Original Article

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Liver Function Abnormalities in Human Immunodeficiency Virus Positive Individuals and its Correlation with Disease Severity

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Abstract

Background: Human immunodeficiency virus (HIV) infection is characterized by an irreversible and profound immunosuppression. Liver enzyme elevations are common in HIV-infected patients, and highly active antiretroviral therapy (HAART) has completely modified the pattern of hepatic events in HIV-infection. The early recognition and diagnosis of hepatic events will be useful in the safe and effective use of HAART and enhance the survival of HIV-infected patients.

Objectives: The present study was done to identify various liver function abnormalities in HIV-positive patients and its correlation with CD4 count.

Materials and Methods: The study included 100 HIV positive patients selected from Sri Ramachandra Medical College and Hospital from the year 2012 to 2014. Complete hemogram, blood urea, serum creatinine, liver function tests (LFTs), CD4 count, hepatitis B surface antigen, anti-hepatitis C virus, and ultrasound abdomen were done for all the patients. The study population was divided into three groups based on CD4 count. Group I included 50 patients with CD4 count <200 cells per cu.mm, 28 patients in Group II with CD4 count between 201 and 350, and Group III included 22 patients with CD4 count more than 350. About 39 patients were on ART and 34 patients were on antituberculous treatment.

Results: 63 patients had an abnormal LFT, out of which 29 patients had the hepatocellular injury, 6 patients had a cholestatic liver injury, and 28 patients had a mixed pattern of liver injury. Ultrasound abdomen revealed fatty liver in 24 patients, hepatomegaly in 8 patients, hepatosplenomegaly in 6 patients, cirrhosis of the liver in 5 patients, splenomegaly in 3 patients, ascites in 3 patients, ileocecal tuberculosis in 2 patients, and hepatocellular carcinoma in 1 patient.

Conclusion: HIV-infected patients are at a higher risk of the liver function abnormalities. The incidence of liver function abnormality increases with severity of the disease.

Key words: CD4 count, Highly active antiretroviral therapy, Human immunodeficiency virus infection, Liver function

INTRODUCTION

Liver enzyme elevations are common in human immunodeficiency virus (HIV) infected patients. The complex pathogenic mechanisms of liver injury make their diagnosis and management difficult. These include hepatotoxicity related to the highly active antiretroviral therapy (HAART) regimen, idiosyncratic or immunoallergic mechanisms, and direct cytotoxicity enhanced by an underlying liver disease. Co-infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection can also worsen liver function either due to direct cytotoxicity or other immune mechanisms involved. In addition to the above alcohol-related liver disease, non-alcoholic steatohepatitis associated with metabolic syndromes (e.g., hyperlipidemia, diabetes, or being overweight) and use of medication or illicit drugs (e.g., methamphetamine) can further contribute to the deterioration of liver function.

At the beginning of HIV era, liver dysfunction mainly corresponded with opportunistic infections (e.g., with

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cytomegalovirus [CMV] or mycobacteria and leishmaniasis), including AIDS-related cholangitis associated with parasitic infections (cryptosporidiosis and microsporidiosis), viral infections (e.g. with CMV), or mycobacterial infections; tumors (lymphoma and Kaposi sarcoma); and drug-related hepatitis (caused by trimethoprim-sulfamethoxazole and other antibiotics). All of these reflected a worse prognosis. The development of HAART (regimens composed of nucleoside reverse-transcriptase inhibitors [NRTIs], protease inhibitors [PIs], and non-NRTIs [NNRTIs]) has resulted in a significant decrease in morbidity and mortality among HIV-infected patients.[1] HAART has modified the pattern of hepatic events in HIV-infection, and the liver should be an important consideration when treating HIV-infected patients.[2]

Pathogenesis of liver fibrosis could be explained by direct effect on hepatocytes, hepatic stellate cells (HSCs), and Kupffer cells (KCs). In the absence of productive infection, gp120 binding to CXCR4 may induce hepatocyte apoptosis and activation of HSCs. NRTIs and HIV itself (via peroxisome proliferator-activated receptor effects) may also contribute to liver disease by inducing the metabolic syndrome. An increase in lipopolysaccharide (LPS) in HIV can stimulate hepatocytes, KCs, and HSCs to produce pro-inflammatory cytokines and chemokines (tumor necrosis-α, transforming growth factor-β and interleukin) which attract activated lymphocytes and monocytes to the liver and further drive fibrosis.

