Original Research Paper

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Respiratory Medicine

A CASE SERIES ON THE EFFECT OF ATT ON LIVER FUNCTION IN FRESHLY DIAGNOSED CASES OF PULMONARY AND EXTRA PULMONARY TUBECULOSIS RECEIVING DOTS THERAPY.

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ABSTRACT **AIMS and OBJECTIVES:** To study the incidence and risk factors involved in development of hepatic damage and overt hepatitis in freshly diagnosed cases of pulmonary and extra pulmonary tuberculosis patients receiving anti tubercular treatment under RNTCP fixed dose combination (DOTS therapy)

METHODS: In this prospective study, 100 freshly diagnosed pulmonary (95) and extra pulmonary tuberculosis(5) patients (67 males and 33 females) attending the outpatient clinic and DOTS Centre were taken up for study and were given ATT in fixed dose combinations as per RNTCP guidelines

RESULTS: The study group of 100 pulmonary and extra pulmonary tuberculosis patients consisted of 67 males and 33 females. Age varied from 15 – 80 years. Twenty eight patients (28%) developed ATT induced liver damage which included 23 (23%) patients who had asymptomatic elevation of liver enzymes and 5 (5%) patients (3 extra pulmonary and 2 pulmonary TB) developed overt drug induced hepatotoxicity. 50% of cases in the age group of 51-60 years and 50% of cases in the age group of > 60 years developed drug induced liver damage.

CONCLUSION: The incidence of asymptomatic elevation of liver enzymes secondary to ATT is 23% and incidence of overt DIH is 5%. Advanced age, high alcohol intake, BMI < 18, radiologically severe disease and pre-treatment hypoalbuminemia and extra pulmonary TB were found to be predisposing factors for the development of ATT induced hepatotoxicity while gender had no impact. Peak incidence of hepatitis occured in the first month of therapy.

KEYWORDS : TB, ATT, hepatotoxicity

INTRODUCTION:

Tuberculosis is a mycobacterial disease treatable with anti-tubercular therapy. commonly used drugs are isoniazid, rifampicin, pyrazinamide in fixed dose combinations. common side effects of the drugs are isoniazid causes peripheral neuropathy and hepatotoxicity, rifampicin causes immune-allergic reactions and hepatotoxicity, pyrazinamide causes joint pains (due to increased serum uric acid) and hepatotoxicity. These three drugs isoniazid , rifampicin , pyrazinamide are hepatotoxic and toxicity manifests in the form of nausea , vomiting , weakness, tiredness and yellowish discolouration of eyes .These side effects can be due to one or two or all three of drugs. out of which pyrazinamide is most hepatotoxic. Hepatotoxicity not only increases mortality and morbidity but also decreases anti tubercular therapy effectiveness owing to non adherence leading to multi drug resistant tuberculosis. so regular monitoring of liver function tests is necessary. Management is by stopping all the three drugs until patient becomes asymptomatic and liver function tests are within normal range. As far as the individual drug is concerned it has been observed clinically that if symptoms of hepatotoxicity occurs within first ten days of initiation of ATT rifampicin is the culprit , if symptoms arise by the end of second week of initiation of ATT ,there are more chances of isoniazid being the culprit and if symptoms arise after three weeks ,most liable drug is pyrazinamide. These side effects are more common in alcoholics . As soon as patient is asymptomatic and LFT are within normal range , the drugs one by one should be restarted. Isoniazid is to be first re-initiated followed by rifampicin followed by pyrazinamide. Generally patient takes 1-2 weeks to tolerate one drug and after two weeks another drug is added and generally after 4 weeks 3rd drug is added.

AIMS AND OBJECTIVES:

1. To study the incidence of overt hepatitis and hepatic damage in patients receiving anti tubercular treatment as per RNTCP (DOTS therapy- daily regimen with fixed dose combination) .
2. To protect the liver from injury by early recognition of side effects of drugs used in the chemotherapy.
3. To know the possible risk factors for the development of drug induced hepatotoxicity .

Inclusion criteria:

Patients diagnosed to have pulmonary and extra pulmonary TB for the first time.

Exclusion criteria:

1. Patients with pulmonary tuberculosis who are defaulters, treatment failure cases, and multidrug-resistant cases.
2. Patients with abnormal baseline liver function tests.
3. Patients with liver cirrhosis , acute viral hepatitis and / or gastrointestinal, renal, or cardiac diseases.

Methodology :

SOURCE of data:

100 freshly diagnosed cases of pulmonary and extra pulmonary tuberculosis males as well as females attending the outpatient department of Alluri Sitarama Raju Academy of Medical Sciences and RNTCP DOTS centre in the hospital are taken up for study.

Study design : A prospective clinical study.

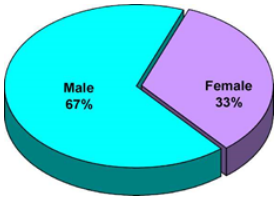
Study period: 1 year from 1st February 2019 to 30th January 2020.

RESULTS :

Sex Distribution :

Out of 100 patients 67 are male and 33 are female.

Chart -1 : Sex Distribution Of Study Population



AGE DISTRIBUTION :

overall ATT induced hepatotoxicity most common in the age group of 41 – 50 yrs.

