42% and 9.3% respectively) of this study. Chaudhuri S et al revealed that both HBeAg and HBV DNA were positive in 32.9%of subjects (wild type) and HBeAg negative with positive anti HBe and positive HBV DNA was found in 34.2% of cases (precore mutant) which was also very high in comparison to this study[13]. Hepatocellular carcinoma was not found in any of the cases in this study. Thirty seven (12.33%) cases were found to have elevated ALT with negative HBeAg in this study. They might be the cases of precore mutant viral infection. However, HBV DNA analysis by PCR is required for its confirmation. Raised ALT, PT and decreased serum albumin were more commonly found in HBeAg negative than HBeAg positive cases. Chronic hepatitis and cirrhosis of liver were found more in anti-HBe positive than anti-HBe negative cases. Agarwal et al showed raised ALT in HBeAg positive cases which is contradictory to this findings[14]. Normal and coarse hepatic echotexture correlated well with normal and abnormal hepatic histology. This is statistically significant. Simonovsky showed that sensitivity of ultrasonography in diagnosing cirrhosis was 91.1% and specificity was 93.5%[15].

In conclusion it may be said that chronic asymptomatic HBsAg positive carriers suffer from chronic hepatitis and cirrhosis in 12% of cases. They require treatment with antiviral drugs if active hepatic inflammation and replicating markers are present. Abnormal biochemical, and ultrasonography findings are more common in HBeAg negative individuals than HBeAg positive individuals which signifies the later stage of the disease. Histological abnormality is more common in anti HBe positive cases than anti HBe negative cases. Risk factors for HBV infection are not identified in most of the cases. Reactivation of infection may occur and they should be followed up at least every year.

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