Various studies demonstrate HIV-infection of hepatic cells. KCs can be infected by HIV *in vivo*.[3] *In vitro* studies suggest that HIV-infection of KCs leads to productive infection.[4-7] HIV can also induce hepatocyte apoptosis *in vitro* via gp120 signaling through CXCR4 in the absence of infection.[8] HIV-infection of GI tract associated CD4+ T-cells leads to increased permeability to bacterial endotoxins such as LPS. Elevated LPS has been shown to contribute to liver disease progression in alcoholic liver disease[9,10] as well as in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis.[11-13] In addition to activation of KCs, LPS also directly activates HSC to produce CCL-2,[14] and *in vitro* following co-culture with monocytes, induces hepatocytes to produce chemokines CXCL9, 10 and 11.[15] These chemokines will induce chemotaxis of both T-cells and monocytes to the liver.

Hepatotoxicity due to ART may be related to agents from some classes, including NRTIs, NNRTIs, and PIs. The severity of hepatotoxicity may range from transient elevations in transaminase levels to hepatic failure and death, via a variety of mechanisms. NNRTI such as nevirapine and efavirenz may cause hypersensitivity. NRTI, primarily didanosine, may cause direct mitochondrial toxicity leading to abnormal liver function. Other mechanisms by which ART causes liver-related toxicity include direct cell stress and disturbances in lipid/sugar metabolism and steatosis, as seen with PIs. Ritonavir, tipranavir, and darunavir have all been associated with elevations in ALT.

The present study was done to observe the pattern of abnormal liver function tests (LFTs) in HIV-positive patients and its correlation with CD4 count.

MATERIALS AND METHODS

This study was a cross-sectional study of 100 HIV-positive patients conducted at Sri Ramachandra Medical College in the Department of Medicine from July 2012 to August 2014 after approval of Hospital Ethics Committee. All patients fulfilling inclusion criteria (all HIV-seropositive patients, seropositivity being confirmed by ELISA) were screened and investigations done. Patients with age <18 years and pregnant patients were excluded from the study.

A questionnaire for detailed history was taken from all patients and a thorough physical examination was done. Abdomen examination was done to demonstrate hepatomegaly, splenomegaly, free fluid or cirrhosis of the liver. Complete blood count, blood urea, sugar, serum creatinine, LFTs including coagulation profile, hepatitis B surface antigen (HBsAg), anti-HCV, and urine analysis were done for all patients. The CD4 lymphocyte count was done by flow cytometry method. Abnormal LFTs were defined as >1.25 ULN in HIV-positive patients.

The collected data were analyzed using Statistical Package of Social Sciences 17.0 for Windows. Data were expressed as the mean ± standard deviation. A $P < 0.05$ was considered statistically significant.

RESULTS

The majority of the patients in the study were aged between 31 and 50 years (73%). 65 patients were males, and 35 patients were females (mean age was 40.91 years). Fever was the most common symptom (63 patients) followed by abdominal pain (22 patients). Pallor was the most common general examination finding (34 patients) followed by pedal edema (6 patients), icterus (5 patients), clubbing (3 patients), and generalized lymphadenopathy (3 patients). About 19 patients were positive for HBsAg, 3 patients were positive for the anti-HCV antibody.

The study population was divided into three groups based on CD4 count. Group I included 50 patients with a CD4

count <200 cells per cu.mm, 28 patients in Group II with a CD4 count between 201 and 350, and Group III included 22 patients with a CD4 count more than 350. 39 patients were on ART and 34 patients were on antituberculous (TB) treatment. The most common opportunistic infection was oral candidiasis (22 patients), pulmonary TB in 19 patients and esophageal candidiasis in 9 patients. 39 patients were receiving HAART. 39 patients (100%) were on NRTI, 34 patients (87.17%) were on NNRTI, 5 patients (12.8%) were on PI. 29 patients were on efavirenz, 28 were on tenofovir, 20 were on lamivudine, 18 were on zidovudine, and 5 patients were on atazanavir therapy.

Normal ultrasound was found in 43 patients. Fatty liver was the most common ultrasound finding (24 patients), hepatomegaly in 8, splenomegaly in 3, and hepatosplenomegaly in 6 patients.

There was a statistically significant correlation for the CD4 count with serum glutamate oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase, and international normalized ratio (INR) abnormality. SGOT, SGPT, alkaline phosphatase, and INR values were more abnormal in the group of patients with a CD4 count <200 cells per cu.mm. There was no statistically significant correlation between, ART, anti-tubercular treatment (ATT), alcohol use, and LFT abnormality in our study.

DISCUSSION

In our study, the mean age of study population was 40.91 years. In the study done by Ejilemele *et al.*,[15] the mean age was 35.6 years. In the study done by Sterling *et al.*,[16] the mean age was 42 years.

