Research Paper

Volume : 5 | Issue : 4 | April 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

A Prospective Study of Liver Function Tests, CD4 CountsAnd Seroprevalence of Hepatitis-B Virus Coinfection With Human Immunodeficiency Virus In A Teaching Hospital Of Rural Setup

Medical Science

KEYWORDS : Human Immunodeficiency Virus, Hepatitis B Virus, Co-infection, Mono infection, CD4 T- cells, Liver Function Tests

DR.N.RAMA KRISHNA. Professor & Head, Dept. of Biochemistry, Gayatri Vidya Parishad Institute of Health Care and Medical Technology, Marikavalasa, Madhurawada, Visakhapatnam – 530048 Andhra Pradesh, India

DR.SIRISHA PAVANA NEKKALA Assistant Professor, Dept. of Pharmacology, Andhra Medical College, Visakhapatnam-530002

DR.BANDARU NARASINGA RAO. Prof. & Head, Dept. of Microbiology, GVP Institute of Health Care and Medical Technology Marikavalasa, Madhurawada,Visakhapatnam-530048

ABSTRACT

Background: Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV) are global health concerns. Due to common routes of transmission, co-infection is common. Their co-existence alters the disease nature and can cause severe liver complications like cirrhosis or malignancy and immunological impairment in infected individuals. Aim: To find the prevalence of HBV co-infection in HIV patients and to assess the hepatotoxicity by estimating liver function tests and CD4 T-cell counts in HIV monoinfected and HIV/HBV co-infected patients. Materials and Methods: A total of 540 consecutive confirmed HIV positive for treatment patients were tested for hepatitis B surface antigen (HBsAg). Clinical staging was done according to Center for Disease Control and Prevention(CDC) classification guidelines. Liver function tests were performed by a random access auto analyser (Medica Easyra); CD4 T-cells were estimated by Partec cyflow counter, Germany. Results: Hepatitis B virus co-infection was detected in 11.48% of HIV positive patients as compared to 1.48% in the HIV negative control group (P < 0.05). Majority of the HIV monoinfected and co-infected patients were below 40 years. HBsAg positivity was higher in males (12.46%) and the route of transmission was heterosexual. Categorical data revealed significantly higher proportion of alanine aminotransferase and aspartate aminotransferase (AST) in the co-infected patients compared to the monoinfected patients (P < 0.05). The HIV/HBV co-infected patients had significantly lower CD4 T-cell counts (P < 0.05) and significantly higher AST, ALT, alkaline phosphatase, serum bilirubin (P < 0.05, P < 0.05, P < 0.05 respectively) and significantly lower albumin values than the monoinfected group (P < 0.05). Males had 2.3 times higher risk than females for co-infection. Conclusion: The prevalence of co-infection was high. Raised levels of liver enzymes and lowered CD4 counts were seen in co-infected patients. These findings underscore the importance of HBV screening of all HIV positive individuals before initiating antiretroviral treatment. The assessment of liver function was used for guiding them for possible therapy for HBV in order to reduce the disease complications.

Introduction:

Human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV) are the three most common chronic viral infections having similar modes of transmission, may have a good chance to co-infect the human beings.[1,29] The infection continues to have a severe and invasive impact on the health of millions of people around the world and the infection is often asymptomatic. [2] Since HIV and HBV have epidemiological similarities as regards route of transmission, patients of HIV have a high probability of getting co-infected with HBV. In the Middle East and Indian subcontinent an estimated 2-5% of the general population is chronically infected with HBV. [3] Approximately 10% of the HIV-infected population worldwide suffers from chronic hepatitis B. [4] Co-infection rates of HBV in HIV patients vary worldwide and largely depend upon the geographical location, risk groups, the type of exposure involved and the socioeconomic condition of that particular region. [5] In Europe and the United States of America, HIV/HBV co-infection is around 6-14%.[6,7] Though the mortality and morbidity rate from HIV/Acquired Immunodeficiency Syndrome (AIDS) have declined as a result of highly active antiretroviral therapy (HAART), liver disease due to chronic HBV infection has become a leading cause of death. In HIV/HBV co-infections, HIV infection causes increased rates of persistent HBV infection, cirrhosis, liver-related mortality and risk of hepatocellular carcinoma at lower CD4 T cell counts. [8] There is insufficiency of data regarding correlation of liver enzymes and CD4 T-cells among HIV/HBV co-infected patients.

