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Study of Markers of Hepatitis B Virus (HBV) Infection among HIV Infected Patients and Its Co-Relation with CD4 Counts in A Tertiary Care Hospital

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Abstract

Introduction: Coinfection with Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) is common worldwide. Although spontaneous clearance of HBV acquired in adulthood occurs in >90% of immunocompetent individuals, HIV-infected individuals are half as likely as HIV uninfected persons to spontaneously clear HBV. Chronic HBV infection occurs in 5-10% of HIV/HBV coinfected individuals.

Objectives

1. To study Prevalence of HBV among HIV infected patients
2. To study the serum markers of HBV infection (HBeAg, IgM anti HBcore and IgG anti HBcore) among HIV-HBV coinfected patients
3. To compare CD4 count among HIV monoinfected and HIV-HBV coinfected patients.

Material and Methods: Prospective study conducted in one and half years after Institutional ethics approval. 700 newly diagnosed ART naïve patients were included in the study. All sera samples were screened by HBsAg ELISA. HBsAg positive samples were further tested by HBeAg, anti HBc IgM and anti HBc IgG ELISA. CD4 cell count estimation was performed by flow cytometry.

Results: Majority of the patients in the study had age between 39-48 years (37.9%) followed by 29-38 years (30.3%), Male to female ratio was 1.38:1. The seroprevalence of HBsAg in HIV was 5.9%. Of the 41 HBsAg positive patients, 19.5% were HBeAg positive, 9.8% anti HBc IgM positive and 97.5% were anti HBc

IgG positive. Mean CD4 count was 638 cells/mm^3 among HIV monoinfected and 429 cell/mm^3 among HIV HBV coinfected patients.

Discussion and Conclusion: Markers of HBV exposure are present in a high proportion among HIV infected individuals. HBeAg positive persons are super transmitters of HBV infection and its presence is considered as a surrogate marker for the presence of HBVDNA. Presence of HBcore antibodies are highly indicative of progression to chronic liver disease. HIV/HBV coinfected persons are likely to have lower CD4 counts. Since HIV HBV share common route of transmission, the study highlights the mandatory screening of all markers of HBV infection prior to initiation of ART to prevent morbidity and mortality associated with chronic liver disease.

Keywords: Prevalence, HBsAg, HBeAg and Anti HBc antibodies, HIV

Introduction

An increasing cause of liver illness that increases the risk of morbidity and mortality in people with HIV is the hepatitis B virus (HBV).[1] HIV patients have a greater likelihood of contracting HBV because of the epidemiological parallels between HIV and HBV with regard to the method of transmission. Hepatitis B is a chronic condition that affects about 10% of people with HIV worldwide.[2] Globally, there are different rates of HBV co-infection among HIV patients, and these rates mostly rely on the region's socioeconomic status, risk groups, kind of exposure, and geographic location.[3] Although the mortality and morbidity of HIV/Acquired Immune Deficiency Syndrome (AIDS) has decreased as a result of highly active antiretroviral therapy (HAART), liver disease from chronic HBV infection has become the leading cause of death. In HIV/HBV co-infections, HIV infection increases the risk of persistent HBV infection, cirrhosis, liver-related mortality, and hepatocellular carcinoma with lower CD4 T cell counts.[4]

After HBV infection, HBsAg (hepatitis b surface antigen) becomes detectable 3-5 weeks before the appearance of clinical symptoms and disappears within 2-6 months when anti-HBs antibody appears. Persistence of hepatitis B surface antigen positivity more than six months after an acute infection is considered evidence of a chronic infection [5]. In chronic hepatitis B infection, HBeAg (Hepatitis B envelope antigen) may be detectable for months and usually years. HBeAg is an important marker of viral replication, infectivity and ongoing liver damage.[6] Hepatitis B core antibodies (HB core) when present, indicate probable progression to fulminant hepatitis. [7]

Coinfection of HBV with HIV changes the natural history of HBV infection, increasing the percentage of patients who are likely to become HBV surface antigen (HBsAg) carriers and have a slower loss of HbeAg in serum.[8] Although there is sufficient information on the seroprevalence of HBsAg in HIV-infected patients, more information is needed on the seroprevalence of HBeAg and HBcore antibodies, an indicator of hepatitis B virus infectivity.[7] Little information is available on seroprevalence of HBeAg and anti-HBc antibody in HIV-HBV co-infected patients. Therefore, this study was conducted to determine the prevalence of HBsAg, HBeAg and anti-HBc in HBV-coinfected HIV patients.

Objectives

1. To study the prevalence of Hepatitis B virus infection among HIV patients.
2. To study the serum markers of Hepatitis B virus infection (HBeAg, IgM anti HBc ELISA and IgG anti HBc ELISA) among HIV-HBV co-infected

patient.

