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Spectrum of Disease Activity in Incidentally Positive HBsAg Patients in Eastern Uttar Pradesh

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Abstract: ***Introduction: It is estimated that over 40 million hepatitis B-infected subjects account for approximately 10–15% of the entire pool of HBV carriers of the world live in India, and most of the affected population is detected incidentally without any symptoms. Hence, we aimed to evaluate the spectrum of disease activity in incidentally positive HBsAg patients in eastern Uttar Pradesh. Methodology: This prospective observational study included 125 individuals with incidentally detected HBsAg positivity. All participants were given a thorough medical history and general and systemic physical examination. Also performed were a complete blood count, liver function tests, and kidney function tests. Virus-specific markers (HBsAg, HCV and HIV) were also detected. In addition, a USG, Fibroscan and chest x-ray were performed. Results: Most patients with high (80.36%) and low viral load (69.57%) were 18-40 years old. Male preponderance was noted in both groups. The hepatic enzyme levels were higher in patients with high viral load. The mean prothrombin time was significantly higher in patients with a high viral load compared to the low viral load(p=0.0234*). Only 1 patient with a high viral load and 3 with a low viral load had chronic liver disease. The mean fibro scan was insignificantly higher in patients with low viral load. No association was observed between APRI and FIB4 with Fibroscan. Conclusion: Asymptomatic HBsAg was detected incidentally more common in men. Hepatic enzymes and prothrombin time were raised in most patients with a high viral load. Patients with a low viral load had high Fibroscan scores.***

Keywords: Hepatitis B virus, hepatitis B surface antigen, incidentally detected HBsAg-positive subjects, Aspartate aminotransferase, Alanine transaminase, Alkaline phosphatase, Fibroscan

1. Introduction

Hepatitis B virus (HBV) infects more than 300 million people chronically worldwide and is a common cause of liver disease and liver cancer. HBV infection leads to a wide spectrum of liver diseases, from acute (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma [1]. The burden of HBV infection is geographically disparate, dependent on the different modes of transmission predominant in the population and the resulting age at infection, which determines the probability of progression to chronic infection. In a developing country like India with an intermediate level of prevalence (2 to 7 %) of hepatitis B, most patients remain undiagnosed as they are asymptomatic [2]. The epidemiology of HBV infection globally is changing because of the impact of universal infant vaccination programs, voluntary blood donations, etc. Data from our region is lacking in this era of rapidly changing epidemiology [3].Many HBsAg-positive patients acquire the infection through perinatal exposure or horizontal transmission. Although on presentation, these patients are asymptomatic and look healthy; a proportion of them show biochemical or histological abnormalities and have been shown to progress to symptomatic chronic liver disease or cirrhosis or develop hepatocellular carcinoma on long-term follow-up. Incidentally detected HBsAg-positive patients seek medical attention because HBsAg is detected during routine check-ups, blood donation, family screening of contacts of patients with HBV-related chronic liver disease, or a routine test showing abnormal ALT or AST. Although incidentally detected, they should be thoroughly investigated to identify liver inflammation and the stage of fibrosis so that potential targets for treatment can be identified and antiviral therapy offered [4].Chronic hepatitis B can be divided into e antigen- (HBeAg) positive or HBeAg-negative disease based on the presence or absence of e antigen. The presence of HBeAg is typically associated with higher rates of viral replication and therefore increased infectivity [5]. Most IDAHS subjects are HBeAg negative and have normal hepatic transaminases [6]. However, they should be considered as patients since viremia is detected in almost all cases using PCR technique, and histopathological evidence of chronic hepatitis B virus infection, is present in varying degrees [7]. These are heterogeneous groups with variable serological and clinical profiles. The determinants of the outcome of chronic hepatitis B appear to be both viral (HBV DNA levels, HBV genotype, some HBV mutation patterns) and host-specific (age, gender, genetic background, immune status). Therefore, we aimed to characterize HBV infection in incidentally detected asymptomatic hepatitis B surface antigen (HBsAg)-positive (IDAHS) among Northern Indian subjects.

