ORIGINAL ARTICLE

SPECTRUM OF HEPATITIS B INFECTION IN SOUTHERN INDIA: A CROSS-SECTIONAL ANALYSIS

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ABSTRACT

Background and Aim: Hepatitis B virus (HBV)-related liver disease is not an uncommon problem in India. There are very few reports on pattern of chronic HBV infection from South India. The aim of the present study was to determine the spectrum of chronic HBV infection among patients attending the liver clinic in a tertiary referral center.

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Materials and Methods: Hepatitis B surface antigen (HBsAg) positive patients registered in the liver clinic between July 2010 and March 2011 were included in the study. All patients had baseline liver function tests, serological markers for HBV infection (hepatitis B e antigen [HBeAg], anti-HBe, anti-HBc total, and anti-HBc IgG, and HBV DNA quantification), serum alpha-fetoprotein, and ultrasound. Based on the viral profile and transaminase levels and ultrasound findings, patients were categorized as immunotolerant, inactive carriers, immune clearance and reactivation phase, and chronic liver disease with or without hepatocellular carcinoma.

Results: Majority of the patients were asymptomatic and incidentally detected during blood donation camps, master health checkup (MHC), or during initial screening. Almost 40% of patients were either in immune inactive phase or had features of chronic liver disease. In the immunotolerant phase (24 patients), women were a decade younger than their male counterparts. Alanine aminotransferase (ALT) levels were similar in both HBeAg-positive and negative patients. The mean HBV DNA values were significantly high in HBeAg-positive men and women. In the immune inactive phase (58 patients), there were only three patients who were HBeAg positive. The ALT levels were in the normal range. HBV DNA values were low or not detectable. Among patients with elevated ALT and HBV DNA levels (immune clearance/immune reactive) (fifty patients), the mean ALT levels were higher in HBeAg-negative patients. HBV DNA quantity was significantly high in patients who were HBeAg positive.

Conclusion: A significant proportion of HBsAg-positive patients is in inactive or in immunotolerant phase and do not require treatment. Patients with elevated ALT and HBV DNA levels need further evaluation to categorize them into immune clearance or immune reactive phase.

Key Words: Chronic hepatitis B, hepatitis B e antigen, hepatitis B virus, hepatitis B virus DNA, immune clearance, immunotolerance

INTRODUCTION

Hepatitis B is a global health problem that affects over four hundred million people worldwide and causes over a million deaths

every year. In India, hepatitis B virus (HBV) is an important cause of hepatocellular carcinoma (HCC).[1-3]

Following an acute HBV infection, the rate of progression from acute to chronic hepatitis B is approximately 90% for a perinatally acquired infection,[4] 20–50% for infections acquired between the age of 1 and 5 years,[5,6] and <5% for an adult-acquired infection.[7]

The natural course of chronic HBV infection is determined by the interplay between virus replication and the host immune response. Other factors that may play a role in the progression of HBV-related liver disease include gender, alcohol consumption, and concomitant infection with other hepatitis virus (es). The outcome of chronic HBV infection depends on the severity of liver disease at the time when HBV replication is arrested.

Chronic HBV infection consists of two phases: an early replicative phase with active liver disease and a late or low replicative phase with remission of liver disease.[8,9] In patients with a perinatally acquired HBV infection, there is an additional immunotolerance phase, in which virus replication is not accompanied by active liver disease.[10] In some patients, reactivation of HBV replication occurs after a varying period of quiescence. The treatment options[11-13] include interferon and oral antivirals (nucleotide and nucleoside analogs).

There are very few reports on the spectrum of chronic HBV infection from different regions of the Indian subcontinent.[14,15] The aim of the present study was to do a cross-sectional analysis of various phases of chronic HBV infection and to determine its sequel at the time of registration at a tertiary referral center for liver disease and liver transplantation.

MATERIALS AND METHODS

The Department of Gastroenterology and Hepatology caters to a large population from North Madras and referrals from other centers for the management of liver disease as well as for registration for liver transplantation. All patients referred to the Department of Gastroenterology or if directly referred to the liver clinic with a liver disease were routinely screened for hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (HCV) antibody,

and for retroviral infection. Pregnant women were also routinely screened for HBsAg. Further evaluation for those found to be HBsAg positive included baseline liver function tests, hepatitis B e antigen (HBeAg), anti-HBe, anti-Hbc (total and anti-HBc IgG), HBsAg and HBV DNA quantification, ultrasound examination, and serum alpha-fetoprotein (S. AFP). Liver biopsy was not considered mandatory for analysis, but when available were included in the analysis.

Individuals who were positive for HBsAg for at least 6 months were included in the final analysis. Anti-HBc, anti-HB IgM, and anti-HBc IgG were done when considered appropriate. Patients positive for anti-HBc IgM were excluded from the study and were followed by for a further 6 months for viral clearance. Alanine aminotransferase (ALT) levels >45 U/L were considered as elevated for both men and women.

