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No Significant Liver Disease or True Immune-tolerant HBeAg Positive Chronic Hepatitis B with Normal Serum ALT Levels

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Abbreviations: HBV: Hepatitis B Virus; ALT:Alanine Aminotransaminase; HBeAg:Hepatitis B eAntigen; HAI:Histology Activity Index; CHB:Chronic Hepatitis B

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1. Abstract

1.1. Background

Hepatitis B e antigen (HBeAg)-positive Chronic hepatitis B (CHB) patients with normal alanine aminotransaminase (ALT) were usually considered to be in the immune-tolerant phase. However, it has been suggested that the current upper limit of normal for ALT should be lowered.

1.2. Aim

To determine the prevalence and factors associated with no significant liver disease in those with normal ALT.

1.3. Method

One-hundred and fifty-one HBeAg-positive CHB patients with normal ALT. Those with liver biopsy showing minimal or mild inflammation with ≤F1 fibrosis were defined as no significant liver disease, those who were truly immune-tolerant.

1.4. Results

One hundred and twenty-nine of the 151 patients (85.4%) had no significant liver disease. Those with no significant liver disease had a lower mean serum ALT (20 vs. 25 U/L, p=0.005) and a higher mean serum HBV DNA (7.85 vs. 7.09 log IU/ml, p=0.001) than those with significant liver disease. Those with no significant liver disease were more likely to have normal serum ALT as according to AASLD 2007 (90.7% vs. 59.1%, p=0.001) or AASLD 2018 (99.2% vs 77.3%, P<0.001) Practice Guidelines when compared with those with significant liver disease. On multivariate regression analysis, normal serum ALT as recommended by AASLD 2018 Practice Guideline was the only independent factor associated with no significant liver disease (p= 0.001, Odds Ratio 37.059, 95% Confidence Interval 4.082-336.452).

1.5. Conclusion

The new "normal" serum ALT recommended by AASLD 2018 Practice Guideline was independently associated with no significant liver disease.

2. Introduction

Hepatitis B virus (HBV) infection is one of the most common viral infections in the World. It has been estimated that chronic hepatitis B (CHB) infection affects approximately 400 million individuals worldwide, or 5% of the World's population [1]. This is of particular concern in the Asia-Pacific region, where CHB infection is prevalent, with a carrier rate of approximately 10% in China. CHB infection can result in 500,000 to 1.2 million deaths annually from either liver cirrhosis or hepatocellular carcinoma [2]. The natural history of CHB infection involves various stages. There are generally four phases in the evolution of CHB infection in those who acquired the infection perinatally, although not all patients would go through every phase. First, the immune-tolerant phase; second the immune-clearance phase; third the residual non-replicative integrated HBV phase, and, finally, a fourth phase with hepatitis B e antigen (HBeAg) negative replication phase resulting from the emergence of a pre-core mutant strain [3].Traditionally, HBeAg positive CHB patients with normal serum ALT levels were considered to be in the immune tolerant phase. This phase is typically characterised by normal serum ALT levels, HBeAg positivity, high levels of HBV DNA with minimal or no inflammation on liver biopsy, whereby antiviral treatment is not recommended.However, there has been evidence to suggest that the upper limit of normal (ULN) was too high as a significant proportion of CHB infected patients with normal serum ALT levels already had significant liver damage at presentation [4,5,6]. One of these studies showed that those with serum ALT above the 20 IU/L were associated with an increased risk of mortality.4,5 This led to Prati et. al. recommending in 2002 that the normal range of serum ALT level should be decreased to 30 U/L for men and 19 U/L for women [6]. A recommendation that was supported in the American Association for the Study of Liver Diseases (AASLD) 2007 Practice Guideline [7]. However, these new

