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Epidemiological and Histological Features of Chronic Hepatitis B with low Level DNA with or without Transaminitis

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Abstract
Aims: *Management of Chronic Hepatitis B patients with HBV DNA below 2000 iu/ml continues to be gray zone area. We evaluated the clinical, epidemiological and histological characteristics of with low level DNA with or without transaminitis.*
Materials and Methods: *90 adult patients of chronic hepatitis B with serum DNA<2000 iu/ml with normal or raised serum ALT levels were included in the study after predetermined inclusion and exclusion criteria. Liver biopsy was performed in all of them for fibrosis assessment on Metavir system.*
Results: *Out of 90 patients, 70 (77.8%) were males and 20 (22.2%) were females. Liver biopsy as staged on Metavir scoring system revealed 60/90 (i.e. 66.7%) patients had F0 i.e. no fibrosis. 30/90 (33%) patients had some fibrosis (≥F1) though significant fibrosis i.e. F2 and F3 was seen in 8/90 (9%) patients.*
Conclusion: *Chronic hepatitis B patients with serum DNA <2000 IU/ml were found to have some fibrosis i.e. Metavir F1, F2, F3 fibrosis in 30 patients (33%), 8 patients i.e. 9% had significant fibrosis (≥F2). All the Chronic hepatitis B patients irrespective of the HBV DNA or ALT levels must have fibrosis assessment. If there is significant fibrosis, on liver biopsy, they should be treated irrespective of DNA levels.*

Introduction

Chronic hepatitis B is a global health problem. Around 400 million people are carriers of HBV in the world today; of these 75% reside in Asia and western pacific.[1] There are around 600,000 deaths annually from hepatitis B related liver diseases.[2]
The spectrum of chronic hepatitis B viral (HBV) infection ranges from inactive carrier state to chronic hepatitis, cirrhosis, hepatic decomposition, hepatocellular carcinoma (HCC) and death.
Hepatitis B virus (HBV) infection is particularly important in the Asia-Pacific region where it is endemic, with majority of the infections being acquired perinatally or in early childhood.
Various guidelines have been formulated for the management of chronic hepatitis B infection cased on HBV DNA levels, serum ALT and

HBeAg presence or absence, the role of the liver biopsy being oft, limited. The last group of patients that is the inactive carrier stage has been a matter of discussion regarding the natural course, histological correlation with the ALT levels and HBV DNA level, and more importantly the management as to whether be followed with ALT and HBV DNA or liver biopsy be done and managed accordingly. The inactive HBV carrier state refers to presence of HBsAg in serum without HBeAg or ALT elevations and with HBVDNA levels less than10,000copies/ml.[3]

Various cut-offs have been proposed for HBV DNA and ALT levels in this group. Interestingly there has been a gradual declining trend in the cut-off levels. Basically all these cut-offs are arbitrary and no cut-off value is absolute in ruling out liver damage. Slightly increased ALT level although within the normal range, has been reported to be significantly associated with risk of liver related mortality in the general population.[4]

Low viremia if prolonged causing insidious and continuous damage as reflected by ALT levels 0.5 to 2 x upper limit of normal (ULN) can cause development of complications in Asian CHB patients.[5] Liver biopsy is the gold standard for assessing liver fibrosis which in turn is the most important prognostic factor for the severity of liver disease. It is particularly important in those patients to whom the current guidelines of treatment do not have a clear answer. APASL does not recommend treatment for the patients with PNALT or minimally raised ALT levels unless they have evidence of advanced fibrosis or cirrhosis and consider sliver biopsy in viremic patients older than 40 years especially in presence of high normal or minimally raised ALT levels.[6]

AASLD advises consideration of the liver biopsy in patients HBeAg positive CHB with fluctuating or minimally elevated ALT levels especially > 40 years of age. Treatment is recommended incases with moderate or severe necroinflammation or significant fibrosis. Among HBeAg negative CHB patients with HBV DNA between 2000-20000 IU/m1 and Border line normal or minimally elevated ALT, treatment is considered if liver biopsy shows moderate/sever inflammation or significant fibrosis.[7]

