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Clinico-Demographic Profile of Drug Induced Hepatitis Patients on First Line Anti Tuberculosis Treatment in New Delhi

Rishi Kant Aharwal[1]*; Vikram Vohra[2]; Amit K Mehto[3]

[1]Assistant Professor, Department of Respiratory Medicine, Sukhsagar Medical College, Jabalpur, India.

[2]Senior Grade I, Consultant Chest Physician, NITRD, New Delhi, India.

[3]Consultant, Policy Wisdom LLC, India.

***Corresponding Author(s): Rishi Kant Aharwal**

Assistant Professor, Department of Respiratory Medicine, Sukhsagar Medical College, Jabalpur, India.

Tel: 9340572202; Email: rishi.noble.doctor@gmail.com

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Keywords: Pulmonary tuberculosis (TB); Antitubercular drugs (ATT); Hepatotoxicity; Liver function; Drug Induced Hepatitis (DIH).

Abstract

Background: Drug Induced Hepatitis (DIH) is a serious adverse effect caused by Anti-Tubercular (ATT) drugs. The prevalence of DIH is much higher in developing countries owing to a higher prevalence of pre-existing chronic illnesses like acute or chronic liver disease and viral hepatitis; alcoholism; malnutrition; indiscriminate drug use; and a higher prevalence of advanced and drug-resistant TB requiring long-term treatment. Hence, this study aims to find out the socio-demographic and clinical factors that are associated with DIH. A better understanding of the associated factors would help clinicians in India pre-empt and prevent DIH.

Methodology: Patients diagnosed with Pulmonary Tuberculosis (PTB) and Extra-Pulmonary Tuberculosis (EPTB) on first line anti-tubercular treatment with confirmed DIH were enrolled in the study between (September 2018 to March 2019). Patients were followed up till the resolution of DIH and data on the sociodemographic factors were collected and analysed. Data on their socio-demographic, clinical and biochemical parameters were collected to find out the most common associated factors with DIH.

Results: A total of 102 patients were followed up, their mean age was 40.05±19.81 years with a male to female ratio of about 3:2. Majority of the patients were of young age group (15 to 30 years) 30.4%. 80.39% of the patients were found to be underweight and more than half of the patients were diagnosed within 1 month of the start of ATT. The most common symptom among the patients were nausea (74.5%) followed by vomiting (72.5%) and abdominal pain. Clinically demonstrable icterus was present in 29 (28.43%) patients. The mean latency period between start of ATT and presentation with DIH was 10.74 days.

Conclusion: Young underweight patients presenting with nausea and vomiting soon after the start of ATT need to be screened for DIH and given prompt management.

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Introduction

Tuberculosis (TB) is one of the most common infectious diseases in the world and remains the number one killer among the infectious diseases affecting adult population in developing countries accounting for 7.22% of all deaths in low-middle countries. For India this proportion is even higher and is 8.14% [1]. The total number of incident TB patients in India (new and relapse) notified during 2021 were 19,33,381 and the the estimated mortality rate among all forms of TB was 37 per 100,000 population [2,3].

The prevalence of DIH has been found to be 9.1%, 11.9% and 8% in studies conducted in Thailand, South Korea and Ethiopia respectively [4-6]. The prevalence of DIH is much higher in developing countries owing to a higher prevalence of acute or chronic liver disease, alcoholism, malnutrition, indiscriminate drug use, advanced TB and other coexisting chronic illnesses [2].

ATT drugs may cause hepatotoxicity ranging from a transient asymptomatic rise in liver enzymes to acute liver failure. Therefore, population based prospective study among patients with positive TB smear and those who have received DOTS treatment needs to be conducted to enable a better understanding of the socio-demographic and clinical features associated with it. It will also help in the estimation of the incidence of DIH, better understanding of its clinical features and to evaluate its impact on anti-TB treatment.

National institute of Tuberculosis and Respiratory Disease is a tertiary care centre for tuberculosis as well as a WHO collaborating centre for tuberculosis in India. It is a referral centre for complicated TB cases from all over the country. Only a few studies addressing these issues have been conducted in India. Hence, this study aims to find out the socio-demographic and clinical factors that are associated with DIH. A study like this is required to gain a better insight into the clinico-demographic pattern of ATT induced Hepatitis over a wider spectrum of tuberculosis patients. A better understanding of the associated factors would help clinicians in India pre-empt and prevent DIH.

Material and Methods

The study was conducted at National Institute of Tuberculosis and Respiratory disease (NITRD), New Delhi. It was Prospective observational study started from September 2018 and completed in March 2019. Patients were enrolled with Inclusion criteria - All diagnosed TB patients (EPTB or PTB) on ATT with DIH who gave consent. The participation of in the study was voluntary and patients were given the right to leave the study at any time and they were explained that the data collected would be anonymised and only be used for analysis and publication purposes. The exclusion criteria was-patients with chronic liver or chronic kidney disease and patients with HIV, Hepatitis A, B, C or E infection. This choice was made to remove any confounding factor that could cause hepatitis outside of ATT induced hepatitis under study. Sampling design was purposive. The data was collected and analysed using MS Excel and SPSS software.