"normal" values were almost half the upper limit of normal of ALT set by most laboratories and these studies did not test for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody. And, in 2017, this "normal" value was re-set to 40 U/L, for both men and women, in the European Association for Study of Liver Diseases (EASL) 2017 Practice Guideline while the AASLD 2018 Practice Guideline for the purpose of guiding management revised the recommended normal ALT levels for men and women to 35 U/L and 25 U/L [8,9]. The discrepancy or lack of unity on what a normal serum ALT level should be, may be due to the absence of studies comparing the virological and histological profiles of HBeAg positive CHB infected patients within these newly recommended "normal" range with those whose serum ALT levels is close to the ULN as defined by most laboratories. Therefore, this study was conducted to determine the prevalence and factors associated with no significant liver disease in HBeAg positive CHB patients with normal serum ALT levels, those who were truly in the immune-tolerant phase.

3. Patients and Methods

3.1. Study Design

Consecutive Asian HBeAg positive CHB infected patients followed-up at the Centre for Digestive Disease from 1st November 2008 to 30th November 2012 were recruited into this study. These patients fulfilled the following criteria: 1) HBsAg positive for at least 18 months; 2) HBeAg positive for at least 18 months; 3) serum HBV DNA more than 105 IU/ml; 4) treatment naïve; 5) serum ALT levels within the upper limit of normal (the normal range of serum ALT was 7-53 U/L for males and 7-33 U/L for females, respectively) for three consecutive readings six months apart; 6) more than 18 years of age; and 7) alcohol intensity of less than 10 gm/day as defined previously [10]. Patients were excluded from the study if they had: 1) previous therapy with nucleoside/nucleotide analogue or immunomodulators; 2) co-infection with HCV, human immunodeficiency virus or hepatitis D virus; or 3) hepatocellular carcinoma at initial liver biopsy.

4. Histology

An ultrasound guided percutaneous liver biopsy was performed with a 16G Temno needle on all patients. Liver biopsy specimens were prepared with haematoxylin and eosin stain, Masson trichrome stain, Prussian blue stain, reticulin stain, orcein stain and periodic acid-Schiff stain. Liver biopsies were scored using the modified histology activity index (HAI) score for inflammation and the Ishak fibrosis stage for staging of fibrosis [11,12]. The necroinflammatory components of the modified HAI score include periportal inflammation or periseptal interface hepatitis (0–4), confluent necrosis (0–6), focal lytic necrosis, apoptosis and focal inflammation (0-4) and portal inflammation (0–4). Modified HAI score was classified as being consistent with normal pattern, minimal chronic hepatitis (0-3), mild chronic hepatitis (4-8), moderate chronic hepatitis (9-12), and severe chronic hepatitis (13-16) as previously defined [11,12].The Ishak score was used for fibrosis staging, which stages fibrosis from 0–6. Patients with at least stage 4 fibrosis on liver biopsy were considered as having severe fibrosis. Those with fibrosis stage 5 and 6 on liver biopsy were defined as liver cirrhosis. Hepatic steatosis was scored according to an accepted scoring system: 0, no steatosis; 1, <33% of hepatocyte with steatosis; 2, 33-66% of hepatocytes affected; 3, >66% of hepatocytes affected [10,12]. The steatosis observed was predominantly macrovesicular. The primary endpoint of the study was to determine the prevalence of no significant liver disease on liver biopsy in HBeAg positive CHB patient with normal serum ALT levels. The secondary endpoint was to determine factors associated with no significant liver disease.Those with liver biopsy showing moderate or severe inflammation or significant fibrosis (≥F2) were defined as significant liver disease on liver biopsy. This was the group of patients in whom treatment would be recommended [7,8,9]. Those with liver biopsy showing minimal or mild inflammation and ≤ F1 fibrosis were considered as the group with no significant liver disease as this is the group of patients in whom treatment was not currently recommended [7,8,9]. This was the group who should be considered to be truly in the immune-tolerant phase.