2. Material and Methods

This prospective observational investigation was conducted for one year at the B.R.D. Medical College, Department of Medicine. After obtaining written/informed consent from the patients and ethical authorization from the institute, 125 incidentally detected HBsAg-positive individuals aged >18 years were included in the study. Those unwilling to participate were excluded. All enrolled patients underwent a comprehensive history and general and systemic physical examination. Complete blood count (Erythrocyte count, TLC, DLC, platelet count), plasma glucose (random), Liver function tests, and Kidney function tests were also performed. In addition, viral markers (HBsAg, HCV and

HIV) were detected. HBeAg, HBV DNA, Anti-HBeAg, USG of the entire abdomen, FIBROSCAN (if necessary), and a chest x-ray were also performed. Subjects with high HBV viral load and/or high ALT (Alanine aminotransferase) were considered potential candidates for antiviral therapy. Those with detectable DNA and/or high ALT were advised for regular 3–6 months follow-up.

Statistical Analysis:
Data were entered in Microsoft Excel and analyzed using statistical software SPSS version 26. The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous variables were presented in number/frequency and were analyzed using the Chi-square test. For comparison of the means between the three groups, analysis by ANOVA test and Spearman correlation with a 95% confidence interval was used. A p-value of < 0.05 or 0.001 was regarded as significant.

3. Results

Among 125 IDHAS, 56 had a high viral load, and 69 had a low viral load. Most patients with high (80.36%) and low viral load (69.57%) were 18-40 years old. Male preponderance was noted in both groups. Although, no substantial association was observed in the age and gender of the patients with viral load. The mean serum bilirubin was higher in patients with high viral load [0.85±0.63] than in low viral load [0.79±0.49]. [Figure-1] Similar was the case with Aspartate aminotransferase (AST), Alanine transaminase (ALT) and Alkaline phosphatase (ALP). The platelet count was higher in patients with low viral load [182500.00±74565.41] than the high viral loads [170120.37±89244.15]. Statistically, no significant association was observed between platelet count and viral load. The mean prothrombin time was noted to be significantly higher in patients with a high viral load [24.40±3.06] compared to the low viral load [20.93±2.20], (p=0.0234*). [Table-1] Only one patient with a high viral load and 3 with a low viral load had chronic liver disease. [Figure-2] The mean fibro scan was insignificantly higher in patients with low viral load [16.49±19.68]. The mean age and platelet count were higher in patients with fibro scan scores <9 kPa than those with scores >9 kPa. On the contrary, the mean AST, ALT and ALP were higher in patients with fibro scan scores >9 kPa. However, no significant association was noted between fibro scan score and other parameters. [Table-2] APRI and FIB4 also showed no association with fibro scan score. [Table-3; Figure-3 and 4]