As per the 2015 WHO practice guidelines for chronic hepatitis B infection,[8] every patient of CHB must have a baseline assessment of fibrosis by non-invasive means (APRI or Fibroscan). In case there is evidence of cirrhosis either clinically or biochemically or on these non-invasive tests, patient should be treated with antivirals irrespective of baseline HBV-DNA levels.CHB with HBeAg —ve with PNALT is not a homogeneous group and those with high normal ALT have characteristics associated with adverse long term outcomes and distinction is not always clear cut between inactive carriers and HBeAg —ve chronic hepatitis.[9] There is a significant fibrosis and inflammation in 37% of patients of CHB with PNALT and liver biopsy should be reconsidered especially with > 40 years of age and high normal ALT.[10] CHB eAg —ve with PIEALT may have histological indication of treatment even at DNA < 2000 1U /ml while PNALT with HBV DNA even > 2000 iu/ml may have only minimal histological lesions which may not require treatment. The use of DNA and ALT levels without resorting to liver biopsy to define inactive carrier state in HBeAg — ve with PNALT may miss histologically significant disease in a proportion of patients because a fair proportion of patients with CHB with PNALT having HBV DNA > 20000 iu/ml have significant fibrosis, in addition around 21%of CHB eAg —ye patients with PNALT and HBVDNA <20000iu/ml have histologically active disease.[11]

The inactive carriers of hepatitis B infection posses substantial risk of HCC and liver related mortality compared with individuals not infected with hepatitis Binfection.[12]

This subset of patients i.e. chronic hepatitis B with low levels of HBV DNA and PNALT or PIEALT have good amount of controversy regarding their course and management. If only HBV DNA and /or ALT levels are considered for

their management, we may miss good portion of these patients and deny them treatment. Though role of liver biopsy has been declining as of late, it may be the best way to get an idea of the disease activity and further management in this group of patients. We feel it imperative to conduct a study in this particular group of patients which would compare the HBV DNA load and ALT levels with the histological severity.

Material and Methods

The study was conducted in the Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Soura, Srinagar and Department of Gastroenterology, Govt. Medical College, Srinagar over a period of 48 months from January 2014 to December 2017.

Inclusion Criteria

- Age more than 18 years
- HBsAg positivity for > 6 months
- No present or past evidence of any symptoms related to liver disease other
- than hepatitis B
- At least 2 visits and follow up of > 12 months.
- HBV DNA level <2000 IU/ml

Exclusion Criteria

- Hepatitis C or D or HIV coinfection.
- Decompensated liver disease
- Hepatocellular carcinoma
- Evidence of liver disease because of other etiology
- Use of hepatotoxic drugs
- Immunosuppressed patients or patients on immunosupressants
- Pregnancy

Formal Informed Consent was taken after properly discussing the procedure of liver biopsy along with the benefits, complications in the language of the patients.

Institutional Ethical Committee: The study was started after getting clearance 8from the Institutional Ethical Committee.

Biochemical and Serologic Tests: Biochemical tests and complete blood cell counts were performed using routine automated analyzers. The upper limit of normal for serum ALT was taken as 40 IU/L. HBsAg, assay was performed with ERBA LISA HEP-B (ELISA) kits Trans Asia Biomedicals Ltd. Daman. HBeAg assay was done using DSI, Volontorio, Italy.

Quantification of Serum HBV DNA Levels: was done by reverse transcriptase polymerase chain reaction (RT-PCR).

Liver biopsy

Percutaneous liver biopsy was performed using liver biopsy gun (BARD Pereipheral Vascular, Inc, USA.) with 16 G needle under ultrasound guidance. Biopsies were fixed in 10% formalin, embedded in paraffin, and stained with HE, Masson's trichrome and reticulin staining for histological assessment. Only liver biopsies with a minimum length of 1.5 cm and at least eight complete portal tracts were considered suitable for further analysis. Fibrosis stage and inflammation grade were assessed by two independent patholo-gists according to the METAVIR scoring system.

Metavir Scoring System

Fibrosis was staged from F0 to F4:
F0: No Fibrosis
F1: portal fibrosis without septa
F2: Portal fibrosis with few septa;
F3: Numerous septa without cirrhosis
F4: Cirrhosis

Statistical Methods: The recorded data was compiled and entered in a spreadsheet (Microsoft Excel) and then exported to data editor of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. Graphically the data was presented by bar and pie diagrams. Student's independent t-test was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. A P-value of less than 0.05 was considered statistically significant

Results/Observations

Table 1: Age and gender distribution of study population

Age (years)	Male		Female		Total
	No.	%age	No.	%age	
< 40	44	62.9	12	60.0	56
≥ 40	26	37.1	8	40.0	34
Total	70	100	20	100	90

Table 1 shows total number of patients included is 90. Out of them majority i.e.70 (77.8%) were males and only 20 (22.2%) were females. Among males 44 were below 40 years of age while 26 were more or equal to 40 years of age. Among females 12 were below 40 years of age while as 8 had age of ≥ 40 years.

