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Research Article

HBe-ANTIGEN NEGATIVE CHRONIC HEPATITIS B: PREVALENCE, VIRAL DNA CHARACTERISTIC AND CLINICAL PROFILE

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A B S T R A C T

Background & Aims: Chronic hepatitis B (CHB) is a disease recognized since 1970. Knowledge regarding its natural history, especially that of HBeAg negative CHB, is still evolving. HBeAg negative CHB is caused by those strains of hepatitis B virus (HBV) which do not produce HBeAg. Previously, HBeAg negative status was considered non replicative phase of HBV infection, but nowadays many of these (about a third) have been found to be in replicative phase. HBeAg negative CHB patients test negative for HBeAg, have persistent or intermittent rise of alanine amino transferase and HBV-DNA in their serum $>10^4$copies/ml. This study was aimed to determine the prevalence of e-CHB, mutations associated with e antigen negativity, clinical and biochemical profile of e-antigen negative and positive CHB patients. Most of the works on e-CHB subjects have been done in western countries and very few data are available from India to address this issue.

Method: The study was carried out in the Department of Gastroenterology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi. This study was performed during January 2010 to December 2011 on patients with chronic hepatitis B. The patients with e antigen negative chronic hepatitis B were considered as case group and e antigen positive were considered as control groups.

Result: The prevalence of HBeAg negative HBV infection in this study was 42.2%.Nearly half (43%) of 161 CHB patients were e-Antigen negative. Liver disease in e-Antigen negative subjects appears to be less advanced than e-antigen positive subjects as cirrhosis was present in 48.5% in e-Antigen negative as compared to e-Antigen positive subjects (64.5%)($p<0.05$). High prevalence (43%) of e-Antigen negative CHB noted in this study is in conformity with the some of the recent reports from India. In our study we did not find any significant difference in mean age of e-Antigen negative and positive subjects, which were 36.4 and 39.0 yrs. respectively.

Conclusion: The results of this study clearly indicate that e-Antigen negative CHB/CLD is quite common and accounts for nearly half of all HBV related chronic liver diseases. Although e-Antigen negative CHB/CLD cases had less severe liver disease and lower DNA level, still the disease was active, progressive and far advanced and presents challenge during routine diagnostic workup as well as therapy.

INTRODUCTION

Background

Chronic hepatitis B (CHB) is a disease recognized since 1970. Hepatitis B is a common disease worldwide, and countries have been divided into three groups according to its endemicity, high, intermediate and low.

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It is estimated that about 200 burdens of the world's population have been exposed to the hepatitis B virus (HBV), of whom 350 million harbour it chronically. India comes in the intermediate endemicity zone (prevalence of 2–7%, with an average of 4%), with a disease cores of about 50 million. Pockets of higher endemicity are found in tribal areas where the high cores is maintained through intracaste marriages, tribal customs, illiteracy and poor exposure to health care resources. The disease passes through three phases in its natural history – (a) immunotolerant phase with e+ve and high DNA load with normal enzymes, (b) immune active phase with surge in enzymes, hepatitis B e antigen (HBeAg) negativity (a state known as e-ve) and clearance of DNA, and

(c) inactive carrier phase with development of HBe antibody (antiHBe), normal enzyme levels and negativity for HBV DNA. A section of inactive carriers may revert back to DNA positivity with e-ve state and develop e-ve hepatitis. Some will remain as occult infection (hepatitis B surface antigen (HBsAg)-negative and HBeAg-negative but DNA-positive). The most prevalent genotype in India is D followed by A, with the exception of east and north eastern India where genotype C is also high (Chandra *et al*. 2007). In the northern half of India there is a gradual trend of increasing genotype C as one moves eastward, and this rise also represents a recent change.(Biswas *et al*. 2012)

Knowledge regarding its natural history, especially that of HBeAg negative CHB, is still evolving. HBeAg negative CHB is caused by those strains of hepatitis B virus (HBV) which do not produce HBeAg. Previously, HBeAg negative status was considered non replicative phase of HBV infection, but nowadays many of these (about a third) have been found to be in replicative phase. HBeAg negative CHB patients test negative for HBeAg, have persistent or intermittent rise of alanine amino transferase and HBV DNA in their serum $>10^4$copies/ml.In 1989, HBV genome of these patients was identified to have two types of mutations: precore and core promoter mutations. These mutations prevent or diminish HBeAg synthesis by an otherwise normally replicating HBV. The prevalence of HBeAg-negative phase of HBV infection is higher in regions where patients predominantly have non-A genotype HBV infection like China and the Mediterranean region (Genotype B, C & D).

