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HEPATOTOXICITY DUE TO ANTITUBERCULOSIS THERAPY: A PROSPECTIVE STUDY FROM A TERTIARY CARE CENTRE

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ABSTRACT

Objective: Tuberculosis is a significant problem in developing countries like India. The objective of the study was to find out the prevalence of anti-tubercular treatment induced hepatotoxicity and to determine the predisposing risk factors, if any. Methods: It was a prospective observational study involving 150 newly diagnosed tuberculosis patients on antitubercular therapy at a tertiare care centre. Clinical and epidemiological data including the risk factors predisposing to liver toxicity were collected through history taking and review of medical records. Baseline liver function tests were conducted before starting the therapy, one week after the therapy and whenever symptoms of hepatotoxicity arise. ATT induced hepatotoxicity was defined in accordance with the international consensus criteria. Statistical analyses were performed using the SPSS version 20.0 in terms of mean ± SD, absolute numbers and percentage. The chi-square test was used to compare the differences in variables between the two groups. $p<0.05$ was considered as significant. **Results:** 32(21.48%) out 150 tuberculosis patients developed hepatotoxicity during the course of treatment out of which 53% were males. ATT induced hepatotoxicity was most commonly associated with TB lymphadenitis 13(40.6%) followed by pleural effusion 9(28.5%), TB meningitis and miliary TB 3(9.3%). Smoking was found to favour development of ATT induced hepatotoxicity (p value-0.030). Rest other risk factors were not found to be statistically significant. **Conclusion:** Smoking was found to be related with the incidence of ATT induced hepatotoxicity significantly although it demands further analysis.

KEYWORDS: Drug induced liver injury, DILI, tuberculosis, ATT.

INTRODUCTION

Tuberculosis continues to be significant health problem across much of developing world. India is found to have the highest number (27%) of tuberculosis patients worldwide according to the Global TB report 2017 by WHO. In 2017, 10 million people fell ill with TB, and 1.6 million died from the disease globally.[1]

Although newer drugs with better efficacy and safety are being studied, the mainstay of tuberculosis treatment continues to revolve around the same drugs identified 5-6 decades ago. These include isoniazid, rifampicin, pyrazinamide and ethambutol. Although, the multidrug therapy is considered to be more advantageous in terms of efficacy, clinical cure achieved and preventing the emergence of resistance to any of the drugs used alone; the risk of adverse events increases to manifolds. Therapy related adverse events include hepatotoxicity, skin reactions, gastrointestinal and neurological disorders that account for significant morbidity leading to reduced effectiveness of therapy. Hepatotoxicity is the commonest of all adverse effects with incidence reported as between 2% and 28%.[2] Isoniazid, rifampicin and pyrazinamide have a propensity to exert toxic effect on hepatic cells, more particular in combination.

Burden of anti-TB drug related hepatotoxicity is based not only on its prevalence, but also on its severity and outcome. Adverse drug reactions to anti-TB drugs could lead to treatment interruptions with a potential for prolonged treatment, resultant poor outcomes including the risk of drug resistance and treatment failure. Mortality of 4-12% has been reported and around 11% of patients treated with combination of isoniazid, rifampicin and pyrazinamide discontinue the treatment.[3] The spectrum of anti-TB drug induced hepatotoxicity can vary from asymptomatic elevations in the liver enzymes to fulminant liver failure often leading to death or liver transplantation.

The underlying mechanisms of antituberculosis treatment induced hepatotoxicity are poorly understood. Therefore, a better understanding of the risk factors would be helpful. Previous studies have shown that the risk factors can be classified as non-genetic and genetic factors.[4] Non-genetic factors include female sex, poor nutritional

status, chronic alcoholism, presence of concomitant liver disease, hepatitis B and C carrier state, hypoalbuminemia, advanced stage of tuberculosis. Other risk factors that have been reported include overweight/obesity, anemia and tobacco smoking. The genetic factors are involved in drug metabolism, transport, and immune and antioxidant responses, and include N-acetyltransferase 2 (NAT2), BTB and CNC homology 1 (BACH1), tumor necrosis factor-a (TNF) and adenosine triphosphate binding cassette B1 (ABCB1). These factors were found to be independently associated with the development of adverse drug reactions in patients with tuberculosis. However, contradictory results have been reported by other workers and consensus regarding their role is lacking.[5-7]

Hence, the present study has been designed to study the prevalence of anti-tubercular treatment induced hepatotoxicity and to determine the risk factors, if any, which predispose to the development of anti tubercular treatment induced hepatotoxicity.