3. To compare the CD4 count among HIV monoinfected and HIV-HBV co-infected patients.

Material and Methods

A Prospective laboratory study was conducted over a period of one and half years in year 2018-2019 in the Department of Microbiology associated with tertiary care hospital. Approval of Institutional Ethics Committee was taken prior to beginning of the study. A total of 700 consecutive confirmed HIV positive treatment naïve patients visiting Integrated Counseling and testing Centre (ICTC), Department of Microbiology for CD4 testing before initiating ART were included in the study. Written Informed Consent was obtained from each prospective patient recruited into the study. Approximately 3-5 ml of blood was collected aseptically from all patients included in the study into plain vacutainer after written informed consent and centrifuged. The sera were separated into 2 ml screw capped vials and storedat -20^0 C for testing.

All sera samples were screened for hepatitis B surface antigen (HBsAg) by HBsAg Enzyme linked immunosorbent assay test (Merilisa HBsAg ELISA manufactured by Meril Diagnostics Pvt. Ltd.) as per manufacturer's instructions. All sera positive for HBsAg were further tested for hepatitis B envelope antigen (HBeAg) and HBcore IgG and IgM antibodies by Enzyme linked immunosorbent assay. HBeAg, HBcAb IgM and anti HBcAb ELISA tests were performed as per manufacturer's instructions. (Manufacturer — Genomix Molecular Diagnostics Pvt Ltd). Details of the CD4 count done by flow cytometry was recorded.

Statistical Analysis

The data on categorical variables is shown as n (% of cases) and the data on continuous variables is presented as Mean and Standard deviation (SD). The statistical significance of distribution of categorical variables across two study groups is tested using Chi-Square test of Fisher's exact probability test. The statistical significance of inter-group comparison of means of continuous variables across two groups is tested using independent sample t test (or un-paired t test) which asymptotically (as n is large) behaved as Z test.

Results

Majority of the patients in the study had age between 39-48 years (37.9%) followed by 29-38 years (30.3%). The mean age of the study population was 40.2 ± 9.3 years and minimum - maximum age group range was 18-60 years. The male to female ratio was 1.38:1. The seroprevalence of HBsAg was found to be 5.9%. Heterosexual contacts were found with higher prevalence of HBV in HIV seropositive participants.

Figure 1: Seroprevalence of HbsAg among HIV positive cases (n=700).

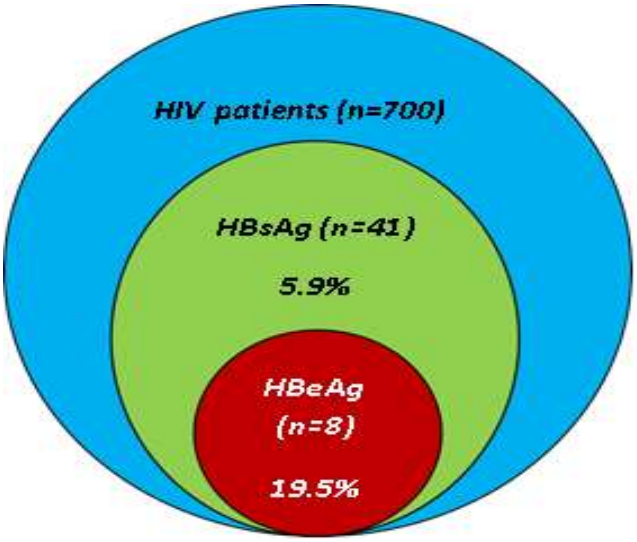

Table 1: Seroprevalence of HBeAg, IgM anti HB core and anti HB core antibodies among HIV-HBV co-infected cases (n=41).

Parameters		No. of cases	% of cases
HBeAg	Positive	8	19.5
	Negative	33	80.5
IgM HBcAb	Positive	4	9.8
	Negative	37	90.2
Anti HBcAb	Positive	40	97.56
	Negative	1	2.43

Table 2: Serological staging of Hepatitis B positive cases

Type of infection	Infectivity	No. of cases	% of cases
Acute hepatitis B infection	High	0	0
	Low	1	100
	Total	1	100.0
Chronic hepatitis B infection	High	8	20
	Low	32	80
	Total	40	100.0

Table 3: Distribution of mean CD4 count in HIV-HBV co-infected cases with respect to various serological markers of hepatitis B virus infection.

Serological markers		No. of cases		Mean CD4	P value
		n	%	cells/mm3	
HBeAg	Positive	8	19.5	414.13	0.818NS
	Negative	33	80.5	433.2	
IgM HBcAb	Positive	4	9.8	505.8	0.414NS
	Negative	37	90.2	421.2	
Anti HBcAb	Positive	40	97.56	422.9	0.204NS
	Negative	1	2.43	691	

Discussion

Co-infection of HBV with HIV complicates the clinical course of HIV-infected patients and can also negatively affect the treatment of HIV infection. Hepatotoxicity is a known complication of HIV treatment with HAART (highly active antiretroviral therapy). Therefore, accurate assessment of HBV infection among HIV-infected individuals is important for therapeutic decision-making.

The World Health Organization (WHO) recommends HBsAg (hepatitis B surface antigen) testing among HIV positive patients in areas with a high prevalence of HBV. The seroprevalence of HBsAg among HIV infected patients in our study was found to be 5.9% (41/700).

