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Original Research Article

Characteristics of patients with HBeAg negative chronic hepatitis B virus infection in Duhok, Kurdistan region

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ABSTRACT

Background: The objective of this study was to characterize patients with HBeAg-negative chronic hepatitis B in Duhok province.
Methods: We recruited all patients with HBeAg negative chronic hepatitis B virus infections who visited viral hepatitis clinic in Azadi Teaching Hospital between September 2015-December 2017. The main evaluation parameters were: serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, serum albumin, total serum bilirubin (TSB), viral load. Few patients were subjected to Fibro-test, Fibroscan, or liver biopsy.
Results: There were 251 patients. The mean age of the patients was 35.75±14.40 years. One hundred fifty-seven cases were male and 94 cases were female. The baseline mean of ALT, AST and viral load was 42.09±2.71U/L, 30.26±19.65U/L, and 1421197.08±14436692.04IU/ml, respectively. Compared with women, men have significantly higher values of ALT and AST, serum albumin, and TSB. There were 217 chronic inactive carrier (IC) patients and 34 chronic active hepatitis (AH) patients. ALT, AST, and viral load levels were significantly higher among AH patients.
Conclusions: The majority of patients showed nil to mild liver injury. The higher level of ALT in males is a supporting guide to follow the American Association for the Study of Liver Diseases (AASLD) considering 30U/L and 19U/L levels for males and females, respectively. There was preponderance of males in AH, which indicates greater frequency of advanced fibrosis in such patients. There was a greater probability of AH in old aged people. Serum albumin and TSB were not good markers for differentiation between AH and IC state. Twenty-four patients had ALT above twice upper limit of normal level, but 34 patients showed AH based on liver biopsy, firboscan or fibrotest.

Keywords: Characteristics, Chronic hepatitis, Duhok, HBeAg negative

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious public health problem, resulting in approximately 2 billion human infections and 257 million chronic infections worldwide.[1] It is estimated that about 15-40% of HBV infected people will progress and eventually develop cirrhosis, hepatic failure and hepatocellular carcinoma (HCC).[2] Diagnosis of HBV infection is made through serological and virological markers. Of these, hepatitis B surface antigen (HBsAg) is the cornerstone for diagnosis of HBV infection. However, other markers are essentially fundamental in differentiating between active and inactive infections. Importantly, hepatitis B e antigen (HBeAg) is indicative of active viral replication.[3] Meantime, measuring serum alanine aminotransferase

(ALT) and HBV-DNA viral load is an important component in evaluating and managing patients with chronic HBV infection.[4] Chronic hepatitis B patients with negative HBeAg are more prone to advanced liver fibrosis than hepatitis B inactive carrier state.[5] In HBeAg negative patients, the differentiation between active hepatitis (AH) and inactive state (IC) sometimes is challenging because there is fluctuation in viral replication represented by serum HBV-DNA viral load and biochemical markers.[6] In Duhok, despite the national vaccination programme against HBV in the general population and also against high risk people, there are still significant numbers of chronic cases observed in clinical practice.[7,8] However, there is no adequate data about characteristics of chronic HBV infection particularly among the challenging entity of HBeAg negative patient. Hence, this study was performed to characterize patients with HBeAg-negative chronic hepatitis B in Duhok province.

METHODS

Setting

The viral hepatitis clinic in Azadi Teaching Hospital is dealing with all viral hepatitis cases. The center is designed to manage viral hepatitis cases. The patients were visiting the center on regular intervals based on their clinical conditions. All of the patients' information was collected in standardized case notes.

Studied population and procedure

We recruited all patients with negative HBeAg negative chronic hepatitis B virus infections who visited the center between September 2015-December 2017. The inclusion criteria were: patients with chronic hepatitis B who were HBeAg negative. The exclusion criteria were HBeAg positive chronic hepatitis B, hepatitis C virus, hepatitis A virus, human immunodeficiency virus, autoimmune hepatitis. The main evaluation parameters were: Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (upper limit of normal, 40 IU/L), serum albumin, total serum bilirubin (TSB), HBV-DNA viral load. Few patients were subjected to Fibro-test, Fibroscan, or liver biopsy when classification of activity was impossible according to laboratory profile and this was done based on treating physician preference. Negative HBeAg chronic HBV was defined as having detectable HBsAg for more than 6 months with negative HBeAg. Chronic active HBeAg negative patients was defined as a serum HBV-DNA levels ≥2000IU/ml and elevated ALT more than 80 IU/L. Whenever diagnosis of AH versus IC was uncertain a diagnosis was made based on Ishak score or metavir score.[9,10]

Statistical analysis

Data were collected and analyzed using SPSS (version 10.0; SPSS Inc, Chicago, IL) software package.