E-negative hepatitis results from mutation in the precore (pc) and basal core promoter (bcp) regions of HBV genome. Such infection results in hepatitis having lower DNA levels compared to e+ve disease and causes disease progression to occur silently to cirrhosis, with intermittent flares (often subclinical). (Guptan *et al*. 1996; Kumar *et al*. 2009)The Precore mutation, involves a G-to-A base pair substitution at nucleotide 1896 in the precore region of the HBV genome. This mutation transforms codon 23 in the mRNA from TGG to a TAG stop codon and the creation of the stop codon results in the formation of a truncated 28 amino-acid peptide and thus the formation of normal HBeAg is completely halted. The Core-promoter mutation involves paired nucleotide substitutions in the core promoter region, most often A-to-T at nucleotide 1762 and G-to-A at nucleotide 1764, leading to reduced HBeAg production. Investigators have also identified other less common mutations in the precore and core promoter regions.Infection with HBeAg-negative HBV strain usually does not occur de novo, but rather emerges during immune clearance of wild-type strain, when increased immune pressure on the wild-type strain leads to selection of the HBeAg-negative mutant. HBeAg negative CHB in contrast to HBeAg positive CHB are older, have low HBV DNA load and with lower chances (<15%) of spontaneous remission. These mutant strains have increased virulence and more aggressive clinical course.

Aims and Objectives

Information regarding HBeAg negative disease has come largely from Western countries and South East Asia. Most of the countries have witnessed a recent trend towards increasing prevalence of HBeAg negative chronic hepatitis B. However, there are very limited data from India to address this issue. Hence, present study has been planned with the following aims and objectives:

1. To detect the prevalence of HBeAg negative chronic hepatitis B in patients with chronic liver disease.
2. To study the clinical, biochemical and virologic profile of e-Antigen positive and negative CHB patients.

METHODS

The study was carried out in the Department of Gastroenterology, Sir Sunderlal Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi. This study was performed during January 2010 to December 2011 on patients with chronic hepatitis B. The patients with e antigen negative chronic hepatitis B were considered as case group and e antigen positive were considered as control groups. Those patients with the feature of HBeAg negative chronic hepatitis B (e-negative CHB) (a) Clinical and biochemical evidence of chronic hepatitis B along with rise of ALT more than 2 folds. (b) HBs antigen positive and HBe antigen negative. (c) HBV DNA >104 copies/ml. (d) Age between 14-65 years. (e) Informed consent is available and patient is agreeing for regular follow up at regular interval are included in the study and considered as case and those patients with HBeAg positive chronic hepatitis B (e-positive CHB)(a)Clinical and biochemical evidence of chronic hepatitis along with rise of ALT more than 2 folds.(b)HBs antigen positive and HBe Antigen positive. (c) HBV DNA > 105 copies/ml. (d) Age between 14-65 years.(e)Informed consent is available and patient is agreeing for regular follow up at regular interval are considered as control for the present study. Patients with extremes of age (<14 years and >65 years), chronic inactive infection, acute viral hepatitis, fulminant hepatic failure and with hepatocellular carcinoma, associated with other medical illness like diabetes mellitus, Ischemic heart disease and congestive cardiac failure and unable to give informed consent,excluded from the study.

Laboratory Methods

Evaluation & Patients Counseling

All the consecutive patients who gave consent for inclusion in ongoing study was evaluated and counseled about HBV and their risk factor also. Their detailed clinical history was taken with special regards to the mode of acquiring infection, family history of liver disease, history of jaundice, ascites, hepatic encephalopathy (HE) and gastrointestinal bleed. Presence of concomitant medical conditions including alcoholism, renal failure and diabetes were recorded. Drug history was taken to look for intake of hepatotoxic drugs. A detailed clinical examination was done to look for the presence of signs of liver failure and associated co morbidities.Routine investigations such as complete blood count, LFT, serum protein, serum albumin, serum creatinine, Prothrombin time, viral markers, upper GI endoscopy, USG of whole abdomen was done. Liver biopsy was done on selected patients. It was done by Badds liver biopsy gun, size 16-18 frenches. It was interpreted according to METAVIR grading system (Bedossa *et al*, 1995). Grade was assigned based on the portal and lobular inflammatory activity and staging was based on the degree of fibrosis. Child-Pugh score **(**Child *et al*., 1964**)** was also calculated.