Fig 1. In India, various studies showed seroprevalence of HBsAg among HIV infected patients ranging from 6 to

16%.[9] Sarkar et al[10] showed seroprevalence of 5.9%. An increased prevalence of 11%, 8.6%, 8.7% was seen in study done by Sharma et al[11], Sherwani N et al[9] , Hooja et al[12], and 15% by Chandra et al[13]. Whereas a decreased seroprevalence of 3.37% was seen in study done by Ketaki et al[14] and 2.99% seen in Patil S et al.[15] The difference in the seroprevalence rate may be due to population studied from different geographical areas with different risk groups. This shows that HIV/HBV co-infection rate varies with the geographical areas related to theendemicity of these viruses.

The prevalence of HBeAg was 19.5% (8/41) in our study (Fig 1.) suggesting that the hepatitis B virus is actively replicating and infecting liver cells thereby ensuring an HBV- transmission pool within HIV HBV co-infected patients. Anti IgM HBcAb seroprevalence was 9.8% (4/41) done by anti IgM HBc antibody ELISA and Anti HBcAb seropositivity was 97.56% (40/41) by Anti HBcAb ELISA that detects both IgG and IgM anti HBcore antibodies. Table 1. The present study had low HBeAg seroprevalence rate of 19.5% and 97.56%patients had chronic hepatitis B virus infection. The study done by Forbi JC et al[16] shows HBeAg seroprevalence of 19.2% similar to our study. In Nigeria, Akinbami et al[7] studied seroprevalence of HBeAg (8.2%), IgM anti HBcore(10.1%) and IgG anti HBcore (60.7%) separately among confirmed HBsAg positive blood donors with prevalence homogenous to present study. However, in a study done by Ketki et al[14] and Sarkar et al[10], HBeAg seropositivity was 38.5% and 61.5% respectively. The presence of serological markers such as HBeAg denotes active viral replication and transmission whereas IgM anti HBcore and IgG anti HBcore antibodies denote acute and chronic HBV infection14. The presence of HbeAg along with HBsAg in the serum of patients makes them super carriers, with efficiency of transmission being almost 30%. These super carriers have elevated levels of HBV DNA in circulation and generally elevated transaminases along with HBeAg.17 In the absence of HBV DNA viral load facility, HBeAg is considered a surrogate marker for the presence of DNA of hepatitis B virus16. Testing for HBeAg can also identify individuals with high risk of developing chronic liver disease. Our study showed 19.5 % HBeAg prevalence among HBsAg positive individuals. This reflects a pool of individuals who are highly infectious and serve in sustaining viral transmission and evolution in HIV infected individuals, suggesting that the future burden of chronic liver disease associated with HBV is likely to be high. 16 Our study reflects a high proportion of HBV infectivity and transmissibility rate among HIV infected individuals. It is therefore important that health care facility should attempt to implement HBeAg testing of HBV positive patients among HIV infected individuals to determine the status of infectivity and to adequately plan proper patient management. Limitation of the present study is that HBV DNA could not be done due to financial constraint. There is paucity of data regarding seroprevalence of HBeAg, IgM anti HBc and Anti HBcore antibody among HIV HBV co-infected patients in India. In the present study, out of 41 HIV HBV co-infected individuals, only 1 case had acute hepatitis B infection and 40 (97.5%) had chronic hepatitis B infection. Table 2. Chronic HBV infection with HBeAg positive were considered with high infectivity while chronic HBV with HBeAg negative were considered with low infectivity. A single case with acute hepatitis B infection found in our study had low infectivity as it was negative for HBeAg.

In this study mean CD4 count amongst HBeAg positive patients was found to be slightly lower than mean CD4 counts among HBeAg negative patients (414.2 cell/mm^3 v/s 433.2 cells/mm^3). Table 3. This finding in the present study is similar to Ketki et al[14] (270 cell/mm^3 v/s 324 cells/mm^3). In study by Firnhaber et al[18], CD4 counts of HBeAg negative patients was found to higher than HBeAg positive patients (189.4v/s 113.11 cells /mm3) while in other study done by Idoko et al[19] done in Nigeria CD4 counts of HBeAg negative patients was also found to higher than HBeAg positive patients (119 v/s 80cells /mm3). In Jaroszewicz et al[20] study, CD4 counts of HBeAg negative patients was also higher than HBeAg positive patients (417 v/s 355cells /mm3). The correlation of mean CD4 T cell count and HBeAg, IgM anti HBcore and anti HBcore Ab was not statistically significant (p value >0.05) in the present study.

Conclusion

Study highlights the need for mandatory screening of hepatitis markers in HIV positive patients. Markers of HBV exposure are present in a high proportion among HIV-infected individuals. Our findings showed that HIV seropositive individuals had a high risk of acquiring HBV infection predominantly through heterosexual contact. Therefore, it is recommended that all HIV positive patients should be screened for HBV before initiation of anti-retroviral therapy, this would help in reducing morbidity and mortality among these patients. Furthermore, presence of HBeAg acts as an indicator of HBV transmissibility and HBcore antibodies when present indicate likely progression to chronic liver disease. The presence of HBeAg is considered as a surrogate marker for the presence of the HBV DNA.

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