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DRUG INDUCED HEPATITIS;

DOES HEPATITIS B AND HEPATITIS C CO-INFECTION INCREASES THE RISK DURING ANTI TUBERCULOUS CHEMOTHERAPY

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ABSTRACT… Aims and Objectives: We evaluated whether HBV +ve and HCV +ve patients are at high risk for developing drug induced hepatitis than control subjects during treatment for tuberculosis with standard short course regimens. **Study design:** Observational cohort study. **Place and duration:** This study was conducted at Department of Medicine, Liaquat University of Medical and Health Sciences Jamshoro from May 2008 to May 2011. **Material and Methods:** All newly diagnosed active tuberculosis patients were included in the study population and they were further screened for hepatitis B surface antigen and HCV antibodies. All patients were divided into three groups. One having no co-infection with hepatitis B and Hepatitis C and was taken as control group, second group was co-infected with hepatitis B and third was co-infected with hepatitis C. short course anti tuberculous regimen was started and patients were followed for six months. **Results:** One hundred and twenty eight tuberculous patients were divided into three groups. 92 in control groups without any co-infection with hepatitis B and C, 10 were HBV +ve and 26 were HCV +ve. During follow up 24 developed drug induced hepatitis, 8(38.33%, n = 24) in control group, 2(8.33%, n = 24) in hepatitis B group and 14(58.33%, n = 24) in hepatitis C group. **Conclusions:** These findings suggest that treatment for tuberculosis in HCV seropositive patients is a risk factor for the development of hepatitis exacerbation and HBV seropositive patients shows no any increased risk of hepatitis exacerbation.

Key words: Hepatitis B, Hepatitis C, drug induced hepatitis

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INTRODUCTION

Tuberculosis is and had remained a major health problem in both developing and developed countries[1] including Pakistan. According to world health organization Pakistan ranks 8th amongst the countries with highest burden of TB in the world and the incidence of sputum positive TB cases in Pakistan is 80/100,000 per year[2]. So in Pakistan a country of 170 million, approximately 1.5 million (1%) people are suffering from tuberculosis, while 260,000 new cases occur each year[2].

Similarly Hepatitis B and hepatitis C are the most common cause of chronic liver disease worldwide,[3] and about 200 million people are infected with HCV worldwide and amongst them 10 million people are in Pakistan[4] amounting to 5% of the general population. Like wise chronic HBV effects 350 million world wide[5] and in Pakistan the overall seroprevalence of HBV in healthy adults amounts to 2.4 %(1.4-11%)[6] of general population. Infection with Hepatitis B virus or hepatitis C virus is a common cause of chronic liver disease and it is a likely possibility that they may co-infect a person suffering from tuberculosis[7]. A recent study found high baseline HBV DNA in patient samples to be a risk factor for DILI[8].

Tuberculosis is effectively treated using short course chemotherapy with first line drugs such as isoniazid, rifampicin, myambutol and pyrazina-

mide[9]. The treatment of tuberculosis is sometimes jeoparadized by the hepatotoxicity of commonly used first line drugs such as isoniazid, rifampicin and pyrazinamide[10]. Various factors have been implicated which increase the risk of hepatotoxicity during anti tuberculous treatment, the most common are advanced age, female sex, alcohol use and malnutrition[11].

Although a vast majority of patients tolerate the drugs, some develop adverse effects of which hepatotoxicity is the most significant[12]. 20% of patients develop asymptomatic elevation of liver enzymes which is self limiting "as a result of adaptation or discontinuance" in a majority of patients,[13] but the outlook may be less favorable in those with develop jaundice, ascites, encephalopathy or acute liver failure[14]. Hepatotoxicity or DILI due to antituberculosis drug-induced liver injury (DILI) encompasses a wide spectrum of liver injury ranging from asymptomatic minimal elevation of liver enzymes to acute liver failure, often leading to death or liver transplantation. Indeed, it is a leading cause of drug-induced liver injury in India and of drug-induced acute liver failure leading to death (DIALF)[15,16]. In a single center registry of 303 patients from Bangalore, antituberculosis drugs contributed to 58% cases of DILI[16].

Whether chronic viral hepatitis due to hepatitis B virus and hepatitis C virus increases the risk of hepatotoxicity during anti tuberculous treatment is not known. The present study was undertaken to evaluate the impact of HBV or HCV co-infection with pulmonary tuberculosis on normal liver biochemical tests using anti tuberculous treatment.