MELD (Kamath *et al*., 2001):
The level of serum creatinine, the international normalized ratio (INR) and the level of serum total bilirubin of each patient were recorded. The MELD score was calculated according to the original formula:
MELD Score=[3.8 $\log_e$ (bilirubin in mg/dl)] + [11.2 × $\log_e$ (INR)] + [9.6 × $\log_e$ (creatinine in mg/dl)] + [6.4 ×aetiology : 0 if cholestatic or alcoholic, 1 otherwise]
MELD score was calculated from MELD calculator provided by the united network for organ sharing website.

Statistical Analysis

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) software version 16.0. The continuous variables were presented by their mean ± standard deviation. The Chi-square test, Student′s t test and Fischer′s exact test were applied to compare differences between categorical variables. The comparison between the means was done by Student′s t-test /Mann-Whitney U test as per requirement of data. Probability values (p) < 0.05 were considered statistically significant.

RESULTS

This study was conducted at the Department of Gastroenterology, Institute of Medical Sciences, Banaras Hindu University, Varanasi between January 2010 to December 2011. One sixty one consecutive subjects with Hepatitis B virus related chronic liver disease (CLD) who gave informed consent were enrolled in our study. These subjects were divided into two groups on the basis of e-Antigen positivity. HBeAg negative subjects (68; 42.2%) with chronic liver disease were considered as study subjects (cases) whereas ninety-three (57.8%) subjects who were HBeAg positive were included as controls. So the prevalence of HBeAg negative HBV infection in this study was 42.2%. Mean ± S.D. age for HBeAg negative subjects was 36.4±12.7 years and that of HBeAg positive subjects was 39.08 ± 14.3 years. There was male preponderance in our study and Male: Female ratio in e-Antigen negative and positive subjects was 5.8 : 1 and 3.9 : 1, respectively. Both the case and control groups were comparable with respect to age and sex (p>0.05). More than 50% of the subjects in both the groups were below 40 years of age.

Demographic Profile

Mean ± S.D. age for HBeAg negative subjects was 36.4±12.7 years and that of HBeAg positive subjects was 39.08 ± 14.3 years. There was male preponderance in our study and Male : Female ratio in e-Antigen negative and positive subjects was 5.8 : 1 and 3.9 : 1, respectively. Both the case and control groups were comparable with respect to age and sex (p>0.05). More than 50% of the subjects in both the groups were below 40 years of age.

Table 1 Demographic profile of e-Antigen negative and e-Antigen positive subjects

Age group (Years)	HBeAg Negative n (%)	HBeAg Positive n (%)
11-20	5 (7.4)	7 (7.5)
21-30	23 (33.8)	29 (31.2)
31-40	19 (27.9)	14 (15.1)
41-50	12 (17.6)	20 (21.5)
>50	9 (13.2)	23 (24.7)
Total	68 (100.0)	93 (100.0)

Stage of Liver Disease

Both cases and controls were further subdivided into chronic hepatitis and cirrhotic subjects. Among 68 HBeAg negative subjects 35 (51.5%) were with chronic hepatitis B and the rest 33 (48.5%) were cirrhotic. In HBeAg positive subjects, distribution of chronic hepatitis B and cirrhosis were 33 (35.5%) and 60 (64.5%) subjects, respectively. e-Antigen positive subjects had higher prevalence of cirrhosis as compared to e-Antigen negative subjects (p<0.05).

Table 2 Prevalence of liver disease in e-antigen negative and positive subjects

Liver disease	e-Antigen negative	e-Antigen positive	p value
Cirrhosis n(%)	33 (48.5)	60 (64.5)	0.043*
Chronic Hepatitis B	35 (51.5)	33 (35.5)	

* Significant at p< 0.05

Patients with cirrhosis in both the cases and controls were mostly decompensated. In e-Antigen negative cirrhotics most of the subjects had Child Pugh class B i.e. 54.54% whereas in e-Antigen positive cirrhotics the percentage of Child class C dominates i.e. 39.8% (p<0.05).

Table 3 Distribution of cirrhotic stage in Child Pugh class

Child Pugh Class	e-Antigen negative n(%)	e-Antigen positive n(%)
A	3 (9.09)	7 (11.67)
B	18 (54.55)	16 (26.67)
C	12 (36.36)	37 (61.66)
Total	33 (100.0)	60 (100.0)

* Significant at p< 0.05
p=0.012*

Clinical Profile

The most frequent symptom reported by the patients enrolled in our study were history of jaundice, abdominal distension, fatigue and anorexia.