Drug Induced Hepatitis (DIH): DIH is defined by the presence of any one of the following criteria:

1. A rise to ≥5 times the normal serum level of transaminases (normal serum glutamate pyruvate transaminase or SGPT: 7-41 U/L and normal serum glutamic oxaloacetate transaminase or SGOT: 12-38 U/L).
2. A rise in the level of serum total bilirubin >1.5 mg/ dL.
3. Any increase in serum transaminase above pre treatment levels together with symptoms of anorexia, nausea, vomiting and jaundice.

BMI of the patients was calculated from the height and weight of the patients using the standard formula to calculate the Quetelet's Index. They were taken as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2) and over weight (>25 kg/m^2) as aper the WHO cut-offs [7].

Results

A Total of 102 patients participated in the study and the mean age ± standard deviation of sample was 40.05±19.8 years. The male to female ratio was around 3:2 with 60.7% of the patients were male and 39.2% were females. The most common age-group that the patient fell into was 15-30 years with n=31 (30.4%), followed by 24 (23.5%) patients belonging to the age group 31-45 years. 10 (9.8%) patients belonged to the age group of less than 14 years.

48 patients (47.0%) reported havong no addictions when asked about alcohol or tobacco where as addicted to alcohol only were 6 patients. Patients addicted to tobacco only were 19 with 13 (68.5%) males and 6 (31.5%) females. 29 patients were addicted to both tobacco and alcohol with all of them being males. It is understandable that since alcohol and tobacco consumption were assessed based on self-reporting there is a high likelihood of under-reporting. It was seen that median BMI was 15.89 (IQR 14.09-17.9) and 80.4% of the patients were found to be underweight.

Most common symptom among the patients were nausea (74.5%) followed by vomiting (72.5%) and abdominal pain was present in (40.2%) patients. When looked for signs, abdominal tenderness on palpation was present in 37 (36.2%) patients and clinically demonstrable icterus was present in 29 (28.4%) patients.

27 patients (26.47%) had sputum smear for AFB status negative while 24 (23.5%) had sputum status scanty positive. 21 (20.5%) patients had sputum smear 1+ grading, while 19 (18.6%) had 2+ grading, 11 (10.7%) had sputum smear 3+ grading.

46 (45%) patients had involvement of more than 4 zones and 34 (33.3%) patients had less than 2 zone involvement, 7 (6.86%) patients had involvement of 2-4 zones. When compared with involvement of site, 53 (62%) had bilateral involvement in chest X-Ray whereas 35 (40%) had unilateral involvement of in chest X-ray.

In the present study the mean ± standard deviation of haemoglobin in patients at the time of admission was 10.36 ± 0.19 gm%. 38 (37.25%) had haemoglobin level less than 10 gm%, while 64 (62.74%) had haemoglobin levels more than 10 gm% and considered as anemic at the time of presentation.

The mean ± standard deviation of Fasting Blood Sugar (FBS) in the present study was 135.6 ± 5.92 mg%. 49 (48%) were diabetics with FBS of more than 126 mg%, while 38 (37.2%) had FBS less than 116 mg%. This data shows that 34 (33.4%) of the patients are newly diagnosed cases of tuberculosis presented with DIH.

The mean ± standard deviation of serum proteins was 7.9 ± 1.62 gm%. 73 (71.5%) of the patients had serum proteins less than 7 gm% while 29 (28.4%) patients had serum protein >7gm%. The mean ± standard deviation of serum albumin was 2.98 ± 0.070 gm%. 87 (85.3%) of patients had serum albumin

levels less than 3.5 gm% while 15 (14.7%) patients had serum albumin levels >3.5 gm%.

Table 1: Elevation of serum glutamate pyruvate transaminase (SGPT), Serum glutamic oxaloacetate transaminase (SGOT) and serum bilirubin level with Number of patients (%) in each groups.

Serum level Grading	Serum SGOT level (5-40IU) normal serum level		Serum SGPT level (IU/L) (7-55 IU) normal serum level		Serum bilirubin level in mg% normal serum level	
	No. of patients	Percentage (%)	No. of patients	Percentage (%)	No. of patients	Percentage (%)
< 3 times normal (IU/L)	12	(11.76%)	57	(55.88%)	36	(35.29%)
3 -5 times normal (IU/L)	37	(36.27%)	24	(55.88%)	16	(15.68%)
>5 times normal (IU/L)	53	(51.96%)	21	(20.5%)	11	(10.78%)

Discussion

Age- In our finding the mean (±) standard deviation age of patients came out to be 40.05 ± 19.5 years. Similar to our findings as per Jeong et al [8] investigation ATT induced hepatitis in 190 patients the mean age came out to be 43.9±17.7 years. In another Indian study carried out by Singla et al [9] to look into risk factors for DIH in tuberculosis patients, the mean age of the patients was 40.76±18.02 years.