Therefore, the present study was undertaken in a Government teaching hospital of rural setup to assess the seroprevalence of Hepatitis B virus and its correlation with CD4 count and liver enzymes among human immunodeficiency virus positive individuals.

Materials and Methods:

The present study was undertaken for a period of 2 years from January 2012 to December 2013. Patients suspected of HIV, attending clinics as well as direct walk-in patients, referred to the Integrated Counselling and Testing Centre were screened for HIV after performing pretest counselling and informed consent. Our laboratory follows the World Health Organization (WHO) and National Aids Control Organisation(NACO) of India testing strategies and as a routine all confirmed HIV positive patients are referred to the antiretroviral therapy (ART) centre attached to the Medical College during post test counselling.

A total of 540 consecutive confirmed HIV positive for treatment treatment patients (age: 20 to >60 years) who were first time visiting at the ART centre were included for the study and anonymously tested for hepatitis B surface antigen (HBsAg). None of these patients gave a history of vaccination against HBV. None of the patients were known that they are HBV positive. Sociodemographic and risk factors were recorded on a proforma. Clinical staging of the disease was also done according to 1993 Centers for Disease Control and Prevention classification (CDC) guidelines for adolescents and adults. [9]A total of 540, age and sex matched, HIV negative blood donors as controls were also included in the study who visited the hospital for other problems.

Serology

All samples (patients and controls) were screened for HBsAg spot test of SD Bioline and the same confirmed by enzyme linked immunosorbent assay test (Hepalisa J. Mitra and Co. Private Limited India.

Biochemistry

Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin, serum alkaline phosphatase (ALP) and serum albumin were carried out for all patients using a fully automated random access autoanalyzer (Medica, Easyra Analyzer, USA; with the test kits supplied by the same company). All the tests were done on the same day of blood collection. Normal and abnormal controls were run in the same batch for internal quality control and External quality control participation with CMC, Vellore is present. CD4 T-cell count estimation was done by Partec Cyflo Counter, Germany.

Results

A total of 540 consecutive HIV positive patients for treatment were included in the study. Among the study subjects there were 377 males and 163 females (M: F ratio- 2.3:1). These patients had an age between 20 and >60 years. HBV co-infection was seen in 62 (11.48%) HIV positive patients. This rate was highly significant ($P < 0.05$) when compared to 1.48% in the control group.

Sociodemographic characteristics of study subjects

The subjects were divided into two groups: Those with HIV alone and those co-infected with HBV. The mean age of HIV-infected patients was 33 years. Majority of the patients (74.25%) were < 40 years of age. In the HIV/HBV co-infected patients the mean age was 37 years. In this group 75.80% were below 40 years of age. Data on risk factors in the HIV monoinfected group revealed that 96.23% of the patients were heterosexual whereas 1.67% were recipients of blood products and in the rest it was unidentified while among the co-infected patients 100% were heterosexual. After Housewives (31.18%), drivers and labourers were the most infected in both groups (17.58%) and (15.89%) respectively.[Table 2].

Patients were categorized according to CDC classification system into groups A, B and C. In the HIV-infected patients 110(22.02%) were classified as group A, 232(48.53%) as group B and 136 (28.45%) as group C. In the co-infected group 7(11.29%) were classified as group A, 22(35.48%) as group B and 33(53.23%) as group C. The CD4 T-cell profile between the HIV and HIV/HBV co-infected group was not significant ($P = 0.1$).