4. Discussion

We found in our study that most patients had a low viral load in the younger age group between 18 to 40 years 48(69.57%) and above 40 years 21 (30.43%). Choudhuri G et al. [8] also found a higher number of patients incidentally detected in the study belonging to the age group less than 40 years(78%) and above 40 years(22%) out of 592 patients. Okwuraiwe A et al. [9] studied a higher prevalence of hepatitis B virus in the age group between 20 to 40 years 349 (59%) out of 594 patients incidentally detected. This may be related to the higher incidence of activities associated with HBV acquisition or reactivation of existing infections in this age group. This age group of patients is supposed to get the infection in the perinatal period or early childhood period, and after that, they become inactive carriers of HBV infection. Even though most patients had low viral loads, individuals below 40 had greater viral loads when viral loads were compared to patient ages. Higher viral loads are found in younger populations. This study anticipates a high HBV DNA level in close to 50% of the population. Our research shows patients below 40 (80.36 %) exhibited considerably greater viral loads than those above 40 (19.64 %). Okwuraiwe A et al. [9] stated that the age group over 50 had a higher viral load. Higher viral loads in patients imply sustained viral replication, which might lead to cirrhosis or hepatocellular cancer in this age group. As a result, treatment should begin as soon as feasible to decrease the burden of viral load and thus to stop the progression. High DNA level was associated with a significantly increased risk of HCC and with progression towards cirrhosis.When considering medication in conjunction with age, ALT level, pregnancy/breastfeeding, liver histology, and viral load values of 2000–200000, the National Institute for Health and Care Excellence (NICE) guidelines consider viral load values of 2000–200000 as critical cut-off criteria. Therefore, considering the viral load is important when determining management choices for an HBV infection. In our study, mean ALT levels were high in patients with higher viral load, indicating the infection is present and also signifies necro-inflammatory changes in the liver or the hepatocellular damage done. The mean ALT level (44.11) was high in the high viral load subject, as in our study and the mean AST level (44.07) was also high in the high viral load subject. Dixit V et al. [4] Transaminase elevation (ALT) was noted in 50% of patients incidentally detected 95% had raised ALT levels in patients with higher Viral load and 5% had normal ALT levels. Abdelsalam Mohamed Ahmed Nail et al. [10] studied 100 asymptomatic patients and incidentally detected them. And found that out of 100 patients, 85 hada higher viral load, and out of 85 patients, 20 patients showed increased levels of ALT and 15 patients showed increased levels of AST.According to Girotraand Arora[11], 42 out of 63 patients had a high viral load, and 63% (or 137) had elevated ALT. This retrospective study was conducted on an asymptomatic patient who incidentally detected HBsAg positive. Al-Mahtab et al. [12]. Also, reported ALT levels were higher in more than 50% of the 702 asymptomatic patients who were inadvertently found. In order to diagnose individuals with chronic hepatitis B virus infection and to begin therapy, it is important to monitor ALT levels. 65 percent of the 317 asymptomatic HBsAg participants in a Canadian study with increased ALT levels greater than 40 IU/L. Our study found no significant association between ALT level and viral load, indicating that the virus is still replicating and causing hepatocellular damage. The current study shows a significant difference between viral loads and prothrombin time. Hepatitis B virus affects the coagulation profile, indirectly indicating hepatocellular damage. Patients with a high viral load had the highest mean ALKP. On Ultrasonography, 1 patient with CLD had greater viral loads, which suggests fibrosis and ongoing viral replication indicating HCC.HBV fibrogenic activity can be characterised as chronic inflammation that, in most patients, progresses clinically to liver fibrosis. The

immune system continually damages the liver due to viral activity, which causes ongoing tissue repair to occur but is unorganised, leading to fibrosis. The current study shows that patients with higher viral loads had high fibro scores>9 kPa based on the non-invasive FibroScan method. In a study conducted in Egypt, 15.9 percent of the cases had substantial fibrosis, and 47.7 percent had mild to moderate fibrosis. In their study, Abdelsalam Mohamed Ahmed Nail et al. [10] found that normal to mild fibrosis affected 59 percent of patients (scores taken below 7 kPa), while moderate to severe fibrosis affected 41% of patients (scores obtained above 7 kPa).APRI values and other non-invasive tests were similarly on the higher side in patients with high fibro scores > 9kPa, which in the form of fibrosis, indicates the severity of the liver disease. In comparison to fibro scans >9 kPa, the mean age and platelet count was higher in fibroscans< 9 kPa. Patients with fibroscan>9 kPa had significantly higher levels of AST, ALT, and ALKP than those with fibroscan 9 kPa. Viral load vs platelet count and viral load vs. age showed a weak association, while significant moderate correlation was seen between viral load vs AST and viral load vs ALT. A very weak correlation with a 95 percent confidence interval was also seen between viral load vs. platelet count. There is a substantial financial barrier in India and other developing countries when a fully asymptomatic person is told he has a hepatitis B infection and must undergo pricey follow-up tests. He could also need intense follow-up, regular serological testing, long-term antiviral medication, and HCC surveillance.

