Liver Function Profile Anomalies in HIV Seropositive Tuberculosis

ABSTRACT

Background: The Human Immunodeficiency Virus (HIV) and the Tuberculosis (TB) co-infection are contributory to each other in causing a progressive decline in the cell mediated immunity and a damage to the hepatobiliary system. The aim of our study was to estimate the extent of liver damage which was caused by these infections before the start of the therapy with hepatotoxic drugs like Antiretroviral Therapy (ART) and Antitubercular Drugs (ATD).

Methods: One hundred and ninety three confirmed HIV positive cases were enrolled in this study. The cases were divided into 2 groups; Group 1-100 subjects with TB and Group 2-93 subjects without TB. 80 age and sex matched controls were also included (Group 0). Some parameters of the serum Liver Function Test (LFT) were estimated biochemically by using an auto analyzer (ERBA XL600, Transasia).

Results: The serum total bilirubin, Alanine Transaminase (ALT), Aspartate Transaminase (AST) and the Alkaline Phosphatase (ALK-P) levels were significantly higher in the cases as compared to those in the controls, except the AST levels. The Group 1 subjects had lower serum total protein and albumin levels and altered albumin/globulin ratios as compared to the controls. A statistically significant difference was absent in the serum total protein levels between the Group 2 cases and the Group 0 controls. No significant differences were observed when the values for serum total protein, albumin and globulin and the albumin: globulin ratios among the two case groups (1 and 2) were compared.

Conclusion: The results have shown the importance of estimating some LFT parameters, prior to the start of ATD and ART in these cases. Hence, a mandatory performance of LFT is recommended, as it is simple and cost effective.

INTRODUCTION

The Human Immunodeficiency Virus (HIV) and Tuberculosis (TB) have been closely linked to each other. Since the emergence of the Acquired Immune Deficiency Syndrome (AIDS), the HIV infection has been found to be contributory to a significant increase in the incidence of TB worldwide [1,2]. TB is the most common opportunistic infection which affects HIV seropositive individuals [1] and it is the most common cause of death in the patients with AIDS [3]. By altering the pathogenesis of TB via a progressive decline in the cell-mediated immunity, HIV has given rise to more of extra pulmonary and disseminated TB and atypical presentations [1].

Approximately 10 million people are estimated to be co-infected with Mycobacterium Tuberculosis (MTb) and HIV. 90% of these dually infected individuals reside in the developing countries, where the rate of this co-infection exceeds 1000 per 1,00,000 populations [4].

The HIV infection is known to be an independent risk factor for the reacquisition of the TB infection and a rapid progression to disease [5,6], due to a decrease in the host's ability to contain the new tuberculosis infection [7]. Alternatively, investigations have shown that MTb increases the viral replication in the T lymphocytes and the monocytes [8-10] and that it accelerates the clinical course of the HIV infection [11]. The involvement of the hepato–biliary system is a major concern in the patients with the HIV infection. Approximately one third of the deaths in the patients with the HIV infection are in some way, related to liver disease. Granulomatous hepatitis has been seen as a consequence of the Mycobacterium infection. In late stages of the HIV infection, a primary TB like pattern with or without a diffuse interstitial or a miliary infiltrate is quite common. The physical findings in miliary tuberculosis include hepatosplenomegaly and lymphadenopathy, especially in the abdomen. The elevation of serum Alkaline Phosphatase (ALK-P) and other abnormal values of the liver enzymes in the Liver Function Test (LFT) are detected in patients with a severe hepatic involvement in the HIV illness. Granulomas are also evident in the liver biopsy specimens in many cases [12].

The Antitubercular Drugs (ATD) frequently cause disturbances in the LFTs in 20-25% of the patients and clinical hepatitis in 3% of the cases. Isoniazid and Pyrazinamide raise the serum transaminase levels, while Rifampicin causes hyperbilirubinaemia and centrilobular necrosis of the liver [13]. Similarly, all the Antiretroviral Drugs (ART) like Nevirapine and Efavirenz and almost all the protease inhibitors are potentially hepatotoxic and they cause elevated serum bilirubin and transaminase levels [14].

In this background, a study was conducted to compare the biochemical indices of liver cell damage and hepato-biliary obstruction in the ART naïve cases in the HIV illness with or without TB.