MATERIAL AND METHODS

This study was conducted at department of Medicine, Liaquat University of Medical and Health sciences Jamshoro from May 2008 to May 2011. Patients of pulmonary tuberculosis were diagnosed on the basis of history, radiography and sputum examination. All newly diagnosed active pulmonary TB patients were further screened for hepatitis B surface antigen (HBsAg EIA Abbot) and HCV antibodies (HCV EIA abbot) assays. Aspartate transaminase (AST) and alanine transaminase (ALT) levels was done. Serum total bilirubin was also measured. Patients having AST/ALT levels of >40 IU/L or serum total bilirubin >2mg/dl were excluded from the study.

In all patients height and weight were noted and BMI was calculated in Kg /m^2. Short course 6 month antituberculous regimen was started. This consisted of daily four drugs combination for 2 months i.e. isoniazid 5mg/kg, rifampicin 10mg/Kg and ethambutol 15mg/kg and pyrazinamide 20mg/kg; followed by daily isoniazid, rifampicin and ethambutol in same doses for additional 4 months. All patients were divided into 3 groups. One having no co-infection with hepatitis B and C and was taken as control group. Second group which were co-infected with hepatitis B and third which was co-infected with hepatitis C.

Patients were followed up weekly for 1 month and then monthly till completion of therapy. Clinical examination and liver biochemical tests were performed on each follow up visit. Drug induced hepatitis was diagnosed if ALT/AST level increased to 3 times or more the upper limit of normal and no other apparent cause for the elevation of liver chemistry was diagnosed. If the patients developed drug induced hepatotoxicity, anti tuberculous treatment was withdrawn until ALT/AST normalized.

STATISTICAL ANALYSIS

The data were entered and analyzed in statistical program SPSS version 16.0. Frequencies and percentages of qualitative data such as gender, Hepatitis B and Hepatitis C were presented as n(%) and Fisher's exact test of chi square was applied to compare the proportions between the groups (HBV +ve, HCV +ve and control). Numerical parameters like age, body mass index (Kg/m^2), baseline AST (IU/L), baseline ALT (IU/L) etc. were presented as Mean + Standard Deviation. All the data were analyzed on 95% confidence interval. P value < 0.05 was considered as statistically significant level for all the comparisons.

RESULTS

From May 2008 to May 2011, 150 patients with active tuberculosis were included in this study. Amongst these, 17 patients were excluded due to abnormal baseline liver biochemistry and 5 were excluded as they were alcoholic, remaining 128 were included in the final study. Male patients were 72 (56.25%, n = 128) and female were 56(43.75%, n = 128) with mean age ± SD (range) of 42±19 (25 - 50 years). Mean BMI ± was 21.6 ± 2.51 (range 16.6-33.2). Mean baseline AST ± SD (range) was 22.0 ± 3.0 (10-55) and mean baseline ALT ± SD (range) was 18.0 ± 2.19 (10-25). Among all patients, 92 (71.87%, n = 128) were only suffering from pulmonary tuberculosis without any co-infection with hepatitis B and hepatitis C and was taken as control group. 10 (7.81%, n = 128) patients were co-infected with hepatitis B, 26 (20.31%, n = 128) were co-infected with hepatitis C. (Table-I).

During the follow up period, 15 patients lost follow up and were considered having no any complications, 89 patients did not developed any hepatotoxicity, remaining 24(18.75%) of 128 patients developed raised ALT and AST during anti tuberculous treatment with peak ALT of 428±298 and peak AST of 528±312. Amongst 92 patients of control group 8(38.33%, n = 24) developed drug induced hepatitis, amongst 10 patients of hepatitis B group, 2(8.33%, n = 24) developed drug induced hepatitis (p value 0.61) Table II.

Liver dysfunction	HBV +ve (n=10)	Control (n=92)	P-value
Drug induced hepatitis (DIH)	2 (20.0%)	8 (8.7%)	0.61*

Table-II. Liver dysfunction in HBV seropositive patients and control subjects during treatment for tuberculosis (n = 102)

** P value is statistically not significant calculated by Fisher's exact test of chi square*

Amongst 26 of hepatitis C group, 14(58.33%, n = 24) developed drug induced hepatitis (p value <0.0001). Table III.

DISCUSSION

Despite the availability of effective anti tuberculous treatment the global burden of tuberculosis is increasing in the past few years[17] and over 9 million new cases of tuberculosis occurs annually through out the world. Similarly the epidemics of Hepatitis B and Hepatitis C virus infections involve many of the population that are at high risk[18]. So it is a likely possibility that a patient of pulmonary tuberculosis may be co-infected with Hepatitis B and / or Hepatitis C.