Gender- In our study, (60.7%) were males while the rest (39.3%) were females. Out of these 62 males (51.61%) belonged to the age group 15-45 years while out of 40 females, (57.5%) belonged to the same age group. As per Singla et al [10] finding, males (54.21%) formed majority of the study population. In the study Agal et al [11] 58% of the study population were males. However several studies have shown preponderance of the female sex for development of DIH [12,13]. The lower percentage of female patients in our study may be due to the fact they occupy a lower socioeconomic status in our society and hence very often do not present to the doctor with their symptoms.

Addiction

In our study (34.31%) patients were addicted to alcohol while (47.05%) patients were addicted to tobacco while 29 patients were addicted to both alcohol and tobacco. Out of the 29 patients addicted to both alcohol and tobacco all 29 were males while only 6 of the female population had smoking as an addiction. Smoking is a known risk factor for DIH due to its resultant oxidative stress on the body was found in the study by Delgado et al [14] and Larrey et al [15] alcohol consumption came out to be significantly associated with DIH. Alcohol predisposes the patient to DIH by producing hepato steatosis and free radical injury to the hepatocytes.

Signs and symptoms of DIH

In our study, the most common symptom was nausea as seen in (74.5%) patients followed by vomiting seen in (72.5%) patients. Abdominal pain was seen in (40.195) patients while icterus was seen in (28.43%) patients. In the study by Agal et al [11] it was found that nausea was found in 100% patients while vomiting was seen in 91.6% patients. Icterus was seen in 71.5% patients. In the study by Singla et al [10] nausea was seen in 90.6% while vomiting was seen in 65.7% while pain abdomen was seen in 28% cases and icterus was seen in 34% cases.

Sputum status

In our study, (73.53%) of the patients were sputum positive, while the rest (26.47%) were sputum negative. In the large retrospective UK based study by Abbara et al [16], sputum positive patients constituted 28% of the total patients who developed DIH.

Chest X-Ray

In our study, 68 patients had chest X-ray involvement encompassing more than 2 radiographic zones of the lung. 53 patients had bilateral involvement of the lung, 68 patients had cavities in their chest X-ray. In the study by Singla et al [17] it was found that 82% of the case group with DIH had moderate to far advanced lesions in their chest X-ray in comparison to 52% of the patients who did not develop DIH. The patients with moderate to far advanced lesions in their chest X-rays were found to be a higher risk of DIH.

Serum Biochemistry

Serum protein and serum albumin

The mean (±) standard deviation of serum proteins in population was 7.9±1.62 gm%, 73 patients had decrease levels of serum protein (<7gm%), 87 patients had serum albumin less than 3.5 gm% while the rest 15 had serum albumin level more than 3.5gm%. In the study by Singla et al [10], the mean (±) standard deviation of serum albumin was 3.5 and 0.68 gm% respectively. Serum albumin was also established as an independent risk factor for DIH in patients on ATT Odds ratio-2.80 (1.82-4.30). In the study by Kumar et al [18], serum albumin was also found to affect outcome variables in tuberculosis patients with DIH. It was found that patients with low serum albumin were associated with a poor outcome and longer duration for remission of DIH.

Serum bilirubin

The mean (±) standard deviation of serum bilirubin levels in our study group was 2.49±0.209 mg%, 11 patients had serum bilirubin more than 5 times ULN, 16 patients had serum bilirubin between 3-5 times ULN, 36 patients had serum bilirubin less than 3 times normal ULN while 39 patients had bilirubin value in normal range less than 1.5 mg%. In the study by Shang et al [19], 33% of patients had serum bilirubin levels between 3-5 times ULN while 66% patients had serum bilirubin less than 3 times ULN.

Serum transaminases

The mean (±) standard deviation of serum SGOT levels in our study group was 249±16.08 IU/l. Majority (51.96%) patients had serum SGOT levels more than 5 times the ULN. (36.27%) of our patients had serum SGOT levels between 3-5 times the ULN, while (11.76%) patients had serum SGOT levels less than 3 times ULN. In the study by Makhlouf et al [20], 53% of patients had serum SGOT levels less than 3 times ULN, 40% patients had serum SGOT levels between 3-5 times ULN, 7 % patients had serum SGOT levels more than 5 times ULN. We believe this can be a predisposing factor in our patients to a greater hepatotoxicity resulting in higher transaminases levels in blood. A progres-

sive increase in transaminases of more than 5 times the ULN seen and this might be a warning that hepatic necrosis leading to hepatic failure might develop subsequently [21]. Therefore, frequent monitoring of transaminases in such patients might be necessary to detect early ATT-hepatotoxicity.

Conclusion

DIH is an extremely common occurrence during ATT treatment and a major cause of morbidity and mortality. We saw that majority of our patients developed this within one week of initiation of ATT. They all had the tell tale signs of malnutrition like low BMI, hypoalbuminaemia, anemia and had diabetes as a major extensive radiological lesions. These all are established risk factors for DIH. Hence patients having any of these risk factors should alert us about the possibility of development of DIH. We should be vigilant and can do routine LFT especially during the IP phase. This will allow us to catch the process in its incipient phase. Let us manage it more efficiently, decrease morbidity and length of hospital stay.

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