5. Virological Studies

HBsAg, HBeAg and anti-HBe, were tested by commercially available enzyme immunoassays (Abbott Laboratories, Chicago, IL, U.S.A.) as previously described [13,14]. Serum HBV DNA was quantified with the Abbott real time HBV assay (Abbott Laboratories, North Chicago, Ill, USA) with a linear range of 10-109 IU/ml every 8-12 weekly as previously described [13,14]. This study was approved by the local Institutional Review Board (CDDIRB-2008-002). Written informed consents were obtained from all patients.

6. Statistical Analysis

All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, New York, USA). The student t-test was used for comparing two continuous variables. Categorical variables were compared using the Chi-square with Yates' correction for continuity or Fisher's exact test. Variables with a p-value ≤ 0.10 in the univariate analysis were included in a multivariate analysis performed with a binary logistic regression analysis with a forward stepwise procedure to determine the most significant factor associated with no significant liver disease. Continuous variables were expressed as mean [standard deviation (SD)]. All statistical analyses were performed on an intention-to-treat basis. Statistical significance was defined as $p<0.05$ (2 tailed).

7. Results

7.1. Patients

One hundred and fifty-one HBeAg positive CHB infected patients were included into the study. The baseline demographics of these 151 patients are shown in Table 1. One hundred and thirty-five of the 151 patients (89.4%) had minimal or mild inflammation on liver biopsy; 29.8% with minimal inflammation and 59.6% with mild inflammation. Only 16 of the 151 patients (10.6%) had moderate to severe liver inflammation on liver biopsy; 6.6% with moderate inflammation and 4.0% with severe inflammation.One hundred and thirty-four of the 151 patients (88.7%) had F0 or F1 fibrosis stage on liver biopsy; 46.4% with F0 fibrosis stage and 42.4% with F1 fibrosis stage. Only 11 of the 151 patients (7.3%) had F2 or F3 fibrosis stage; 4.6% with F3 fibrosis stage; while 2.6% with F4 fibrosis stage. There were no patients with liver cirrhosis.

7. 2.Factors Associated with No Significant Liver Disease on Histology in those with Normal Serum ALT Levels

A total of 129 of the 151 patients (85.4%) had no significant liver disease on liver biopsy while 22 of the 151 patients (14.6%) had significant liver disease on biopsy. Their baseline demographics are shown in Table 2. Those with no significant liver disease had a lower serum ALT level than those with significant liver disease (p= 0.005) [Table 2]. The serum HBV DNA level was also significantly higher in those with no significant liver disease when compared with those with significant liver disease (p= 0.001) [Table 2].When the patients were age-matched to decades, those aged between 18-29 years of age were more likely to have no significant liver disease (p= 0.041) [Table 2].Those with normal serum ALT as according to recommendations made in AASLD 2007 or AASLD 2018 Practice Guidelines were significantly associated with a higher chance of having no significant liver disease (p= 0.001 and p< 0.001, respectively) [Table 2].There was no difference in the mean age, presence of steatosis or grade of steatosis between those with no significant liver disease and those with significant liver disease (all p= NS) [Table 2].

Table 1: Baseline Demographics.

Variables	n=151
Mean age (SD); years	31 (9)
Age by decade:	
Age 18-29 years	63 (41.7%)
Age 30-39 years	62 (41.1%)
Age 41-49 years	19 (12.6%)
Age≥ 50 years	7 (4.6%)
Sex, M:F	93:58
Median ALT (IQR); U/L	20 (8)
Median HBV DNA (IQR); log IU/ml	7.21 (1.01)
Mean modified HAI score (SD) at initial liver biopsy	5.22 (3.11)
Grade of Inflammation:	
Minimal hepatitis	45 (29.8%)
Mild hepatitis	90 (59.6%)
Moderate hepatitis	10 (6.6%)
Severe hepatitis	6 (4.0%)
Mean fibrosis stage (SD) at initial liver biopsy	0.80 (1.14)
Fibrosis stage:	
F0	70 (46.4%)
F1	64 (42.4%)
F2	7 (4.6%)
F3	4 (2.6%)
F4	6 (4.0%)
Median number (IQR) of portal tracts	12 (3)

7.3. Independent Predictors of No Significant Liver Disease

On multivariate regression analysis, only the normal serum ALT level recommended by AASLD 2018 Practice Guideline was independently associated with no significant liver disease (p= 0.001, Odds Ratio 37.059, 95% Confidence Interval 4.082-336.452).