METHODS

It was a prospective observational study conducted at Holy Family Hospital, a tertiary care centre, New Delhi for duration of nine months. The study protocol was approved by Institutional Ethics Committee prior to the commencement of the study. Total 150 patients were included in the study. The sample size was decided on the basis of pilot study. All the newly diagnosed tuberculosis patients of either sex presenting to OPD or admitted in the Department of Medicine were included in the study. Exclusion criteria includes patients with hepatocellular malignancies, concomitant acute viral hepatitis, patients who were started on modified anti tubercular treatment due to altered liver function test (LFT) right at the outset and patients receiving other potentially hepatotoxic medication.

All the patients who participated in the study were given clear explanations about the purpose and nature of the study in the language they understood. Written informed consent was taken from every patient who participated in the study.

Clinical and epidemiological data including gender, age, alcohol abuse, tobacco smoking and other concomitant diseases were collected through an interview using a standardized questionnaire and review of each patient's medical records. The relevant data collected from case sheets were properly documented in a separate data collection form. Pretreatment baseline LFTs were performed in all patients using standard laboratory procedures. Patients were kept under the close observation and instructed to report any unusual symptoms (nausea, anorexia, malaise, jaundice and vomiting) that may come across during their treatment period. After initiating the drug therapy, SGOT, SGPT and serum bilirubin was done after 1 week and then every month once. These tests were done whenever the patient has symptoms suggestive of hepatitis- viz: nausea, anorexia, malaise, jaundice and vomiting.

Patients with hepatotoxicity induced by anti-TB drugs were defined in accordance with the international consensus criteria. Anti tubercular drug treatment induced hepatotoxicity will be defined by the criteria mentioned by the Joint Tuberculosis Committee of the British Thoracic Society recommendations and the recent guidelines published by the American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society (ATS/CDC/IDSA).[8]

Laboratory investigations include: liver function tests- Serum Bilirubin (direct) by diazo method, AST (aspartate transaminase) and ALT (alanine transaminase) by UV kinetic method, ALP (alkaline phosphatase) by DNP method in the pathology lab of the hospital.

In the patients developing hepatotoxicity, medications were stopped immediately and serum transaminase levels will be measured. They were then put on modified ATT and AST, ALT and billirubin was documented weekly till they return to normal. Thereafter, first line ATT medication will be restarted one by one every week after monitoring liver function tests. The patient will be followed up till the completion of treatment.

Sample collection: 5ml of venous blood samples were collected from the patients and healthy subjects in the morning, after an overnight fast in heparinized bulbs. The samples were centrifuged at 2000rpm for 15min and plasma was separated.

Statistical analysis: Statistical analyses were performed using the SPSS version 20.0. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as absolute numbers and percentage. The chi-square test was used to compare the differences in variables between the two groups. Student's t-test was used for continuous, normal variables. A two-sided p value less than 0.05 was considered statistically significant. For all statistical tests, p value less than 0.05 was taken to indicate a significant difference.

RESULTS

Total 150 patients newly diagnosed with tuberculosis were included in the study, out of which one patient died before establishing the diagnosis. So 149 patients were involved in the study and were followed up for the entire duration of therapy. Among them, 75 (50.34%) were females. The ages of the patients ranged from 11 years to 90 years with the mean (±SD) age being 39 (± 16.6) years, but the highest number of participants was found in the age group of 21–30 years, which is 54 (36.24%).

Out of 149 participants, 17 of them were taking different antibiotics during the study period, of which nine (52.94%) were males and eight (47.05%) were

females. None of them were reported to be taking paracetamol or other potentially hepatotoxic drugs during the study period. The most common site of tuberculosis was lymph nodes 51 (34.23%) followed by pleura 29 (19.46%) and lungs 14 (9.4%). 20 (13.42%) patients were chronic smokers and 52(34.89%) were found to be alcoholic.

Based on the criteria adopted for defining hepatotoxicity, it was observed that 32 (21.48%) patients developed hepatotoxicity during the course of ATT therapy which was confirmed by clinical examination and liver function tests. Out of 32 patients, 17 (53%) were males and 15(47%) were females. Majority of patients were in the age group of 51 to 60 years 5(29.41%). The incidence of ATT induced hepatotoxicity was most commonly associated with TB lymphadenitis 13(40.6%) followed by pleural effusion 9(28.5%), TB meningitis and miliary TB 3(9.3%).(Figure 1).