Table 1: Age and Sex Distribution of Cases in the Study

PARAMETER	HIV Monoinfection No. (%) n =478	HIV Co-Infection No. (%) n =62
Male Femle	330 (69.03) 148 (30.97)	47 (75.81) 15 (24.19)
Age 20-30 31-40 41-50 51-60 >61	139(29.08) 215(44.98) 86 (17.99) 38(7.95) 0 (0.00)	15(24.19) 32(51.61) 9(14.52) 4(6.45) 2(3.23)

Table 2: Socio-demographic characteristics and CD4 levels of HIV monoinfected and HIV/hepatitis B virus co-infected patients

Educational Status No Formal Education Formal Education	374(78.24) 104(21.76)	40(64.52) 22(35.48)
Occupational Status Housewives Drivers Labourers Unemployed Industrial Worker Service (Private/Government) Students Others	 149(31.18) 84(17.58) 76(15.89) 43(8.99) 50(10.46) 45(9.41) 15(3.14) 16(3.35)	 14(22.58) 11(17.74) 10(16.12) 8(12.90) 7(11.29) 4(6.45) 3(4.84) 5(8.08)
Risk Factors High Risk Sexual Contact Blood Transfusion Unknown	460 (96.23) 8(1.67) 10(2.10)	62(100.00) 0(0.00) 0(0.00)
CD4 Count >500 201-500 <200	110(23.02) 232(48.53) 136 (28.45)	7(11.29) 22(35.48) 33(53.23)

Profile of liver enzymes and its correlation with CD4 Count:

The mean and S.D values of Total Bilirubin, ALT, AST, ALP and ALB levels in HIV monoinfected patients were 0.67±0.52mg/dl 41.56±31.87 U/L, 64.84±44.32 U/L, 234.35±215.30 IU/L and 3.94±0.46gm/dl respectively. The mean and S.D values of Total Bilirubin, ALT, AST, ALP and ALB levels in HIV/HBV co-infected patients were 1.04±0.78mg/dl 68.37±27.49 U/L, 87.49±38.46 U/L, 874.45±156.69 IU/L and 2.97±0.34gm/dl respectively. The baseline values are shown in Table 3. Co-infected patients had higher proportions of elevated values of Total Bilirubin, ALT, AST, ALP than HIV alone. Where as the mean value of Albumin is decreased and the differences were statistically significant ($P < 0.05$) in all.

Table 3: Correlation of CD4 and liver enzymes among HIV monoinfected and HIV/HBV co-infected individuals

Status (Number)	CD4	Total Bilirubin	AST	ALT	ALP	ALB
HIV Monoinfected (406)	316.47± 236.54	0.67± 0.52	64.84± 44.32	41.56±31.87	234.35±215.30	3.94±0.46
HIV/ HBV Co-Infected (54)	204.54± 198.64	1.04± 0.78	87.49± 38.46	68.37±27.49	874.45±156.69	2.97±0.34
Significance	P=<0.05 Significant	P=<0.05 Significant	P=<0.05 Significant	P=<0.05 Significant	P=<0.05 Significant	P=<0.05 Significant

AST: Aspartate aminotransferase, **ALT**: Alanine aminotransferase , **ALP**: *Alkaline phosphatase* test, **ALB**: *Albumin*

Correlation of CD4 cells with liver enzymes:

The HIV/HBV co-infected patients had significantly lower CD4 T-cell counts than the HIV monoinfected group and significantly higher serum total bilirubin, ALT, AST, ALP and significantly lower serum albumin values. [Table 3].

Discussion

In the present study, the seroprevalence of HBV in treated HIV positive patients and studied the correlation of levels of liver enzymes and CD4 counts in HIV monoinfected and HIV/HBV co-infected patients. The prevalence of hepatitis B among the study group was 11.48% which is comparable to studies from different parts of India.[1,10,11,29] However, some studies have reported a lower rate of HIV/HBV co-infection.[12,13] In the present study the prevalence of co-infection was higher in males than in females (12.46% vs. 9.20%). The difference was not statistically significant ($P = 0.5$). This finding is comparable with studies from Africa and India.[14,15] This can be explained on the basis of higher rate of sexual promiscuity and other exposure risks in males than females. The major risk factor was heterosexual accounting of patients. This is in concurrence with other studies from India.[10,16] Majority of the HIV positive patients (74.25%) had an age between 20 and 40 years and a similar trend was seen in HIV/HBV co-infected patients (75.80%) indicating a common mode of transmission of these viruses which has been documented by other studies.[1,16,29]