7.4. Value of AASLD 2018 or AASLD 2007 Practice Guidelines in Predicting Those who are Truly Immune-Tolerant

The use of the normal serum ALT levels recommended by AASLD 2018 Practice Guideline in predicting HBeAg positive CHB who had no significant liver disease had a sensitivity of 99.2%, a specificity of 22.7%, with a positive and negative predictive value of 88.3% and 83.3%, respectively.Whereas the AASLD 2007 Practice Guideline had a sensitivity of 90.7%, a specificity of 42.9%, with a positive and negative predictive value of 90.0% and 42.9%, respectively, in predicting HBeAg positive CHB who had no significant liver disease.

Table 2: Demographics in those with and without significant liver disease on liver biopsy.

Characteristics	No Significant liver Disease (n=129)	Significant Liver Disease (n=22)	P-value
Mean age (SD); years	31 (9)	34 (10)	0.862
Sex; M:F	81: 48	12: 10	0.484
Mean Alanine aminotransaminase (SD) at time of biopsy, U/L	20 (7)	25 (13)	0.005
Mean HBV DNA (SD) at time of biopsy, log_{10}IU/ml	7.85 (1.39)	7.09 (0.89)	0.001
Age by decade:			
18-29 years	63	0	0.041
30-39 years	58	4	0.229
40-49 years	17	2	0.166
≥50 years	7	0	1.000
Normal ALT according to AASLD 2007	117 (90.7%)	13 (59.1%)	0.001
Normal ALT according to AASLD 2018	128 (99.2%)	17 (77.3%)	<0.001
No. of portal tracts	12 (3)	11 (2)	0.434
Steatosis:			0.885
Present	49 (38.0%)	8 (36.4%)	
Absent	80 (62.0%)	14 (63.6%)	
Grade of steatosis:			0.565
1	21 (16.3%)	5 (22.7%)	
2	16 (12.4%)	2 (9.1%)	
3	12 (9.3%)	1 (4.5%)	

8. Discussion

This study highlights several characteristics of HBeAg positive CHB infected patients with normal serum ALT levels, and compares demographic, virological and histological features of HBeAg positive patients with serum ALT levels within the "normal" range as recommended by the AASLD 2007 and AASLD 2018 Practice Guidelines to those with serum ALT levels close to the ULN range as defined by most laboratories [7,8,9]. The main finding in this study was that HBeAg positive CHB infected patients with serum ALT levels within the range recommended by these two guidelines were more likely to have no significant liver disease on liver biopsy. This explains why a previous study found that HBeAg positive Chinese CHB patients with serum ALT levels close to the ULN range as defined by most laboratories were more likely to develop progressive disease [15]. Of these two guidelines, the AASLD 2018 Practice Guideline was the single independent factor associated with no significant liver disease. This group of patients who were HBeAg positive, had normal serum ALT level and no significant liver disease on liver biopsy were those truly in the immune-tolerant phase.The AASLD 2018 Practice Guideline had a higher sensitivity when compared with the AASLD 2007 Practice Guideline. Even though the specificity of the AASLD 2018 Practice Guideline was only 22.7% whereas the AASLD 2007 Practice Guideline had a specificity of 42.9%, we would still recommend the use of the AASLD 2018 Guideline due to its higher sensitivity, higher negative predictive value and almost similar positive predictive value when compared with the AASLD 2007 Practice Guideline. As the negative predictive value of the AASLD 2018 Practice Guideline was 83.3%, one would only miss 16.7% of HBeAg positive CHB patients with significant liver disease who required anti-HBV therapy. On the other hand, the AASLD 2007 Practice Guideline with a negative predictive value of only 42.9%, one would have missed 57.1% CHB patients with significant liver disease who would require antiviral therapy.