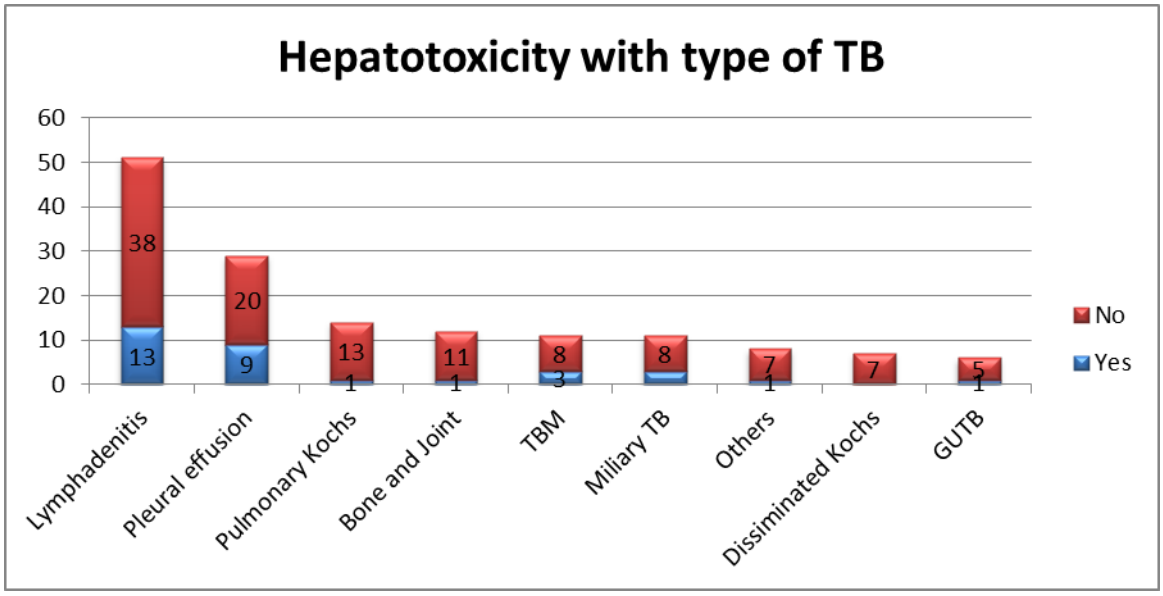

Figure 1: Hepatotoxicity with type of tuberculosis.

Baseline and peak values (mean ± SD) of patients with ATT induced hepatotoxicity is shown in table 1.

Table 1: AST, ALT and total bilirubin levels (mean±SD) of patients.

		Patients without ATT induced hepatotoxicity	Patients with ATT induced hepatotoxicity
AST	Baseline	25.12±7.38	29.67±9.63
	Peak value during treatment	32.81±15.19	280.37±67.80
ALT	Baseline	28±6.26	27.39±8.20
	Peak value during treatment	30.66±8.33	222.54±7.48
Total bilirubin	Baseline	0.38±0.34	0.47±0.26
	Peak value during treatment	0.76±0.82	10±0.91

It was found that smoking favours development of ATT induced hepatotoxicity (p value-0.030) Rest other factors were not found to be statistically significant. (Table 2) None of the patients were found to be infected with hepatitis. Only one patient was having HIV co-infection who did not develop hepatotoxicity.

Table 2: Risk factors assessment in patients.

Characteristics	Hepatotoxicity n(%)		P value
	Yes (n=32)	No (n=117)	
Gender			0.659
Female	17 (53.12%)	57 (48.71%)	
Male	15 (46.87%)	60 (51.28%)	
Age			0.713
>30 years	15 (46.87%)	48 (41.02%)	
<30 years	17 (53.12%)	69 (58.97%)	
Smoking			0.030

Yes	08 (25%)	12 (10.25%)	
No	24 (75%)	105 (89.75%)	
Chronic alcoholic			0.944
Yes	11 (34.3%)	41 (35.04%)	
No	21 (65.6%)	76 (64.95%)	
Past history of TB			0.759
Yes	5 (15.62%)	21 (17.94%)	
No	27 (84.37%)	96 (82.05%)	
Sputum AFB positive			0.525
Yes	01 (3.12%)	7 (5.98%)	
No	31 (96.87%)	110 (94.01%)	
Viral infections			
HIV			-
Yes	0	2 (1.70%)	
No	32	115 (98.29%)	
HBsAg	-		
HCV	-		
Anemia			0.854
Yes	09 (28.12%)	31 (26.49%)	
No	23 (71.87%)	86 (73.50%)	
Comorbidities			
IHD/ heart failure/ valvular disease	1 (3.12%)	3 (2.56%)	0.862
DM	1 (3.12%)	8 (6.83%)	0.435
CLD	1 (3.12%)	1 (0.85%)	0.323
COPD	1 (3.12%)	5 (4.27%)	0.769

DISCUSSION

The study showed prevalence of anti-TB drugs-induced hepatotoxicity in new cases to be 21.48%. The prevalence was found to be higher than studies conducted in different parts of the country.[7,9] The high prevalence could partly be explained through referral bias as the centre is a tertiary care unit. In literature, there is a wide disparity in the reported incidence of ATT-induced hepatitis ranging from 2 to 39%.[5,7,10] The incidence has been reported to be higher in developing countries. The variation in the incidence of anti-TB-drug induced hepatotoxicity worldwide may be attributed to the differences in patients' characteristics, indiscriminate use of drugs and the definition criteria of hepatotoxicity.