RESULTS

Two hundred fifty one patients were included in this study. The mean age of the patients was 35.75±14.40 years. One hundred fifty seven cases were male and 94 cases were female with a male: female ratio of 1.67:1. Table 1 shows baseline characteristics of the studied population.

Table 1: Baseline characteristics of the study populations.

Variable		Mean ±SD (no = 251)
Sex	Male	157 (62.5%)
	Female	94 (37.5%)
Age		35.75±14.40
ALT U/L		42.09±2.71
AST U/L		30.26±19.65
S. albumin mg/dl		4.50±0.57
TSB mg/dl		0.78±0.74
HBV-DNA VL IU/ml		1421197.08±14436692.04

ALT: alanine aminotransferase, AST: aspartate aminotransferase, S. albumin: serum albumin, TSB; total serum bilirubin, HBV: hepatitis B virus

The baseline mean of ALT, AST and HBV-DNA VL was 42.09±2.71U/L, 30.26±19.65U/L, and 1421197.08± 14436692.04IU/ml, respectively. In Figure 1, 2, and 3, the proportion of these parameters are demonstrated below.

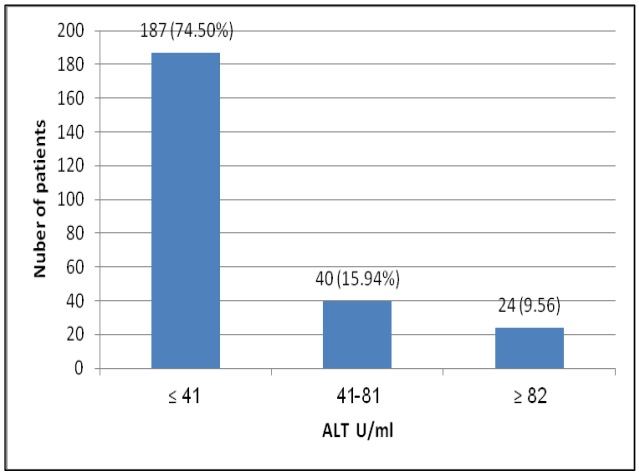

Figure 1: Distribution of patients according to baseline ALT.

The baseline characteristics of the patients were stratified by gender to show whether there is significant association (Table 2). Compared with women, men have significantly higher values of ALT and AST, serum albumin, and TSB. There were 217 IC state patients and 34 AH patients. The gender, age, AST, s. albumin, and TSB were compared between active versus IC state (Table 3). ALT, AST, and viral load levels were significantly higher among AH patients.

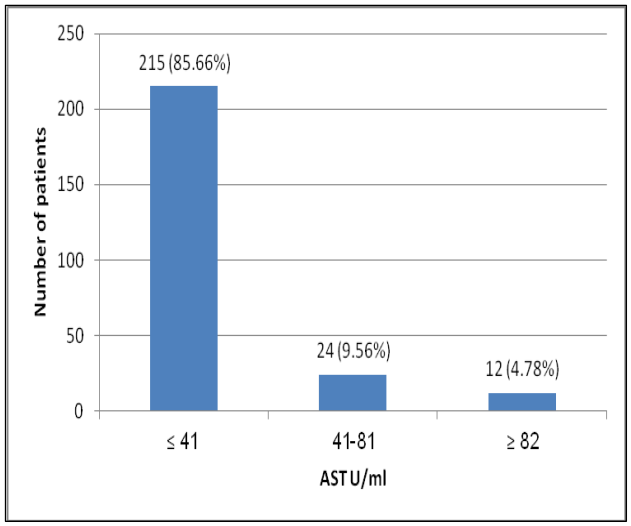

Figure 2: Distribution of patients according to baseline AST.