Table 4 Clinical profile of e-Antigen negative (Cases) and e-Antigen positive (Controls) subjects

Parameters	HbeAg Negative n (%)	HBeAg Positive n (%)	p value
Anorexia	14 (20.6)	14 (15.1)	0.36
Fatigue	18 (26.5)	38 (40.9)	0.058
Jaundice	37 (54.4)	50 (53.8)	0.935
Encephalopathy	10 (14.7)	14 (15.1)	0.951
Upper GI bleed	20 (29.4)	16 (17.2)	0.066
Abdominal distension (Ascites)	28 (41.2)	53 (57.1)	0.047*
Alcohol intake	16 (23.5)	20 (21.5)	0.761
Incidentally detected	33 (48.5)	30 (32.3)	0.03*
Hepatomegaly	15 (22.1)	19 (20.4)	0.803
Splenomegaly	19 (27.9)	25 (26.9)	0.882

* Significant at p< 0.05

The symptoms like upper GI bleed, encephalopathy and jaundice were comparable in both case and control groups, however ascites was more frequent among e-Antigen positive (57.1%) than in e-Antigen negative cases (41.2%) (p=0.047). e-Antigen negative subjects were more commonly detected incidentally during various screening tests like blood donation, VISA application, and family screening, etc. (p=0.03).

Laboratory Parameters

The laboratory parameters of e-Antigen negative and e-Antigen positive subjects were compared in the bellow table.

Table 5 Biochemical parameters of e-Antigen negative (Cases) and e-Antigen positive (Controls) subjects

Variable	HBeAg Negative Mean ± S.D. (Range)	HBeAg Positive Mean ± S.D. (Range)	p value
Hemoglobin (g/dl)	11.58 ± 3.13 (3.8 – 17.8)	11.51 ± 2.48 (4 – 15.8)	0.875
Total leucocyte count ($\times10^9$/L)	7.63 ± 3.17 (0.18 – 15.5)	7.10 ± 3.06 (0.18 – 17)	0.288
Total platelet count ($\times10^9$/L)	142.6 ± 77.3 (33 – 377)	136.3 ± 94.4 (23 – 780)	0.651
Total Bilirubin (mg/dL)	2.22 ± 3.61 (0.2 – 21.1)	3.39 ± 5.54 (0.3 – 32.3)	0.133
ALT (IU/L)	77.80 ± 68.99 (24 – 485)	116.34±131.39 (16 - 885)	0.029*
AST (IU/L)	77.34 ± 68.17 (21-522)	145.29 ± 171.75 (28 – 1103)	0.002**
Alkaline phosphatase (IU/L)	251.58 ± 175.03 (43 – 853)	262.05 ± 164.02 (45 – 1114)	0.698
Serum Albumin (g/dL)	3.66 ± 0.88 (2.0 – 5.0)	3.36 ± 0.85 (1.1 – 4.8)	0.032*
Prothombin time (sec.)	18.38 ± 5.42 (12.4 – 36.8)	19.95 ± 6.36 (12.9 – 45)	0.102
INR	1.42 ± 0.48 (0.95-3.36)	1.56 ± 0.58 (0.99 – 3.93)	0.113
Serum creatinine (mg/dl)	1.00 ± 0.27 (0.2 – 1.8)	1.07 ± 0.43 (0.1 – 3.1)	0.217
HBV DNA Quantitative ($\log_{10}$ copies/ml)	5.42 ± 1.54 (3.15– 9.4)	6.89 ± 1.66 (3 – 10)	0.000**
MELD (Mean ± S.D.)	10.76 ± 6.73 (1 – 27)	13.33 ± 7.37 (3 – 33)	0.025*