Based on the viral profile and transaminase levels and ultrasound findings, patients were categorized as immunotolerant, immune clearance/reactive, and inactive carriers. Based on the clinical presentation, the sequel of chronic HBV infection was categorized as asymptomatic/incidental, chronic hepatitis, cirrhosis liver with or without decompensation, and HCC.

Patient information included age, gender, date of detection and duration of HBsAg positivity, family history of liver disease including HCC, past history of tattoo, blood transfusion, jaundice, and surgery. All family members including children of index HBsAg-positive patients were screened for HBsAg and further evaluated, if found positive. HBsAg-negative patients were vaccinated against HBV infection.

Definition

In HBV immunotolerance phase (replicative phase) (perinatal acquired infection), HBeAg is positive, HBV DNA levels are high, and ALT levels are normal. Patients are asymptomatic, and liver biopsy changes are often minimal in this phase. Treatment is not routinely recommended during this phase except under research protocol.

In HBV immune clearance phase (active phase), the HBV DNA and ALT levels (active liver disease) are both elevated with evidence of chronic hepatitis on liver biopsy. Patients are often

asymptomatic or occasionally present with chronic liver disease with decompensation. Treatment may be recommended during this phase in the absence of advanced fibrosis or cirrhosis irrespective of HBeAg status.

In HBV inactive phase or low or nonreplicative phase, patients are HBeAg is negative, anti-HBe is positive, and HBV DNA levels are either not detectable or are low (<2000 IU/mL). ALT levels are normal. Liver biopsy shows resolution of necroinflammation. Treatment is routinely not recommended during this phase.

HBeAg-negative chronic hepatitis: ALT and HBV DNA levels show fluctuations or a sustained biochemical remission and liver biopsy shows chronic inflammation. These patients fail to produce HBeAg due to precore or core promoter gene variation. Patients are older with advanced liver disease.

In HBV reactive phase, there is histological evidence of liver damage and more rapid disease progression. Treatment for HBV infection is absolutely indicated in reactivation of chronic HBV after chemotherapy or immunosuppression.

RESULTS

Majority of patients were asymptomatic and incidentally detected to be positive during blood donation camps, during MHC, or during initial screening in the Gastroenterology Department at the time of registration. Table 1 shows the risk factors for HBV transmission and spectrum of chronic liver disease amongst the different category of study subjects. Almost 40% of patients were either in immune inactive phase or had features of chronic liver disease. Five of seven pregnant women and three of the five family members were in the immune inactive phase. There were an equal number of cirrhotic patients in the immune inactive, immunotolerant, and immune clearance/reactive phase. One patient in the entire series was positive for both HBV and retrovirus, and three were positive for HBV and HCV. Two asymptomatic patients were on immunosuppressants and required prophylactic antivirals.

There were seven patients who had HBV-related HCC during the study period. The mean age was 55 years. Except for one female patient all were men. Serum AFP was significantly elevated in all the patients. Mean ALT level was 96.6 IU/L. Five

Table 1: Risk factors for HBV transmission and spectrum of chronic liver disease amongst the different category of study subjects

	Immune inactive (58)	Immune tolerant (24)	High ALT high DNA (50)
Past blood transfusion (1)	1	-	-
Dentist (1)	1	-	-
Family history (5)	3	-	2
Pregnancy (7)	5	1	1
Incidental (97)	41	16	40
Chronic hepatitis (9)	6	1	2
Cirrhosis (20)	6	7	7
Hepatoma	5		2

Immune inactive: Normal ALT, HBV DNA; immune tolerant: Normal ALT, high HBV DNA; high ALT high HBV DNA (clearance/reactive) chronic hepatitis: Histology proven; HBV: Hepatitis B virus; ALT: Alanine aminotransferase

of the seven patients had very low HBV DNA levels, three were HBeAg positive, and remaining negative. Two of the three patients underwent liver transplantation, and one had hepatic resection of the affected lobe.

In the immun tolerant phase [Table 2], women were a decade younger than their male counterparts. ALT levels were similar in both HBeAg positive and negative patients. The mean HBsAg quantity was significantly higher among HBeAg-positive men than for HBeAg-negative women. The mean HBV DNA values were significantly high for HBeAg-positive men and women, indicating greater infectivity and transmission.

In the immune inactive phase [Table 3], there were only three patients who were HBeAg positive. The mean age for men and women was similar. The ALT levels were in the same normal range. Quantitatively, the HBsAg was more among men than women. HBV DNA values were low or not detectable in both men and women.