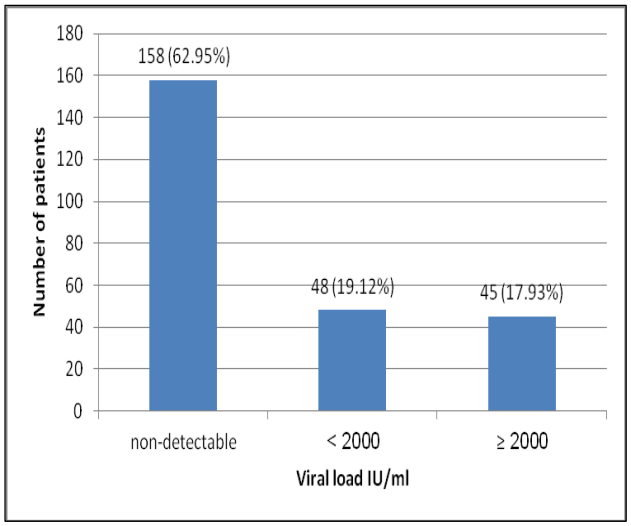

Figure 3: Distribution of patients according to HBV-DNA viral load.

Table 2: Comparison of baseline characteristics according gender.

Variable	Male (157)	Female (94)	OR (95% CI)	P value
Age	36.36±14.64	34.74±13.95	1.6200 (-2.0752 to 5.3152)	0.3887
ALT U/L	49.04±50.18	30.49±22.07	18.5500 (7.7759 to 29.3241)	0.0008
AST U/L	32.48±20.07	26.58±18.36	5.9000 (0.9045 to 10.8955)	0.0208
S. albumin mg/dl	4.56±0.58	4.41±0.54	0.1500 (0.0048 to 0.2952)	0.043
TSB mg/dl	0.89±0.85	0.61±0.44	0.2800 (0.0939 to 0.4661)	0.0033
HBV-DNA VL IU/ml	2266860.90±18201461.12	8758.55±32685.71	2258102.3500 (-1442365.7671-5958570.4671)	0.2306

ALT: alanine aminotransferase, AST: aspartate aminotransferase, S. albumin: serum albumin, TSB; total serum bilirubin, HBV: hepatitis B virus

Table 3: Comparison of baseline characteristics between active and inactive chronic hepatitis.

Variable	IC state (217; 86.45%)	AH (34; 13.55%)	OR (95% CI)	P value
Sex	Male	133 (52.99) 24 (9.56)	3.592 (1.516-0.652)	0.344
	Female	84 (33.47) 10 (3.98)		
Age	28.74±17.44	33.35±15.18	4.6100 (-1.6229 to 10.8429)	0.1465
ALT u/l	28.74±17.45	127.35±56.71	98.6100 (89.0651 to 108.1549)	0.0001
AST u/l	24.46±8.77	67.34±27.77	42.8800 (38.1585 to 47.6015)	0.0001
S. albumin mg/dl	4.51±0.58	4.44±0.49	-0.0700 (-0.2767 to 0.1367)	0.5053
TSB mg/dl	0.78±0.77	0.81±0.47	0.0300 (-0.2378 to 0.2978)	0.8256
HBV-DNA VL IU/ml	672.53±3606.06	16663894.91±50723761.99	16663222.38 (9955106.4654 to 23371338.2946)	0.0001

DISCUSSION

Although, most patients with HBeAg negative profile show normal liver enzymes, they should be evaluated regularly.[11] The presentation of HBeAg negative patients is a major challenge in patient managements.[12]

In our study, the frequency of male chronic HBeAg negative patients was more than females (62.5% versus 37.5%), which is in parallel with other studies.[7,13,14] The reason to this finding is because males are exposed to risk factors for acquiring HBV infection more than females and it might also be related to opposite effects of sex

hormones. The finding of sex hormones effects is documented by studies from experimental animals, which revealed that androgen stimulates viral transcription, whereas estrogen suppresses the transcription.[15] In this study, the patients were young (35.75±14.40 yr), which was in concordance with other studies from this region.[13] This finding is of particular concern as it is a lifetime potential for developing advanced liver diseases and hence regular clinical, laboratory, and radiological follow-ups of patients with chronic HBeAg negative profile are mandatory.