5. Conclusion

In conclusion, asymptomatic HBsAg detected incidentally is more prevalent in men. Most subjects with a high viral load had elevated levels of hepatic enzymes and prothrombin time. The platelet count was higher when the viral load was minimal. Fibroscan scores were high in patients with a low viral burden. We found no association between the Fibroscan score and levels of hepatic enzymes. There was no association between APRI, FIB4, and fibro scan score. We recommend conducting community-based surveys in disease-endemic areas to detect IDAHS. In addition, we recommend regular follow-up for IDAHS subjects to detect as early as feasible HBV-related consequences.

Conflict of Interest: All authors declare no conflict of interest.

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Consent

As per international or university standards, the authors have collected and preserved written participant consent.

Ethical Approval

As per international or university standards, the author(s) has collected and preserved written ethical permission.

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Tables and Figures

Table 1: Clinico-demographic parameters of enrolled patients (n=125).

Clinico-demographics		High Viral Load [n=56]		Low Viral Load [n=69]		P-Value
		MEAN/N	**SD/%**	**MEAN/N**	**SD/%**	
Age (Yrs)	18-40	45	80.36%	48	69.57%	X=1.890 p=0.1692
	>40	11	19.64%	21	30.43%	
Gender	Female	23	41.07%	28	40.58%	X=0.003094 p=0.9556
	Male	33	58.93%	41	59.42%	
Serum Bilirubin Total (mg/dL)		0.85	0.63	0.79	0.49	t=0.5989 p=0.5503
AST (IU/L)		44.07	31.49	43.58	27.82	t=0.09230 p=0.9266
ALT (IU/L)		44.11	23.85	43.20	27.86	t=0.1935 p=0.8469
ALP (IU/L)		257.12	150.37	222.26	106.13	t=1.516 p=0.1320
Platelet Count		170120.37	89244.15	182500.00	74565.41	t=0.8450 p=0.3998
Prothrombin Time		24.40	3.06	20.93	2.20	t=2.567 **p=0.0234***
Fibro Scan (kPa)		14.93	9.14	16.49	19.68	t=0.5469 p=0.5854

Table 2: Association between fibro scan score and other parameters

Parameters	Fibroscan Score				P-Value
	< 9 kPa [n=7]		>9 kPa [n=5]		
	Mean	SD	Mean	SD	
Age	48.45	9.92	39.22	12.24	t=1.445 p=0.1790
AST (IU/L)	33.91	9.10	57.00	31.31	t=1.876 p=0.0901
ALT (IU/L)	31.18	10.68	56.11	29.62	t=2.079 p=0.0643
ALP(IU/ml)	194.89	59.73	258.38	91.70	t=1.462 p=0.1756
Platelet Count	177666.67	99751.91	104500.00	25623.88	t=1.583 p=0.1446

Table 3: Association between APRI, FIB4 and fibro scan score.

Non-Invasive Test		FIBROSCAN SCORE		P-Value
		< 9 kPa [n=11]	**>9 kPa [n=9]**	
APRI	Median (Range)	0.5454 [0.1672-1.210]	0.8510 [0.2828-3.3]	
	≤1	8	4	X=1.650 p=0.1990
	>1	3	5	
FIB 4	Median (Range)	0.7827 [0.3289-1.5136]	0.7691 [0.1684-2.022]	
	≤2.6	11	9	---
	>2.6	0	0	