As they already had significant liver disease, they would be more likely to develop progressive disease without antiviral therapy despite their normal serum ALT levels as defined by most laboratories. This was first observed in chronic HCV patients with persistently normal serum ALT levels where those with fibrosis stage 2 are more likely to develop fibrosis progression when compared with those who had fibrosis stage 0 or 1 at baseline [16,17].

This study also showed that those who were aged between 18-29 years of age were more likely to have no significant liver disease. However, age by increasing decade was not associated with a higher or lower chance of having more significant liver disease.Those with no significant liver disease also had a higher serum HBV DNA when compared with those with significant liver disease. This may imply that HBeAg positive CHB patients should only be considered as having minimal or no inflammation on liver biopsy if their serum ALT were within the AASLD 2018 Practice Guideline, serum HBV DNA level was more than 7.5 log10 IU/ml and are young; at least younger than 30 years of age. A liver biopsy may have to be considered in those with serum ALT; although still within the laboratory normal limits; were above the AASLD 2018 Practice Guideline for normal serum ALT level with serum HBV DNA less than 7.5 log10 IU/ml, before labeling them as "immune-tolerant" CHB patients with minimal liver disease. If significant fibrosis or inflammation were documented on liver biopsy, they should be carefully evaluated for antiviral therapy despite their relatively normal serum ALT levels. This is because this group of patients may already be in the immune-clearance phase. Finally, although hepatic steatosis was associated with worse fibrosis stage in chronic HCV infection,18,19 neither the presence of steatosis nor the grade of steatosis seems to be associated with significant liver disease in HBeAg positive CHB patients with normal serum ALT level. This lack of association between steatosis and significant liver disease seemed counter-intuitive but it corresponds to our previous finding where steatosis was also not associated with fibrosis stage in CHB patients in the immune-clearance phase [10]. An explanation for this may be because the patients in both these studies were relatively young. Steatosis may only have been present for a short duration and have not had time to result in worsening of liver histology.This study has a few limitations. Firstly, this study did not employ newer noninvasive and reproducible methods for measuring liver stiffness as Fibroscan only became available in our Centre towards the end of 2012. Although histological scoring systems can be unreliable due to sampling error and inter-observer variability among pathologists, it is still considered by many to be the gold standard [20,21]. Furthermore, it can provide grade of inflammation in addition to fibrosis stage whereas Fibroscan can only provide us with fibrosis stage. In order to minimise bias, this study employed a single pathologist who was blinded to the clinical data to interpret all biopsy samples. Secondly, as patients in this study were all Asians, the results cannot be generalised to Caucasians. Thirdly, this study did not have longitudinal data or data on whether anti-HBV therapy can significantly decrease the ALT levels in those whose serum ALT level was above the AASLD 2018 Practice Guideline but still within the normal range set by most laboratories. Fourthly, the EASL 2017 Practice Guideline was not studied as this recommendation was only made after this study was designed in 2008. So, no females with serum ALT levels between 35-40 U/L were included into the study as females with serum ALT above 35 U/L were considered abnormal according to our laboratory. Therefore, the EASL 2017 Practice Guideline that still considered females with serum ALT level of 35-40 U/L to be normal may result in a higher number of patients with significant liver disease being mislabeled as immune-tolerant. Lastly, this study also did not measure quantitative HBsAg or HBeAg levels [9]. In conclusion, the new "normal" serum ALT level recommended by AASLD 2018 Practice Guideline is a good predictor of CHB patients who are in the immune-tolerant phase. HBeAg positive CHB patients with serum ALT levels, although normal by most laboratory values, above the AASLD 2018 Practice Guideline should be carefully assessed with either liver biopsy or alternative non-invasive methods for assessing liver fibrosis and inflammation for consideration of therapy.

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