Table-1: age distribution of patients with liver damage

Age in Yrs	Elevated enzymes		Non-elevated enzymes		Total
	No	%	No	%	No
Up to 20	1	3.6	19	26.4	20
21-30	5	17.9	17	23.6	22
31-40	6	21.4	16	22.2	22

41-50	8	28.6	15	20.8	23
51-60	4	14.3	4	5.6	8
>60	4	14.3	1	1.4	5
Total	28	100.0	72	100.0	100

Percentage of Patients with Liver Damage: out of 100 patients 28 had elevated liver enzymes . Out of 28 patients with elevated enzymes , 5 patients had overt drug induced hepatotoxicity with symptoms in which 3 are pulmonary tuberculosis and 2 are extra pulmonary tuberculosis. Remaining 23 patients had aymptomatic enzyme elevation out of them 15 are pulmonary tuberculosis and 8 are extra pulmonary tuberculosis.

Table -2 : Risk factors for elevated enzymes:

RISK FACTORS	ENZYMES ELEVATED	NOT ELEVATED	TOTAL CASES
Male	22	45	67
Female	6	27	33
BMI < 18	14	20	34
Alcohol	13	11	24
Severe chest x-ray findings	15	15	30
Se.albumin < 3.5g/dl	22	15	37

Male sex , BMI <18 , alcohol consumption , radiologically severe disease , pre treatment hypoalbuminemia are found to be risk factors for drug induced hepatotoxicity

DISCUSSION:

DIH was defined as normalization of liver function after withdrawl of all anti tuberculosis drugs and the presence of atleast one of the following criteria

a. A rise of five times the upper limit of normal levels of serum aspartate aminotransferase and /or alanine amino transferase

b. A rise in the level of serum total bilirubin >1.5mg/dl

c. Any increase in AST and/or ALT above pre treatment levels together with anorexia , nausea , vomiting and jaundice

d. absence of serological evidence of infection with hepatitis virus A, B, C or E

100 cases of freshly diagnosed pulmonary and extrapulmonary TB were given anti tubercular therapy under DOTs. Baseline liver function tests were done and repeated at 2^{nd} ,4^{th} and 8^{th} weeks to identify drug induced hepatotoxicity . Out of 100 cases 67 were males and 23 were females and all patients were in age between 15 -80yrs. Maximum number of cases were found between 15 to 40 yrs of age (64%) . the patients who developed drug induced liver damage in the form of asymptomatic elevation of liver enzymes and bilirubin and who developed drug induced hepatotoxicity were grouped as elevated group and others who did not show any significant change in liver enzymes and bilirubin were classified as non elevated group . ATT induced liver damage was seen in 28 % of cases out of which 5% cases had Drug induced hepatotoxicity and remaining 23% had asymptomatic elevations in liver enzymes . This was comparable to study done by SK.RAJAN.et al where 22% of cases of ATT induced liver damage , 18 % showed non symptomatic elevations in the liver enzymes and 6% showed overt jaundice. In the drug induced hepatotoxicity group , medications were stopped and serum transaminases were measured weekly until they returned to normal levels. Thereafter , anti TB drugs were gradually reintroduced.

RISK FACTORS :

The relatively higher incidence of hepatotoxicity in the developing countries has been attributed to various factors . Out of 28 cases 5% of case are < 20yrs , 22.7% of cases were between 21-30 yrs , 27.2% of cases between 31 -40 yrs ,34.7 % of cases between **41-50 yrs** , 50% of cases between 51 -60 yrs and 80% of cases > 60yrs of age .these results indicate that advancing age is an independent risk factor for drug induced hepatotoxicity. The patients in the age of > 50years are 5.36 times more likely to have liver damage as compared to the patients in the age group of <50 years . 46.4% of enzyme elevated cases and 15% non enzyme elevated cases have **high alcohol intake .** so the patients with history of high alcohol intake are 4.46 more likely to have elevated liver enzymes as compared to non alcoholics while receiving ATT . 50% of cases of elevated group and 27.8% cases of non elevated group had **BMI < 18** . poor nutritional status has been considered to be one of the factors contributing to the high incidence of hepatitis induced by ATT. So BMI can be independent factor to predict the risk of ATT induced liver damage . Patients with BMI <18 are 2.42 times more likely to have elevated liver enzymes . Findings of this study are comparable with study done with SK Rajan et al who found that 9 out of 11 cases of drug induced hepatitis had BMI < 18. 78.6 % of elevated group and 15% of non elevated group have **pre treatment hypoalbuminemia** of < 3.5gm /dl .patients presenting with pre-treatment hypoalbuminemia are 14 times more likely to have ATT induced liver damage than patients presenting with normal serum albumin levels. Out of 34 Cases of **extrapulmonary TB** 8 cases showed non enzymatic elevation of liver enzyme and 3 cases showed DIH indicating that extra pulmonary TB is an independent risk factor for drug induced liver damage.

CONCLUSION:

Incidence of ATT induced liver damage is around 28% . incidence of DIH is around 5% and asymptomatic elevations of liver enzymes is around 23% .peak incidence occurs in 3^{rd} to 4^{th} week after starting ATT. Advancing age, history of high alcohol intake , BMI <18 , radiologically severe disease and pre treatment hypoalbuminemia are significant risk factors for the development of ATT induced liver damage while female sex is not a risk factor. Patients in the age group of >50 years are 5.36 times more likely to have drug induced liver damage than patients < 50 years alcoholics are 4.46 times more likely to have drug induced liver damage as compared to non alcoholics. Patients wth BMI < 18 are 2.4 times more likely to develop ATT induced liver damage than patients with BMI >18 . Among all risk factors pre treatment hypoalbuminemia has more predictive value with respect to drug induced liver damage followed by high alcohol intake and radiologically severe disease. Among liver function tests serum bilirubin , alanine transaminase, aspartate transaminase levels increase proportionately with extent of drug induced liver damage. Alanine transaminase is a good surrogate marker to assess the extent of liver damage.

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