In both the HIV monoinfected and HIV/HBV co-infected patients seropositivity was high in truck drivers (17.58 & 17.74%) and labourers (15.89 & 16.12%) because of poor educational status and limited knowledge and awareness in common of HIV transmission and away from the family for a longer period of truck drivers from sexual life. The mean CD4 T-cell counts in the HIV monoinfected patients

Volume : 5 | Issue : 4 | April 2016 • ISSN No 2277 - 8179 | IF : 3.508 | IC Value : 69.48

was 315 cells/μL while in the HIV/HBV co-infected group it was 204 cells/μL which is similar to a study from Jaipur and Gondar but lower mean CD4 T-cell values have been reported by a Nigerian study.[12,17,18] A study in India has reported a mean CD4 T-cell of 334 cells/μL in HIV monoinfected patients comparable with our study but a higher mean CD4 T-cell count of 294 cells/μL in co-infected patients.[1,12,29] In the present study 50% of HIV/HBV co-infected patients were in CDC stage C indicating that the incidence of HBV co-infection rises with HIV disease progression. Significant difference of co-infection existed between the symptomatic and asymptomatic groups of HIV-infected patients ($P < 0.05$). HIV disease reportedly leads to massive impairment of cell mediated responses and enhances the kinetics of hepatotropic viral replication.[1,29] This causes increased rates of chronicity, faster disease progression, prolonged HBV viremia and increased liver-related morbidity. Patients with AIDS apparently are less likely to clear HBV infection after exposure or more likely to reactivate a latent HBV infection or both. [19,20] Furthermore some HBV factors on HIV transcription favour enhanced HIV replication leading to faster CD4 T-cell decline in HIV/HBV co-infected individuals.[21]

Elevated transaminases and reduced albumin are a marker of liver inflammation and have been shown to be common in HIV/AIDS patients. In the present study compared with people harbouring only HIV, more number of HIV/HBV co-infected patients had elevated liver enzymes. Categorical univariate analysis of transaminases in HIV co-infected and HIV monoinfected patients revealed elevated ALT in 58.6% versus 26.7% and AST in 88.2% versus 53.3% levels respectively. The difference was statistically significant ($P < 0.05$). The same trend is observed in ALP levels. A study among Nigerian patients showed abnormal liver enzymes in 87.6% patients out of whom only 2.3% were co-infected with Hepatitis B. [22] Another study from India showed elevated ALT levels in 43.3% of their co-infected patients. [16] In HIV positive patients the increase in hepatic enzymes could be secondary to multiple factors such as alcoholism, lipid lowering drugs, antibiotics, co-infection with hepatotropic viruses or opportunistic organisms as well as direct hepatic damage caused by HIV. [23] Even though more number of co-infected patients have elevated transaminases this elevation is mild and associated with higher risk of progression to cirrhosis. [24,25,30] This was apparent in the present study as there was only mild elevation of both ALT and AST in HIV/HBV co-infected patients and a mild elevation of only AST in the HIV monoinfected patients. This finding may be related to the impairment of immunity in advanced HIV, which despite higher rates of HBV replication, results in less inflammation and necrosis. Thus, in HIV-infected patients, HBV co-infection is an independent predictor for cirrhosis, hepatocellular carcinoma, and mortality associated with anti-retroviral therapy. [26,27,28,30] The present study has certain limitations. Firstly, this is a cross-sectional study unable to adequately establish a causal relationship between the time of exposure and subsequent infection. Secondly, repeated measurements of liver function tests were not done as it is known that liver-related morbidity can take a fluctuating course. This could have missed a few short lasting episodes of liver enzyme elevations.

Conclusions

We recommend that all HIV positive patients should be routinely screened for HBV markers before initiation of HAART as Co-infections of HBV and with HIV have been reportedly associated with reduced survival, increased risk of progression to liver disease and increased risk of hepatotoxicity associated with anti-retroviral therapy. This practice would guide correct choice of drug combination. Also there should be a regular monitoring of liver enzymes and CD4 T-cell counts. This would help in reducing morbidity and mortality from antiretroviral drug associated hepatotoxicity among these patients. Moreover, continuous stress on education is necessary in order to increase the literacy rate subsequently to decrease HIV and HBV prevalence.

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