Table 2: Distribution of study population with respect to serum ALT

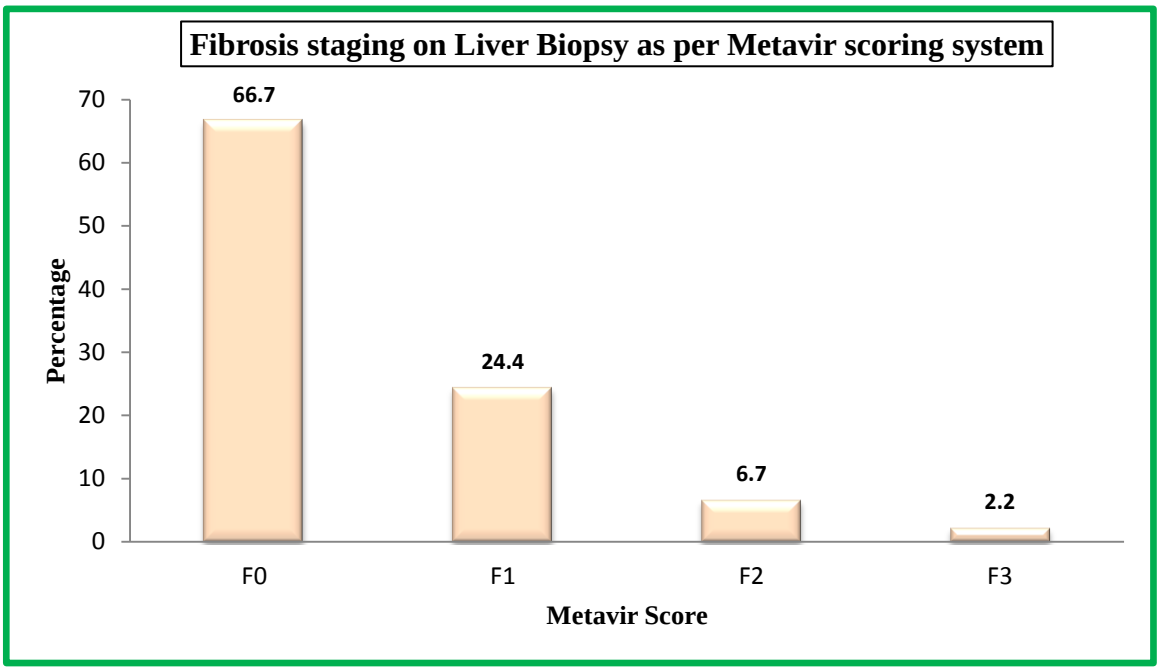
ALT (IU/ml)	Frequency	Percentage
< 40	38	42.2
≥ 40	52	57.8
Total	90	100
Mean±SD=51.36±27.29		

Table 2 shows that 52 (57.8%) of the patients had mean ALT ≥ 40 IU/ml while 38 (42.2%) had mean ALT < 40 IU/ml. The mean level of ALT in patients was 51.36±27.27 IU/ml.

Table 3: Serum DNA levels of study population

Serum DNA Levels (IU/ml)	Frequency	Percentage
< 1000	54	60
≥ 1000	36	40
Total	90	100
Mean±SD=802.5±248.2 (3.8-1800)		

Table 3 shows that mean serum DNA levels of the study group was 802 IU/ml (3.8-1800). 54 (60%) patients had levels ≤ 1000 IU/ml while 36 (40%) had levels of > 1000 IU/ml.



Liver biopsy as staged on Metavir scoring system revealed 60 patients (66.7%) had F0 i.e. no fibrosis. Approximately 30 patients (33%) patients had some fibrosis (≥F1) though significant fibrosis i.e. F2 and F3 was seen in 8 (9%) patients.