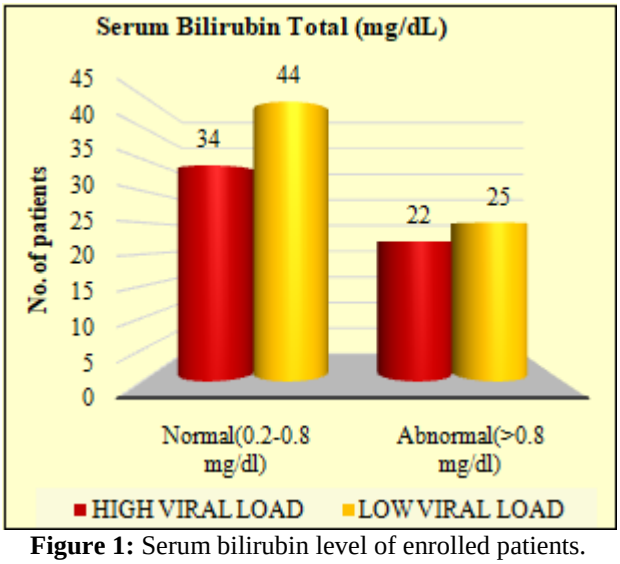

Figure 1: Serum bilirubin level of enrolled patients.

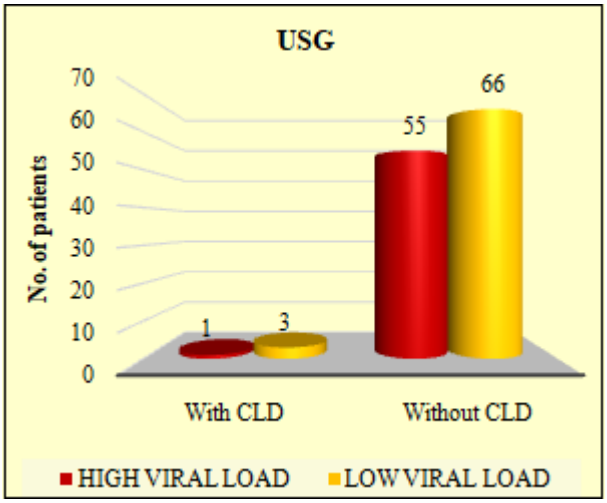

Figure 2: Chronic Liver Disease in enrolled patients

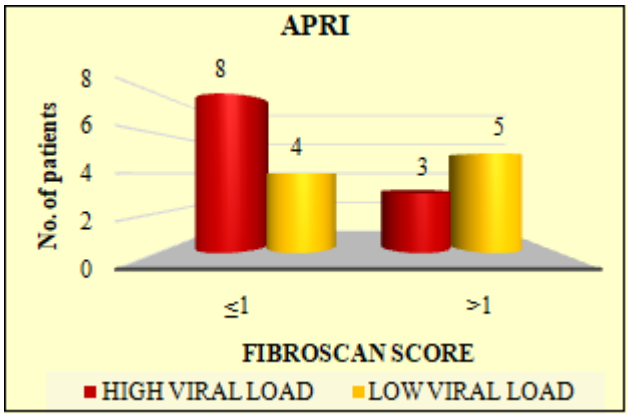

Figure 3: Association between APRI and fibro scan score

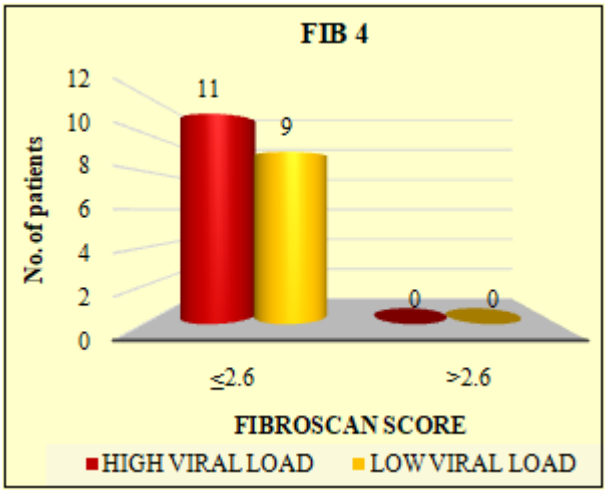

Figure 4: Association between FIB4 and fibro scan score.