63% patients had abnormal LFT. Out of which 29 patients (46%) were classified as hepatocellular injury, six patients (9.5%) had a cholestatic liver injury and 28 patients (44.5%) had mixed pattern. In the study by Ejilemele *et al.*, out of 129 patients, 113 patients (87.6%) had LFT abnormality. Out of which 94 patients (85.5%) had hepatocellular injury, 16 patients (14.5%) had a cholestatic liver injury. In the study by Ocama *et al.*, 8% patients had a hepatocellular injury, 63% patients had the cholestatic pattern and 19% patients had a mixed pattern of injury. Thus, our study results were similar to the study by Ejilemele *et al.*, where the most common LFT abnormality was hepatocellular injury.

Elevated SGOT, SGPT, ALP was observed in 67%, 60%, and 36% of patients, respectively. In the study done by Sterling *et al.*, elevated SGOT, SGPT, and ALP were observed in 31.5%, 23.8%, and 46.9% of patients, respectively. In relation to CD4 count, 40 patients had elevated SGOT in the Group I, 18 patients had elevated SGOT in the Group II and nine patients in the Group III with a *P* value of 0.005 which is statistically significant. 38 patients had elevated SGPT in the Group I, 17 patients

Table 1: CD4 count and total bilirubin

CD4 count	Total bilirubin<1.5 (%)	Total bilirubin>1.5 (%)	Total
<200	44 (50)	6 (50)	50
201-350	25 (28.4)	3 (25)	28
>350	19 (21.6)	3 (25)	22
Total	88	12	100

P=0.951

Table 2: CD4 count and SGOT

CD4 count	SGOT<44 (%)	SGOT>44 (%)	Total
<200	10 (30.3)	40 (59.7)	50
201-350	10 (30.3)	18 (26.9)	28
>350	13 (39.4)	9 (13.4)	22
Total	33	67	100

P=0.005. SGOT: Serum glutamate oxaloacetate transaminase

Table 3: CD4 count and SGPT

CD4 count	SGPT<51	SGPT>51	Total
<200	12 (30)	38 (63.3)	50
201-350	11 (27.5)	17 (28.3)	28
>350	17 (42.5)	5 (8.3)	22
Total	40	60	100

P<0.001. SGPT: Serum glutamic pyruvate transaminase

Table 4: CD4 count and ALP

CD4 count	ALP<161 (%)	ALP>161 (%)	Total
<200	22 (34.4)	28 (77.8)	50
201-350	22 (34.4)	6 (16.7)	28
>350	20 (31.2)	2 (5.6)	22
Total	64	36	100

P<0.001. ALP: Alkaline phosphatase

Table 5: CD4 count and INR

CD4 count	INR<1.1 (%)	INR>1.1 (%)	Total
<200	39 (60)	11 (31.4)	50
201-350	13 (20)	15 (42.9)	28
>350	13 (20)	9 (25.7)	22
Total	65	35	100

P=0.016. INR: International normalized ratio

Table 6: CD4 count and albumin

CD4 count	Albumin<3.2 (%)	Albumin>3.2 (%)	Total
<200	30 (49.2)	20 (51.3)	50
201-350	16 (26.2)	12 (30.8)	28
>350	15 (24.6)	7 (17.9)	22
Total	61	39	100

P=0.714

had elevated SGPT in the Group II and five patients in the Group III with a $P < 0.001$ which is statistically significant. 28 patients had elevated ALP in the Group I, 6 patients had elevated ALP in the Group II and 2 patients in the Group III with a $P < 0.001$ which is statistically significant. Hence, there was significant correlation between CD4 count and LFT abnormality. LFT abnormalities are inversely proportional to CD4 count. This finding correlated well with Sterling *et al.* study.

Correlation between anti-TB therapy and LFT abnormality was not statistically significant in our study. In the study by Ponsiano *et al.*, use of isoniazid was the common cause of hepatotoxicity. Anti-TB drugs induced liver injury is the most common cause drug-induced liver injury, but in our study, there was no statistically significant relationship between ATT and LFT abnormality. This may be because the group of patients not on ATT had LFT abnormality due to other causes like use of ART, low CD4 count, direct effect of HIV and co-infections.

Limitations of the Study

This is not a case-control study, where the study population is not compared with control group (normal individuals). The most important limitation of our study was a lack of histology. Hence, the clinical significance of mild liver enzyme elevations could not be assessed. Our study population was very less, which does not reflect the entire scenario of HIV-infected individuals. Hence, further study with a larger study population and liver histology is recommended in our country.

CONCLUSION

HIV-infected patients are at higher risk of liver function abnormalities. The incidence of liver function abnormality increases with severity of disease. It is, therefore, important to characterize the nature of liver dysfunction to institute appropriate management.

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