Table 4: Descriptive analysis of ALT vs Biopsy

Fibrosis	ALT < 40 IU/ml		ALT ≥ 40 IU/ml		Total	
	No.	%age	No.	%age	No.	%age
No/ Insignificant	36	94.7	46	88.5	82	91.1
Yes	2	5.3	6	11.5	8	8.9
Total	38	100	52	100	90	100
Chi-square=0.433; P-value=0.510						

Table 4 shows relation between fibrosis on biopsy and cut off levels of ALT.

Out of 82 patients who had no or insignificant fibrosis 36 had ALT levels of < 40IU/ml while as 46 had ALT level of ≥ 40 IU/ml.

Out of 8 patients who had significant fibrosis 6 had levels of ALT ≥ 40 IU/ml and only 2 had ALT level < 40 IU/ml, the difference was statistically not significant. (p>0.4).

The mean level of ALT among patients with fibrosis on biopsy was higher (62.50 IU/ml) as compared to those patients without fibrosis (50.27 IU/ml) but the difference was also statistically insignificant.

Discussion

Historically, the treatment guidelines for chronic hepatitis B have been basedupon various cut-offs of serum HBV DNA, Serum ALT, features of decomposition or presence of significant fibrosis. The cohort of the patients which we studied is somewhat a grayzone because patients with HBVDNA below 2000 IU/ml have always been managed with reassurance and follow-up. But the fact is that no cut-off of HBVDNA or ALT can rule out the fibrosis altogether.

Martinot –Peignoux B et al[13] studied inactive carriers of hepatitis B (DNA <2000 and normal AlT) and found mild fibrosis in the cases biopsied. Ikeda K et al[14] studied a group of patients with normal ALT and found 27 out of 116 patients had significant fibrosis and 6 had cirrhosis (out of 116).

Lin CL et al[9] in their study found that HBeAg negative patients with PNALT were not a homogenous group and those with high normal ALT shared some characteristics which are associated with adverse long term outcomes.

Sarin SK et al[11] in their study found that among 9 biopsies done on 52 patients with PNALT and HBVDNA < 104 copies /ml, 7 patients (77.8%) had ≤ F1 fibrosis and 2 patients had ≥F2 fibrosis and concluded that use of Serum ALT and HBV DNA levels without restoring to liver biopsy to define inactive carriers may miss histologically significant disease in a proportion of patients.

Chen JD et al[12] found that carriers of hepatitis B are at a substantial risk for HCC and liver related mortality compared to individuals not infected with hepatitis B. In addition a long term follow up study of asymptomatic HBsAg carriers done in our neighboring country Bangladesh by Rahman MM et al[15], they found that 32 % had mild fibrosis, 2 % had moderate fibrosis, 2% had cirrhosis and 0.11% developed HCC.11 patients were having F1 fibrosis on liver biopsy. The mean ALT in these patients was 56.9 IU/ml.30 patients were having F0 ie No fibrosis on liver biopsy.4 patients (9%) had significant fibrosis ≥ F2 on Metavir system. All of them were males, mean ALT of these patients was 62.5 IU/ml compared to overall mean ALT of 51 IU/ml .The mean HBV DNA in these patients who had significant fibrosis was 741 IU/ml although the overall mean HBV DNA was 802 IU/ml.

At the end, we are of the opinion that all the patients of Chronic hepatitis with whatever DNA

levels and ALT must be assessed for fibrosis. The method of fibrosis assessment in the patients with low DNA and normal or raised ALT would obviously be out of the non-invasive cluster of tests either biochemical or imaging based. But till the time we find a non-invasive replacement for liver biopsy especially on this group of patients, liver biopsy will continue to be the first option.

But we agree that our study had small number of patients and hence a larger study with more number of patients is needed.

Conclusion

1) Chronic hepatitis B patients with serum DNA <2000 IU/ml were found to have some fibrosis i.e. Metavir F1, F2, F3 fibrosis in 30 patients (33%), 8 patients i.e. 9% had significant fibrosis (≥F2).
2) All the Chronic hepatitis B patients irrespective of the HBV DNA or ALT levels must have fibrosis assessment. If there is significant fibrosis on liver biopsy, they should be treated irrespective of DNA levels.
3) We must carry out a larger study comparing the fibrosis assessment of non-invasive modalities vis a vis liver biopsy so as to validate them as replacement for liver biopsy.

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