ASSOCIATION BETWEEN VIRAL INFECTIONS AND LIVER FUNCTION TESTS

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ABSTRACT

In a developing and infectious disease prone country like India, increased prevalence of infection with HbsAg, HCV and HIV are on the increase. As of December 2014, World Health Organisation statistics shows globally 33% of population with HbsAg, 150millions with HCV and 37 millions with HIV infections. Numerous studies done previously have indicated alterations in liver function due to infections caused by the above three types of deadly viruses. The aim of this study was to find out the association between viral infections and liver function test. This study was carried out with a reasonable number of patients involving both sexes in each type of infection. This study has proved that some analytes like ALT, GGTP, TP and Albumin showed alterations in viral infectious diseases as per the statistical significance obtained. Further Studies are required in this field with large number of viral infected patients to monitor alterations in Liver function tests in each type of infection and to make LFT as routine diagnostic investigation for such infected patients.

KEY WORDS:
LFT, ALT, HbsAg, HIV and HCV

INRODUCTION

Liver Function Tests (LFT) are often the first line of marker for diseases of the liver. Interpreting abnormal LFT will be useful to diagnose any underlying liver disease in a common scenario in Primary Care. However, other tests of the liver such as liver biopsy should also be done to confirm the diagnosis of a particular disorder, and/or to monitor the activity of the disorder and response to treatment. People with Human Immunodeficiency Virus (HIV) who have a damaged immune system are also at risk of infection that may affect the liver, and therefore doing regular liver function tests in all viral infectious diseases will help detect these. Some anti-HIV drugs can cause side-effects that affect the liver. For people who are positive for Hepatitis C Virus (HCV), Alanine Transaminase (ALT) is the most commonly monitored enzyme among the liver function tests. A positive result on an antibody test along with elevated ALT levels may provide a fairly good indication that an individual is infected with HCV.

HIV & HBV

Abnormalities of LFT have been shown to be common in HIV/AIDS patients in developed countries. Studies have shown that these abnormalities may be due to direct inflammation induced by the HIV virus on the liver cell. It may also be due to gall bladder disease and infection with bacterial, viral or other opportunistic agents and abnormalities of liver enzymes are common in HIV patients in this environment. It is therefore important to characterise the nature of this abnormality and to institute appropriate management. However, more studies are required in this field of HIV related liver disease in Niger(Ejilemele AA et al., 2007). Mild to moderate increase in liver enzymes are common in HIV patients without HCV/Hepatitis B Virus (HBV) and absence of primary immunodeficiency is independently associated with elevations in both Aspartate Transaminase (AST) and ALT, while features typical of hepatic steatosis Diabetes Mellitus (DM) and Body Mass Index (BMI) are only associated with increased ALP(Sterling RK et al., 2008). Liver disease in HIV infected individuals encompasses the spectrum from abnormal LFTs, liver decompensation, with and without evidence of cirrhosis on biopsy, to Non-Alcoholic Liver Disease (NALD) and in its more severe form, Non-Alcoholic Steatohepatitis (NASH) and hepatocellular cancer (HCC). HIV can infect multiple cells in the liver, leading to enhanced intrahepatic apoptosis, activation and fibrosis. HIV can also alter gastro-intestinal tract permeability, leading to increased levels of circulating

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lipopolysaccharide that may have an impact on liver function (Megan Crane et al., 2012).

LFT abnormalities and fibrosis scores were only significantly higher in co-infected patients in the immune clearance and Hepatitis B surface antigen (HbsAg) negative chronic hepatitis phases. LFT abnormalities in Nigerians with Hepatitis B Virus (HBV) infection and co-infection with HIV was found to have a negative impacts on hepatic function (Frozindu MO et al., 2013). The liver is a major part of reticuloendothelial system and is a site of HIV replication and is an organ for many opportunistic infections and so in HIV infected individuals, abnormal LFT can develop as a result of hepatic parenchymal disease. LFT are deranged in HIV positive patients as compared to control. Increased AST and ALT levels may identify patients requiring further investigations as a diagnostic and prognostic tool (Ivan Netto et al., 2009). A statistically significant difference was absent in the serum total protein levels between cases and 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 were compared (Subir Kumar Deyetal., 2009).

Primary HIV-1 infection is often under-diagnosed because of its nonspecific presentations. Elevated AST and ALT levels are one of the clinical manifestations, but is infrequently reported in the literature and elevated levels may be an initial manifestation of primary HIV infection and is more common than expected. Primary HIV-1 infection will serve as one of the differential diagnosis to be considered in young men presenting with unexplained, new-onset liver function impairment (Chen YJ et al., 2010). There is an association between HIV viral load and aminotransferases as markers of hepatic damage leading to improved recognition, diagnosis and potential therapy of hepatic damage in HIV infected patients (José Antonio Mata-Marinetal., 2009). Recent reports of transmission by intravenous gamma-globulin preparations of A, B, C and non-A non-B hepatitis (NANBH), including several cases that progressed to severe liver damage and death, have raised concerns about the safe use of intravenous gamma-globulins. Transient minor elevations were observed for ALT, AST, γ-GT and ALP. None of the elevations were considered indicative of NANBH or of any chronic hepatic disease. Transient presence of hepatitis A, B and C antibodies were observed in some patients. All patients remained negative for HbsAg throughout the study. HIV antibodies resulted always negative in all patients (Antonelli A et al., 1992).