Demographic features	Mean ± Standard Deviation (Range)	Frequency	%age
Age (in years)	42.0±19.13 (25 to 50)	-	-
Gender Male Female	 - -	 72 56	 56.25% 43.75%
BMI (Kg/m^2)	21.6±2.51 (16.6 to 33.2)	-	-
Baseline AST (IU/L)	22.0+3.0 (10 to 55)	-	-
Baseline ALT (IU/L)	18 +2.19 (10 to 25)	-	-
TB without co-infection	-	92	71.87%
HBV +ve	-	10	7.81%
HCV +ve	-	26	20.31%

Table-I. Demographic features of the patients (n = 128)

Liver dysfunction	HCV +ve (n=26)	Control (n=92)	P-value
Drug induced hepatitis (DIH)	14 (53.84%)	8 (8.7%)	0.61*

Table-III. Liver dysfunction in HCV seropositive patients and control subjects during treatment for tuberculosis (n = 118)

** P value is statistically highly significant calculated by Fisher's exact test of chi square*

Standard anti tuberculous therapy although very effective but may cause hepatotoxicity. In this study we observed that whether Hepatitis B and hepatitis C co-infection with tuberculosis may do increases the risk of hepatotoxicity or not and we found that HCV co infection was an independent risk factor for hepatotoxicity during anti tuberculous treatment and HBV co infection was not associated with higher rate of hepatotoxicity.

We compared our results with other researchers in other parts of the world and found same conclusion with regards to HCV infection. Ungo et al. found that approximately 30% of HCV infected tuberculous patients developed hepatotoxcity compared with 11% of non HCV infected individual taking antituberculosis therapy[19] and our study showed that approximately 54% of HCV infected developed hepatotoxicity compared to 8.7% which were not infected with Hepatitis C. (p value <0.0001)Similarly Kwon et al found elevation of lives enzymes in 41% who were HCV+ve and 20% who were HCV-ve[20]. So our study and all these studies proved that HCV co-infection is an independent risk factor for the development of hepatotoxicity in a patient on standard anti tuberculosis therapy.

With respect to hepatitis B co-infections the results were variable. Lei Pan et al. conducted the study on 217 tuberculous patients out of which 66 developed hepatotoxicity after receiving anti tuberculous treatment amongst which 59% were HBV +ve as compared to 24% which were without HBV a very significant difference[21].

Another similar study was conducted by Huang LH et al. and he found that 20.74% tuberculous patients developed hepatotixicity after receiving anti- tuberculous therapy amongst which 74.69% in HBsAg +ve group 25.31% in HBsAg –ve group a very significant difference[22]. However, study conducted by JY Chien et al. did not found a major difference with respect to hepatotoxicity in HBV +ve and HBV-ve group using anti- tuberculous therapy[23] whereas in our results in HBV+ve patients hepatotoxicity occurred in 20% and HBV-ve hepatotoxicity occurred in 8.7% (p value 0.61) which did not show significant association between HBV co infection and the development of hepatotoxicity.

It is not exactly known how the chronic viral hepatitis and anti tuberculous therapy may cause liver inflammation and damage. Scheur PJ et al. have suggested that cytotoxic effect as well as stimulation of the immune response may play a role in hepatic damage by chronic viral hepatitis[24]. Similarly it has been documented that both INH and rifanpicin may have an immunologic effect on liver leading to hepatic damage in chronic viral hepatitis caused hepatic damage. How the use of anti-tuberculous drug exaggerate hepatoxicity in chronic viral hepatitis patients is not known but significant difference has been observed on liver biopsy. Chronic viral hepatitis caused hepatic damage and drug induced hepatic damage may show the presence of lymphoid aggregates or fat deposits whereas drug induced hepatitis may leads to necrosis in zone 3[25]. However we have not performed liver biopsies due to ethical reasons but it was shown that chronic viral hepatitis infected tuberculosis persons are more prone to develop hepatotoxicity on anti tuberculous therapy.

Lastly, this study suggests that chronic viral hepatitis infection may play an important role in the development of hepatotoxicity in patients using anti tuberculous drugs and there are large numbers of patients in this part of the world who are co infected with tuberculous and chronic viral hepatitis may need to be considered for serologic screening of hepatitis B & C so that an eye may be kept on liver biochemistry on follow up.

CONCLUSIONS

In patients of tuberculosis on anti tuberculous therapy, HCV co-infection is an independent risk factor for the development of hepatitis exacerbation.

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"To succeed in life,

you need two things:

ignorance and confidence."

Mark Twain