MATERIALS AND METHODS

Between January 2003 and January 2012, a total of 273 subjects were selected for this study. 193 subjects who had been confirmed...
to be positive for the HIV antibodies after they had undergone proper laboratory tests in the School of Tropical Medicine/ ICTC clinic, following their referral to the Department of Chest Medicine of a teaching hospital in Kolkata, India, were selected as the cases. The serous samples from all the suspects were screened for the HIV antibody by a rapid immunochromatography test. Those who were found to be reactive were subjected to an Enzyme Linked Immunosorbent Assay (ELISA) or another kit of a different principle was considered as HIV+ve in this study. The cases were further divided into two separate groups, based on the presence or absence of spumt positive pulmonary tuberculosis in them (100 and 93 respectively).There was no case of tuberculosis of the gums or the oropharyngeal region. 80 seronegative (HIV) subjects who had attended the out-patients department or were admitted in the Department of Chest Medicine for non-tubercular pulmonary illness and who were devoid of any hepato-biliary disorder, musculo-skeletal disease or malignancy were selected as the controls. Ethical clearance was obtained for this study. Written consents were obtained from all the cases and the controls. The

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 (n=100)</th>
<th>Group 2 (n=93)</th>
<th>Group 0 (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male# (%)</td>
<td>Female# (%)</td>
<td>Male# (%)</td>
</tr>
<tr>
<td>Male# (%)</td>
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<td>25 (25)</td>
<td>60 (75)</td>
</tr>
<tr>
<td>Female# (%)</td>
<td>25 (25)</td>
<td>72 (77.42)</td>
<td>20 (22.58)</td>
</tr>
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<td>Mean age (In years) ± SD</td>
<td>32.56 ± 2.83</td>
<td>30.9 ± 0.71</td>
<td>30.03 ± 10.6</td>
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</tbody>
</table>

**[Table/Fig-1]: Age and sex distribution of cases and controls**

NB- Group 0- controls, Group 1-cases with both HIV and TB, Group 2- cases with HIV only. Abbreviations- ± Standard deviation, # Number

<table>
<thead>
<tr>
<th>Parameters</th>
<th>(I) Grouping</th>
<th>(J) Grouping</th>
<th>Mean Difference (I-J)</th>
<th>Std. Error</th>
<th>Level of significance (p value)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>-0.68867</td>
<td>.16596</td>
<td>.000</td>
</tr>
<tr>
<td>ALK-P</td>
<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>-229.40000</td>
<td>24.61646</td>
<td>.000</td>
</tr>
<tr>
<td>Albumin</td>
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<td>1 vs</td>
<td>-102.66078</td>
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<td>.000</td>
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<tr>
<td>Globulin</td>
<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>126.73922</td>
<td>25.58471</td>
<td>.000</td>
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<tr>
<td>Albumin: globulin ratio</td>
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<td>1 vs</td>
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<td>.11524</td>
<td>.000</td>
</tr>
<tr>
<td>ALT</td>
<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>-1.09922</td>
<td>.11463</td>
<td>.000</td>
</tr>
<tr>
<td>AST</td>
<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>0.14812</td>
<td>.11978</td>
<td>.654</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0 vs 1 vs</td>
<td>1 vs</td>
<td>-2.8897</td>
<td>.16986</td>
<td>.000</td>
</tr>
</tbody>
</table>

**[Table/Fig-2]: Comparison of different LFT parameters in three study groups**

* The mean difference is significant at the <0.05 level

Control group =0 (I), Cases with both HIV and TB =1(J ), Cases with HIV only =2 (J)

*(I-J) : Difference between mean values between cases and controls and those between the two case groups, Abbreviation- vs Versus
RESULTS

All the cases and the controls were distributed in three groups. Group 0 constituted the controls (n=80). Group 1 constituted the cases with both HIV and TB (n=100) and Group 2 included the HIV cases only(n=93). The age and sex distribution among the cases and the controls are shown in [Table/Fig-1].

The results showed [Table/Fig-2] statistically significant higher levels of serum total bilirubin among the cases (both Groups 1 & 2) as compared to those in the controls (Group 0). Similarly, there was a significant increase in the activities of the enzymes in the groups of ALAST and ALK-P in all the cases (both Groups 1 and 2) as compared to those in the controls (Group 0). The Group 1 subjects had lower serum total protein and albumin levels and altered albumin/globulin ratios as compared to those in the controls (Group 0). The Group 2 cases did not show any statistically significant difference in the serum total protein levels as compared to those in the controls (Group 0).