A more robust immune restoration was observed among HBV/HCV coinfected subjects who developed liver enzyme elevation after antiretroviral (ARV) initiation compared with other groups. This finding suggests that ARV-related liver enzyme elevation may be related in part to immune reconstitution, as measured by changes in CD4 T-cell counts (Ofotokun I et al., 1992) Increased levels of ALT and AST were significantly associated with HBV/HIV coinfection status. Gender and liver function tests are important predictors for HBV/HIV coinfection and screening for HBV coinfection in HIV-positive patients is recommended (EltonyMugomeri et al., 2015). The most common presentation was fever (90%), weakness (79%), weight loss (62%) and diarrhoea (62%). The CD4 cell count was between 200-500/µL (33%). LFT showed hyperglobulinemia in patients having CD4 cell count <500/µL. Increased ALP was observed in 63% with CD4 cell count <200/µL. 66.6% had HbsAg reactivity, 33.3% had positive anti-HCV antibody and 50% had abnormal liver histology. One third of these had systemic opportunistic infections like tuberculosis. No correlation could be made between hepatic histology and LFT (Bhattachary N et al., 2006).

Co-infection of HIV and HBV is an emerging problem that should be addressed immediately. Hepatic damage in case of co-infected patients should not be assessed only on the basis of serum liver enzymes as their rise is not significant enough in these cases. Liver biopsy accompanied by liver function tests may provide a clearer picture of macroinflammation. Such co-infected individuals also face increased risk of hepatotoxicity from ARV. Individuals with HIV-HBV co-infection should have both the infections completely assessed in order to decide on the best therapeutic option for both viruses (Tamal Mukherjee et al., 2013).

HbsAg

The prevalence of chronic hepatitis C (CHC) is 0.09%. The LFT abnormality in total subjects was 11.4%. The LFT abnormality of chronic hepatitis B (CHB) and CHC subjects was 21.72% and 63.2% respectively. The prevalence of CHB and C was lower than that of previous studies. The prevalence of CHB in the 2nd decade was still high (Kim SB et al., 2009). HBV DNA level may not indicate the severity of liver inflammation or fibrosis in chronic HBV infection. Patients with HbsAg negative often are complicated with more severity of liver fibrosis. In routine LFT bothBilirubin and ALT correlates with liver inflammation grading or fibrosis staging; but not with fibrosis staging alone (Xu QH et al., 2008). A significant dose-response relationship existed between liver function abnormalities and N, N-Dimethylfarnamamide (DMF) exposure among workers in Taiwan, HBV carrier status or increased BMI had synergistic effects with DMF in causing abnormal LFTs and clinical chronic liver diseases (Luo JC et al., 2001).

Presence of HBV-DNA in maternal blood during the third trimester of pregnancy is significantly associated with maternal serum ALT levels in HbsAg-negative chronic HBV-infected pregnant women. Women with an ALT/sodium ratio greater than 0.092 have the higher probability of HBV-DNA presence in maternal blood whereas an ALT/sodium ratio greater than 0.11 could discriminate those women with HBV-DNA levels higher than 2000 IU/ml (ELEFTsiniotis et al., 2013). HBV was predominantly associated with underlying Chronic Liver Disease (CLD) among this group of patients in India and suggest that HBV coinfection in HCV-infected patients should not be excluded by negative HbsAg status alone (SARAVANAN S et al., 2009). Prevalence of HbsAg positive cases in Guilan province was higher than in other studies. Although frequency of HCV-Abs was similar to other studies, frequency of increased ALT was less, and that all hemophiliacs should be vaccinated against HBV and should have regular program for checking HCV (Mansour-Ghanaei et al., 2002).
MATERIAL METHODS

A total of 52 non hospitalised patients consisting of males and females in the age group of 21 to 74 years attending the infectious diseases clinic and who were investigated for liver function tests as well as HbsAg, HCV and HIV were enrolled for this study. As the sole aim of this study was to find out the association between LFT and HbsAg, HCV and HIV, inclusion or exclusion criteria were not followed.

Diuri CS 1300 B and Dialab reagents were used to measure LFT and VitrosEQI analyser was used to measure HbsAg, HCV and HIV analytes. While the accuracy of all LFT results obtained in this study were validated by the use of Bio-Rad accuracy controls at two levels, the accuracy for HbsAg, HCV and HIV tests were validated using Ortho Clinical Diagnostic commercial controls available. For statistical analysis of data, a software downloaded from the website http://www.vassarstats.net was used to calculate correlation coefficient (r), students 't' distribution (t) and probability (p) between normal and viral infections groups.