* Significant at p <0.05; ** Significant at p <0.001

The laboratory profile of e-Antigen negative and e-Antigen positive subjects were comparable in terms of hemoglobin level, total leucocyte count, total platelet count, prothrombin time and alkaline phosphatase levels. However, HBeAg negative subjects had significantly lower (than HBeAg positive subjects), mean ALT level (77.8 vs 116.3 IU/ml; p<0.015) and mean AST level (77.3 vs 145.2 IU/ml, p<0.05), quantitative HBV DNA level (5.4 vs 6.9 log10 copies/mL; p<0.001), MELD score (10.7 versus 13.3; p=0.025) and higher serum albumin level (3.6 vs 3.3 gm/dl; p<0.05). In our study, Anemia (Hb<12) was detected in 40.2% cases. Mean hemoglobin level in bleeders and non-bleeders were 7.9±2.3 and 11.7±5.4 gm/dl. Neutropenia (TLC < 4×10^9/L) was detected in 9 (13.2%) cases which was mostly due to hypersplenism in these subjects. Decreased total platelet count (<1×10^9/L) was observed in 29 (42.6%) subjects. Serum bilirubin was >5 mg/dL was observed in only 7 (10.29%) subjects. Serum ALT and AST level were higher in majority of patient except in few patients who were cirrhotics. Prothrombin time was abnormal in 38 (55.9%) subjects. Severe coagulopathy (INR>2) were detected in 10 (14.7%) subjects while 48 (70.6%) had only mild coagulopathy (INR ~ 1-2). MELD was significantly high (>14) in 18 subjects (26.5%). Only 2 (2.9%) patients were had serum creatinine>1.5 gm/dl probably due to type 2 HRS in these patients.

DISCUSSION

Hepatitis B virus (HBV) infection remains an important public health problem affecting more than 400 million persons worldwide and is a major cause of morbidity and mortality. India lies in the intermediate prevalence zone for HBV endemicity with an estimated HBsAg carrier rate of 4.7% that extrapolates to 40 million infected individuals (Thyagrajan *et al*.,1996). Our knowledge of chronic hepatitis has undergone a dramatic change over the last 20 years. It was earlier believed that seroconversion from HBeAg to anti-HBe status is accompanied by a cessation of hepatitis B virus replication and remission of liver disease. In the early 1980s, it was observed that replicative HBV can exist even in the absence of detectable HBeAg. These special populations of chronic hepatitis B (CHB) patients with viral replication were branded as 'anti HBe positive' or 'HBe negative CHB (e-CHB). HBeAg negative CHB patients test negative for HBeAg, have persistent or intermittent rise of alanine aminotransferase and HBV DNA in their serum >10^4 copies/ml (Hadziyannis *et al*., 1995). The e-CHB was initially thought to be confined to the Mediterranean area but now is considered to have widespread existence. This study was aimed to determine the prevalence of e-CHB, mutations associated with e antigen negativity, clinical and biochemical profile of e-antigen negative and positive CHB patients. Most of the works on e-CHB subjects have been done in western countries and very few data are available from India to address this issue. In Italy 41% of patients with CHB during the period between 1975 and 1985 were HBeAg negative but in 1995-2000 this was increased to 90% (Rizetto *et al*., 2000). The median prevalence of e-CHB worldwide is about 32% with highest prevalence in the Mediterranean region and lowest in the US and North European region (Funk *et al*., 2002).Nearly half (43%) of 161 CHB patients were e-Antigen negative. High prevalence (43%) of e-Antigen negative CHB noted in this study is in conformity with the some of the recent reports from India, where 43% (Sarin *et al*., 2006) and 44% (Lahiri *et al*., 2007) of CHB subjects were found to have e-Antigen negative status. However, some of the earlier reports from our country noted very low e-Antigen negative status i.e. 18% by Amrapurkar *et al*. (2002) and 4% by Chowdhury *et al*. (2005). Lower prevalence of e-Antigen negative CHB in these studies might be due to use of less sensitive DNA estimation techniques (lower detection limit 7×10^5 copies/ml) whereas many of e-Antigen negative cases have DNA level in the range of 10^4 and 10^5 copies/ml. In the study from Mumbai (Amrapurkar *et al*., 2002) 46% of e-Antigen negative cases had significant chronic liver disease but only 18% were categorized as e-Antigen negative CHB because of cut-off DNA level of 7×10^5 copies/ml. Moreover, these studies have calculated prevalence of chronic hepatitis/CLD among e-Antigen negative subjects rather than prevalence of e-Antigen negativity among CLD subjects. Lastly, the prevalence of e-Antigen negative liver disease appears to be increasing worldwide in recent times.In our study we did not find any significant difference in mean age of e-Antigen negative and positive subjects which were 36.4 and 39.0 yrs respectively. Our finding were consistent with data of Guptan *et al*. (1996); Sarin *et al*. (2006) but in contrast to our observation Khaled *et al*. (2006) observed higher age of e-Antigen negative in comparison to e-Antigen positive subjects (41.3 vs 23.5 yrs). This discrepancy is explained by the fact that Khaled *et al*. (2006) also included immunotolerant patients in their study which are usually e-Antigen positive and were of younger age. Most of our patients were young adult males in their prime years of life as majority were aged below 40 years (mean age 36 years and male : female ratio 5.8 : 1). Therefore, the disease appears to affect young adults, resulting in significant morbidity and mortality in most productive years of life. Several other studies conducted in our country have