Since the pathogenesis of hepatic injury by ATT is not very clear and only a small subset of individuals develops hepatic injury, various risk factors predisposing to hepatotoxicity were studied. While many studies focused on clinical factors associated with hepatic damage, others paid attention to genetic factors.

The present study interests in association of clinical factors with hepatotoxicity. Some studies have reported that the risk of ATT induced hepatitis increases with advancing age, the highest incidence being in individuals older than 50 years. However, in the present study, age is not found to be related to ATT-induced hepatotoxicity as also reported in few studies.[7,11] We did not find any sex preponderance in our study as also noticed in some studies.[6,7] Contrary to observations in earlier studies no significant difference was found in the alcohol intake and prevalence of hepatotoxicity.[7,12]

Smoking was found to be related with the incidence of anti-TB-DIH significantly (p value-0.030) although it demands further analysis. This was an interesting finding as few studies found a decreased risk of developing anti-TB drug induced hepatotoxicity in active smokers when compared to non-smokers.[13]

Co-infection with hepatitis B virus, HCV, or HIV was not found to be associated with hepatotoxicity in the current study.[7,14] Viral diseases like hepatitis B and C as well as HIV or an underlying silent chronic liver disease were found to be significant risk factors in development of ATT-induced hepatotoxicity.[8,11,15] However, there was only one patient with HIV coinfection and none with HBsAg or anti-HCV antibody among those with hepatotoxicity in the current study.

It is important to note that asymptomatic transaminase elevations occur in 20% of patients treated with standard antituberculosis regimens; prior to treatment or immediately after the start of treatment. Usually these elevations resolve spontaneously.[2] The exact role of regular monitoring of liver function tests in patients receiving antituberculosis drugs remains controversial. Certain guidelines only emphasize the need of clinical monitoring without mentioning regular biochemical monitoring while a number of authorities recommend routine biochemical monitoring among the high risk groups. Furthermore, opinions on the frequency and duration of biochemical monitoring also differ. While more frequent testing may be more likely to pick up those cases with rapid progression, cost-effectiveness and patient acceptance are practical issues among those

without clinical symptoms. Whether monitoring should be performed throughout the whole course of anti-TB treatment or just during the initial treatment phase also requires deliberation.

Since it is very difficult to predict which patient will develop hepatotoxicity on antituberculosis treatment, health education should be provided to alert all patients undergoing treatment with potentially hepatotoxic anti-TB drugs. Awareness about the symptoms suggestive of injury to liver like loss of appetite, nausea, vomiting, fever, and jaundice is crucial. They should be advised to report such symptoms promptly. Also, during medical consultations in the course of anti-TB treatment, all patients should be assessed clinically for symptoms and signs suggestive of hepatitis. Directly observed treatment (DOTs), apart from ensuring treatment adherence, also provides an opportunity to monitor the patients closely for such symptoms and signs. In the case of clinical suspicion of significant reaction, the anti-TB drugs may have to be stopped even before the availability of the test results.

Although the guidelines from the American thoracic society (ATS), British thoracic society (BTS) and the Task Force are more or less the same, there are some differences. The ATS does not recommend baseline liver function testing for healthy patients, but only advises it in patients with possible risk for ATDH (e.g. patients with liver disorders), whereas the Task Force and BTS advise performing baseline liver function testing in all patients. After TB treatment has been stopped because of hepatotoxicity, both the BTS and ATS advise restarting the antituberculosis drugs one at a time. The Task Force advises restarting all the drugs simultaneously; after a second episode of hepatotoxicity the drugs need to be reintroduced consecutively.[2]

A hepatoprotective effect of *N*-acetylcysteine and silymarin on antitubercular treatment induced hepatotoxicity has been shown in rats. More studies are needed on the protective effect of such compounds in humans and possible interactions with antituberculosis drugs.[2]

However, the study has some limitations. Our findings may not be generalized as the data emanated from a relatively few patients attending a single tertiary hospital. Further studies involving large sample size with assessment of genetic factors may provide better understanding of risk factors.

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