The Group 1 cases had higher total bilirubin levels and ALT and ALK-P activities as compared to the Group 2 cases. No significant differences were observed when the values for serum total protein, albumin and globulin and the albumin:globulin ratios among the two case groups (1 and 2) were compared with each other [Table/Fig-3].

The results of our study clearly indicated the derangement of most LFTs in the cases as compared to the controls. The values were more in the cases with tuberculosis. This may be due to the degeneration of the connective tissue of the liver [29] and it may also be the result of the hepatobiliary obstruction that had occurred in the subjects. The structural abnormalities like papillary stenosis, sclerosing cholangitis, cholecytitis and a thickened gall bladder wall [30] in these HIV patients could be attributed to the TB like opportunistic infection [30, 31].

Our observations were similar to the findings of Dwarkin et al., [32] who found a significant rise in the serum ALK-P levels [33] in the cases with HIV and to those of Cello et al., [16] who found increased levels of ALK-P and cholecytitis in the subjects with AIDS.

The observed reduction in our study suggested a chronic hepatic dysfunction and suppression of the synthetic function of the liver [18]. Reversal of the albumin/globulin ratio was seen among the cases. A similar pattern had been reported by Mohammed [19] who had noticed that the HIV patients had generalized lymphadenopathy and polycyonal hyperglibinopathy which involved IgG, IgA and IgM, which had caused an altered albumin: globulin ratio. A similar pattern of hypergammaglobulinaemia had been confirmed in the HIV patients in northern Nigeria [20]. Except for the serum total protein levels, the cases with both HIV and TB had a more significant alteration of these values than those with HIV alone. This finding suggested that the HIV-related immunosuppression prevents the containment of TB to a localized portion of a single organ system [21].

Opportunistic infection of the liver by M. tuberculosis is a common complication in HIV. It is implicated as the cause of the liver parenchymal damage [22].

Moreover, previous studies have suggested that the liver is an important site of the HIV replication [23]. HIV attacks the liver cells directly [24], causing cell death and the release of the cellular contents into the surrounding medium, of which the enzymes constitute 20% [25]. This may be responsible for the increase in the serum liver enzymes in the infected patients. As a support to our findings, various studies have shown a significant increase in the serum AST, ALT and the ALK-P activities in the ART naive, HIV positive cases as compared to the control subjects [26-28].

In our study, the serum ALK-P, ALT and the total bilirubin levels were higher in all the HIV cases as compared to the controls. The values were more in the cases with tuberculosis. This may be due to the degeneration of the connective tissue of the liver [29] and it may also be the result of the hepatobiliary obstruction that had occurred in the subjects. The structural abnormalities like papillary stenosis, sclerosing cholangitis, cholecytitis and a thickened gall bladder wall [30] in these HIV patients could be attributed to the TB like opportunistic infection [30, 31].

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Imaging studies which were done by Ultrasonography (USG) in AIDS patients had shown that the HIV infected patients had hepatomegaly, steatosis, cholecytitis and biliary tract abnormalities, which had caused the altered LFTs, which had been seen here also. The granulomatous hepatitis which had occurred in these cases due to Mycobacterium TB, represented the reactivation of the latent disease [34].

This study had limitations that must be considered. The numbers of the patients in the study groups were not large. Many other investigations, though they were desirable, could not be performed because of limitations.

Thus, care must be taken during the extrapolation of the present findings with those of other populations and other racial groups. Despite these limitations, we believe that our study will be helpful, as the assays of the above mentioned LFT parameters are simple and cost effective.

The results of our study clearly indicated the derangement of most
of the LFT parameters (serum bilirubin, total protein, albumin and globulin, the albumin/globulin ratio, ALTAST and ALK-P) in the HIV infection. This effect on the above mentioned parameters on the LFT was further aggravated by opportunistic infections with Mycobacterium tuberculosis in the TB-HIV co-infection. Nowadays, it is recommended that the LFT must be performed on a routine basis in HIV+ve subjects before the start of the ART. Though it is desirable that the LFT must be done as a routine before giving ATD to the newly diagnosed TB (all forms) patients, this is not adhered to in the routine practice.

Our study demonstrates that LFT must be made mandatory before giving ATD. A similar observation was made by Pukenyte et al., [35]. In such cases or when it is done for other indications, the unexplained high levels of ALK-P should raise the suspicion of a co-existing HIV infection, which was hitherto undetected. Thus, ALK-P can be used as a fruitful marker for identifying more underlying HIV infection.

REFERENCES