reported similar scenario (Guptan *et al*., 1996; Amrapurkar *et al*., 2002; Sarin *et al*., 2006).Possible contributing factors for increasing prevalence of e-CHB subjects are vertical transmission of HBV, longer duration of infection, a greater degree of attention, transmission of HBV from e-negative patients and more active treatment of e-Antigen positive subjects etc. A population study is needed to determine if there is a genuine increase in the proportion of HBeAg negative patients with chronic liver disease in India. The liver disease is e-Antigen negative subjects appears to be less advanced than e-Antigen positive subjects as cirrhosis was manifested in 48% vs. 64% in e-Antigen positive ($p<0.05$). In e-Antigen negative cirrhotics 36% had Child C cirrhosis in contrast to 61% Child C in e-Antigen positive subjects ($p<0.01$). Likewise decompensation in the form of ascites was less frequent in e-Antigen negative subjects (41% vs. 57%, $p<0.05$). This is consistent with the findings of Lahiri *et al*. (2007) who also detected cirrhosis more common in e-Antigen positive subjects in comparison to e-Antigen negative subjects. e-Antigen positive have more aggressive clinical course as compared to e-Antigen negative subjects. In most of the patients, viremia titer and necroinflammatory activity declined markedly after emergence of Anti-HBe antibody. Whatever the mechanism, the anti HBeAg helps to control viral replication to a much reduced level. So, the HBeAgseroconversion can be regarded as a turning point in the natural history of HBV infection. This may be the reason why e-antigen negative patients tend to have less severe stage of liver disease. The common symptoms reported by the patients in our study were history of jaundice (54.4%), abdominal distention (ascites) (41.2%), fatigue (26.5%), anorexia (20.6%), upper GI bleed (29.4%), and encephalopathy (14.7%). These symptoms were comparable with those in HBeAg positive subjects except ascites which was more frequent in e-antigen positive subjects ($p=0.047$). This corroborates with the symptomatic profile of e-antigen negative subjects in study by Guptan *et al*. (1996). However ascites in Guptan study was more frequent in e-Antigen negative subjects. This may be due to the fact that in our study more number of patients with e-antigen negative were detected at an earlier stage of disease incidentally by various screening tests during blood donation, VISA application etc. ($p<0.05$). In our study, the laboratory parameters of e-Antigen negative and e-Antigen positive subjects were comparable in terms of hemoglobin level, total leucocytes count, total platelet count, prothrombin time and alkaline phosphatase. However, e-antigen negative subjects had significantly lower mean ALT level (77.8 vs. 116.3 IU/ml; $p<0.015$), mean AST level (77.3 vs. 145.2 IU/ml, $p<0.05$), quantitative HBV DNA level (5.4 vs. 6.9 log10 copies/ml; $p<0.001$), MELD score (10.7 vs. 13.3; $p=0.025$) and higher serum albumin level (3.6 vs. 3.3 gm/dl; $p<0.05$). Our finding was consistent with the findings of Khaled *et al*., (2006), and Sarin *et al*. (2006) who found ALT levels, HBV DNA levels higher in e-Antigen positive subjects as compared with e-Antigen negative subjects. Higher level of ALT, AST, HBV DNA and MELD score reflects high necroinflammatory activity and more active viral replication in e-Antigen positive subjects. It suggests that viral replication is accompanied by cytolysis and it may be correlated with disease activity. We acknowledge that our observation was based on biochemical parameters at a single time point and patient with CHB, particularly HBeAg negative, tends to have fluctuating serum level of aminotransferases and HBV DNA. Follow up of these patients is needed to determine the course of disease in studied population.

CONCLUSION

The results of this study clearly indicate that e-Antigen negative CHB/CLD is quite common and accounts for nearly half of all HBV related chronic liver diseases. Although e-Antigen negative CHB/CLD cases had less severe liver disease and lower DNA level, still the disease was active, progressive and far advanced and presents challenge during routine diagnostic workup as well as therapy.

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