In our study, we found that 74.50% of the patients had normal ALT values, which indicates that no liver injury occurred. The remainder showed a higher ALT level, which may be an indication for hepatocellular damage. The liver injury in hepatitis B is the result of cell mediated hepatic injury rather than cyopathic effect of the virus.[16] A higher percentage (85.66%) of patients showed normal AST level that could be explained by mild injury of liver hepatocytes.[17]

Generally, ALT and AST are recognized markers for liver diseases. ALT is more reliable than AST because it concentrates in hepatic cell cytozole and acts as a surrogate marker in mild liver injury.[17] In the present study, HBV-DNA was ≥2000IU/ml in 17.93% of patients, which is the cut-off limit to differentiate between IC and HBeAg negative AH.[18]

Comparing baseline characteristics of the HBeAg negative patients according to gender, we found that male gender was positively associated with higher ALT, AST, serum albumin and TSB values. These findings are supported by findings of other studies.[19] The higher level of ALT in males in this study is a supporting guide to follow the American Association for the Study of Liver Diseases *(*AASLD) for considering 30U/L and 19U/L levels for males and females, respectively.[20] Therefore, it is important to use these cut-off values in our clinical practice for managing HBeAg negative patients in Duhok. The level of AST in males was higher than in females, which could be explained by the increase in the muscle mass of males rather than direct link with chronic hepatitis B infection.

It was noted in this study that the IC and AH groups showed preponderance of males (52.99% and 9.56%, respectively). This is in line with the finding of other studies, which confirmed predominance of male in HBeAg negative patients and greater frequency of AH with advanced staging fibrosis.[14] In the current study, the mean age of the AH patients was greater than IC patients, which was similar to findings of other studies e.g. Fattovich et al.[21] It is well known that there is a greater probability of AH in old aged people; on the meantime the probability of IC is higher in young aged people.[22] In general, there is a 0.6% chance for people older than 40 years to develop AH compared to younger aged people.[21]

Generally, HBeAg negative AH patients were found to have significantly higher serum ALT and AST values compared with those who were HBeAg negative IC patients. This finding is self-evident according to the criteria for classification of AH versus IC HBeAg negative patients.[18,23] It is well documented that the increasing of ALT level is correlated with the fibrosis progression in liver disease, while AST is a good predictor of necro-inflammatory activity of chronic hepatitis B patients.[24] In this study, although 34 patients (13.55%) had AH, only 24 patients (9.56%) had ALT above twice upper limit of normal values (Figure 1 and Table 3). Hence, if we considered the initial laboratory profile of ALT and viral load, about 10 patients would be missed as IC state. There is a marked fluctuation in ALT level of patients with HBeAg-negative chronic hepatitis B and 20-30% of such patients with normal ALT show histologically approved AH at the time of the presentation.[25] Therefore, it is crucial to consider liver biopsy or non-invasive studies such as fibroscan in patients in whom it is difficult to distinguish IC from AH. As a result, it is important to routinely introduce these procedures for management of HBeAg negative patients in Duhok.

The association of serum albumin between the two groups of AH and IC patients was not significant in our study. This is well described by other authors confirming low specificity of serum albumin in differentiation between active and inactive state.[26] Serum albumin is synthesized in the liver only and therefore; a low level indicates marked hepatic impairment.[8] Our study showed that there was no association between TSB level and whether or not the patient has AH or IC. Although, increased TSB is a poor prognostic sign for advanced liver diseases, it is not a good marker for evaluation of active versus inactive hepatitis B patients.[27] The mean viral load was higher in HBeAg negative AH patients compared to IC patients (P=0.0001). In overall, HBeAg negative patients with low viral load are associated with a less extent hepatic damage.[28,29]

The main limitations in this study were its retrospective analysis; the same reference value of ALT and AST was used for men and women. Additionally, liver biopsy, fibroscan and fibrotest were used in selected patients in which differentiation between IC and HBeAg negative AH was impossible based on laboratory parameters. In conclusion, the frequency of male chronic HBeAg negative patients was more than females (62.5% versus 37.5%) and the patients were young (35.75±14.40 yr). The majority of patients in our study showed nil to mild liver injury. The higher level of ALT in males is a supporting guide to follow the AASLD for considering 30U/L and 19U/L levels for males and females, respectively. There was preponderance of males in AH which indicates greater frequency of advanced fibrosis in such patients. There was a greater probability of AH in old aged people. The ALT, AST and viral load were significantly higher among AH patients. Serum lbumin

and TSB were not good markers for differentiation between AH and IC state. Twenty-four patients had ALT above twice upper limit of normal level but 34 patients showed AH based on liver biopsy, firboscan or fibrotest. Further prospective studies with large sample sizes are warranted to more precisely ascertain characteristics of patients with HBeAg negative chronic hepatitis B.

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