RESULTS

Table I Mean analyte values for Normal and Infectious groups

<table>
<thead>
<tr>
<th>Groups</th>
<th>AB</th>
<th>TP</th>
<th>ALB</th>
<th>ALT</th>
<th>ALP</th>
<th>GGTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=35</td>
<td>0.67</td>
<td>0.14</td>
<td>6.91</td>
<td>4.02</td>
<td>20.31</td>
<td>82.69</td>
</tr>
<tr>
<td>HbsAg</td>
<td>0.72</td>
<td>0.26</td>
<td>6.67</td>
<td>3.95</td>
<td>55.14</td>
<td>85.74</td>
</tr>
<tr>
<td>(n=8)</td>
<td>NORMAL</td>
<td>0.71</td>
<td>0.13</td>
<td>7.16</td>
<td>4.04</td>
<td>17.63</td>
</tr>
<tr>
<td>HCV</td>
<td>1.94</td>
<td>1.54</td>
<td>7.25</td>
<td>3.88</td>
<td>81.75</td>
<td>86.75</td>
</tr>
<tr>
<td>HIB</td>
<td>0.69</td>
<td>0.13</td>
<td>7.13</td>
<td>4.08</td>
<td>17.33</td>
<td>82.89</td>
</tr>
<tr>
<td>HIV</td>
<td>1.01</td>
<td>0.47</td>
<td>7.11</td>
<td>3.59</td>
<td>44.67</td>
<td>109.44</td>
</tr>
</tbody>
</table>

Table II Statistical Parameters ( r , t & p ) ; Normal Vs Infected patients

<table>
<thead>
<tr>
<th>Groups</th>
<th>Analytes</th>
<th>Comparison</th>
<th>r</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg</td>
<td>TP</td>
<td>Normal Vs</td>
<td>0.7016</td>
<td>5.6560</td>
<td>0.0000150</td>
</tr>
<tr>
<td>(n=35)</td>
<td>ALB</td>
<td>Infected</td>
<td>0.4939</td>
<td>3.2630</td>
<td>0.0012835</td>
</tr>
<tr>
<td></td>
<td>ALT</td>
<td>Infected</td>
<td>0.4694</td>
<td>3.0540</td>
<td>0.0022230</td>
</tr>
<tr>
<td>HCV</td>
<td>GGTP</td>
<td>Normal Vs</td>
<td>1.3687</td>
<td>2.299</td>
<td>0.031</td>
</tr>
<tr>
<td>(n=8)</td>
<td></td>
<td>Infected</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>DB</td>
<td>Normal Vs</td>
<td>-0.5470</td>
<td>-1.729</td>
<td>0.06374</td>
</tr>
<tr>
<td>(n=9)</td>
<td></td>
<td>Infected</td>
<td>0.9026</td>
<td>5.547</td>
<td>0.00043</td>
</tr>
</tbody>
</table>

The Statistical results obtained for all viral infected patients – HbsAg (n=35), HCV (n=8) and HIV (n=9) and normal patients for both Male and Female are presented in Table- I. The Table I gives the mean values for each analyte studied (normal as well infected group). From the data presented in this Table I, visual observation indicate elevations in the mean values of TB, DB, ALT, GGTP in HCV and HIV and decrease in ALB in infected patients compared to normal group.

Table II shows the statistical comparisons between infected and normal groups. In HbsAg infected group, higher significant association was found in TP, ALB and ALT, and in HCV infection, a moderate significant was observed only for GGTP with P=0.03 and in HIV infected patients DB and TP showed significant associations with P= 0.06 and <0.0001 respectively. From this statistical data, it is clear that liver function is indeed affected and majority of LFT tests like TP, ALB, ALT, GGTP and Direct Bilirubin are altered in viral infected patients. Albumin shows a negative association in HIV infected patients.
suggested that liver synthetic capacity of ALB is affected in HIV infection.

DISCUSSION

Many previous studies have confirmed that increase in liver enzymes occur in HIV infected patients and elevated Transaminases levels are common in such cases (Megan Cranet al., Ivan Netto et al., Chen YJ et al., Antonelli A et al.). Our study outcome also confirms such previous observations and majority of LFT tests are altered in all three types of infections. Previous studies have shown that in HbsAg and HCV infected patients, abnormalities in LFT are observed in TB and ALT (Kim SB et al., Xu QH et al., Kim YJ et al.). As per our study, in HbsAg infection LFT alterations were observed in TP, ALB and ALT and in HCV infection GGTP g et al tered. Our study has clearly shown that majority of LFT tests were altered in viral infectious diseases when compared to normal controls. The outcome of our study suggests that LFT should be made a routine test for infectious diseases involving HbsAg, HCV and HIV.

CONCLUSION

This study was done using a reasonable number of patients infected with HbsAg, HCV and HIV to find out the alterations in LFT. Statistical analysis done clearly demonstrated that some principal analytes like ALT and GGTP were found to be elevated in such infections. Out of routine 7 LFT, 5 principal analytes viz TP, ALB, ALT, GGTP and DB were found to be altered in HbsAg infections, TP, ALB, ALT in HCV infections, notably GGTP and DB and TP in HCV infections. Further studies with large number of patients are required to confirm the inclusion of LFT as a routine test in all three types of infections.

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