Among patients with elevated ALT and HBV DNA levels (immune clearance/immune reactive) [Table 4], the mean age for men and women in HBeAg-positive patients was similar. In HBeAg-negative

Table 2: Immune tolerant phase: Comparison of HBeAg positive and Negative cases

	HBeAg positive (9)	HBeAg negative (15)
Mean age men (years±SD)	44 (6 men)	41 (9 men)
Mean age women (years±SD), *n*:8	34 (2 women)	32.16 (6 women)
Mean ALT (IU/L)		
Men	23	24.33
Women	37.5	22
HBsAg (U/L)		
Men	28,609	5557.7
Women	12,500	24,211.5
HBV DNA (quantity) IU/mL		
Men	17,298,656	4,041,551
Women	681,240.5	11,000

HBV: Hepatitis B virus; ALT: Alanine aminotransferase; SD: Standard deviation; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen

Table 3: Immune inactive phase: Gender Comparison

	Men (32)	Women (26)
Mean age (years±SD)	35.96±12.64	32.11±12.06
Mean ALT (IU/L)	32.93±10.95	29.44±10.78
HBsAg (U/L): 27 patients		
Range	11-33,034	206.43-23,705.96
Mean value	6750.95	3797.88
Median	9241.74	6484.18
HBV DNA (quantity) IU/mL		
Range	Not detectable to 1400	Not detectable to 1285
Mean value	121.07	186.26

HBV: Hepatitis B virus; ALT: Alanine aminotransferase; SD: Standard deviation; HBsAg: Hepatitis B surface antigen

patients, women were slightly younger. The mean ALT levels were higher in HBeAg-negative patients. HBV DNA quantity was significantly high in men and women who were HBeAg positive indicating higher

Table 4: Comparison between HBeAg positive and negative subjects with high ALT [>45 IU/L]and high HBV DNA

	HBeAg positive (22)	HBeAg negative (28)
Mean age (years±SD)	43.88±15.95 (17 men)	40.18±12.77 (22 men)
Mean age women (years±SD)	40±21.78 (5 women)	32±8.57 (6 women)
Mean ALT (IU/L)	99.72	111.75
Men	113.47	110.72
Women	53	116
HBsAg (U/L): 16 patients		
Men	8559.70	6271.71
Women	9543.6	9392.61
HBV DNA (quantity) IU/mL		
Men	4,373,377.17	764,623.8
Women	64,911,979.8	429,373

HBeAg negative: >2000 U/L; HBeAg positive >20000 U/L). HBV: Hepatitis B virus; ALT: Alanine aminotransferase; SD: Standard deviation; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen

infectivity and transmissibility rates. There was no correlation between HBsAg and HBV DNA quantity with HBeAg positivity.

DISCUSSION

HBV infection is the most common cause of chronic liver disease in the Asia-Pacific region. Nearly 40 million people out of the global HBV infection pool of 350 million are from India. So far, studies on HBV epidemiology and estimates of the burden of infection due to HBV in India have included patient populations as well as arbitrarily chosen population samples that have been small in size. Such studies often fail to reflect the demographic heterogeneity of the general population.[16,17]

The goals of hepatitis B therapy are to prevent disease progression and improve patient survival and quality of life. Treatment protocol for an individual depends on the phase of HBV infection. Currently, treatment is recommended for patients in the immune

clearance, immune reactive phase, during pregnancy, those on immunosuppressants/immunosuppressed, with liver cirrhosis, and patients with HBV-related HCC awaiting for liver transplantation.[13]

In the present study, a significant number of patients were in the inactive/immunotolerant phase not requiring treatment. However, there are at least two reports[18,19] stressing on the need to treat patients in immunotolerant phase with high HBV DNA load. Significant fibrosis and inflammation have been reported in 37% of patients with persistently normal ALT and HBV DNA levels >10,000 copies/ml. Contradictory to this, two further reports concluded that in immunotolerant phase of chronic HBV infection, most patients had no or minimal fibrosis, despite elevated HBV DNA levels. Age and duration of illness possibly predict severity of liver injury in the presence of high HBV DNA levels.[20,21]

Patients in immune clearance and reactive phase need to be treated. A significant proportion of our patients despite being asymptomatic had high ALT and HBV DNA levels. The study, however, could not differentiate the immune clearance from the reactive group of patients as in the majority of the patients, the cause for the flare was not discernible.

In the present series, clinically, five of the seven pregnant women, six of nine patients in chronic hepatitis, and five of seven patients with HCC had low ALT and HBV DNA levels (<2000 IU/L). Among cirrhotic patients, there were almost an equal number of patients with biochemical and serological markers suggestive of immune inactive, immunotolerant, and immune clearance/reactive phase, respectively [Table 1].

Shanmugam *et al*.[22] from Chennai, in an analysis of 560 HBV DNA samples, 26% (146/560) of samples showed evidence of viremia. Among the 154 HBeAg-positive cases, HBV DNA was positive in 118 cases (77%), significantly ($P < 0.001$) higher than the anti-HBe positive (7%) (28/406) cases. Significant increase in liver disease ($P < 0.01$) with ALT enzyme elevation ($P < 0.001$) was observed in both HBe and anti-HBe viremic cases.

CONCLUSION

A significant number of HBsAg-positive patients belong to either immune inactive or immunotolerant phase, not requiring

treatment. Patients with elevated ALT and HBV DNA levels need an in-depth evaluation to categorize these patients into immune clearance and immune reactive phase, which was not possible in the present study, due to financial constraints.

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Conflicts of interest

There are no conflicts of interest.

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