Journal of Neuroinfectious Diseases

Misra UK, et al., J Neuroinfect Dis 2014, 5:2
http://dx.doi.org/10.4172/ 2314-7326.1000146

Research Article Open Access

Predictors of Drug Induced Hepatotoxicity in Tuberculous Meningitis

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Received date: January 1, 2014; **Accepted date:** March 25, 2014; **Published date:** April 2, 2014

Abstract

Background: There is paucity of studies on Drug Induced Hepatitis (DIH) following Anti-Tubercular Therapy (ATT) in the patients with Tuberculosis Meningitis (TBM). In this study, the frequency, spectrum and predictors of DIH in TBM have been reported.

Methods: 150 TBM patients without history of prior liver disease were prospectively included. The clinical details, laboratory findings and MRI changes were noted. Presence of seizure, antiepileptic drugs and CSF opening pressure were noted. The diagnosis of DIH was based on 3-5 fold rise in transaminase at least after 3 days of ATT whose baseline liver function was normal without apparent cause of liver dysfunction and >50% improvement in liver function on discontinuation of ATT. The predictors of DIH and its influence on death and outcome at 3, 6 and 9 months were assessed.

Results: The median age of the patients was 28.5years. 65 (43.3%) patients developed DIH after a median duration of 22 (3–210) days. After discontinuation of hepatotoxic ATT, the liver function normalized within a median of 13(3-90) days. DIH resulted in repeated interruption of treatment in 18 patients. DIH was related to seizures, raised intracranial pressure, enzyme inducing antiepileptic drugs, and low serum albumin. On multivariate analysis, serum albumin (OR 1.4 95% CI 1.30-13.26, P=0.02) and seizure (OR 1.65 95%CI 1.54-17.53, P=0.01) were independently associated with DIH. Death and functional outcome at 9months were not related to DIH.

Conclusion: DIH occurs in 43.3% patients with TBM and is related to hypoalbuminemia and seizure. Attention should be paid to manage under-nutrition and avoid enzyme inducing antiepileptic drugs.

Keywords: Tuberculosis meningitis; Drug induced hepatitis; Rifampicin; Isoniazid; Pyrazinamide; Hypo albuminemia; Seizure; Antiepileptic

Introduction

Tuberculosis is a global emergency. About 20% world's burden of tuberculosis is in India [1]. Despite the efficacy of first line anti tubercular drugs, hepatotoxicity of RHZ (rifampicin, isoniazid, pyrazinamide) is common, leading to interruption of treatment [2]. A meta-analysis evaluating toxic hepatitis of isoniazid and rifampicin revealed hepatotoxicity of isoniazid alone in 0.6%, multidrug isoniazid regimen without rifampicin in 1.6%, rifampicin regimen without isoniazid in 1.1% and regimen containing rifampicin and isoniazid both in 2.73%. In children, the regimen containing isoniazid and rifampicin both resulted in hepatotoxicity in 6.9% [3]. The exact mechanism of DIH is not known but is attributed to old age, alcohol, malnutrition, pre-existing liver disease, HIV, slow acetylation, concomitant medications and genetic factors [4-9]. DIH following Anti-Tubercular Treatment (ATT) is commoner in the developing countries; the reported incidence of DIH is 3% in USA, 4% in UK, 11% in Germany, 9.9% in Argentina, 13% in Hong Kong, 36% in Japan, 26% in Taiwan and 8%-36% in India [10,11]. The higher incidence of DIH in the Asian countries might be due to ethnic susceptibility, inherent peculiarity of drug metabolism and/or the presence of various known risk factors like viral hepatitis or under-nutrition. Most of the studies on anti-tubercular DIH are on the patients with pulmonary tuberculosis. It has been suggested that the patients with disseminated tuberculosis and serious illness have a higher frequency of DIH. We have observed a high frequency of DIH in patients with Central Nervous System (CNS) tuberculosis. There are only few studies on DIH in CNS tuberculosis [12]. This study therefore has been undertaken to evaluate the frequency, pattern, predictors and outcome of DIH in patients with TBM.

Materials and Methods

This prospective study was conducted in a tertiary care referral teaching hospital in India. The consecutive patients with TBM during August 2010 to December 2011 were included. The study protocol was approved by the Institute Ethics Committee and patients or first degree relatives gave the consent.

Diagnosis

The diagnosis of TBM was based on clinical, radiological and Cerebrospinal Fluid (CSF) criteria. The essential criteria was presence of meningitic symptoms comprising of fever, headache and vomiting for 2 weeks or more in whom malaria, septic and fungal meningitis were excluded. The supportive criteria included:

1) CSF cells 0.2×10^9/L or more with predominant lymphocyte, protein >1 g/L, sterile bacterial (other than acid fast bacilli) and fungal culture and negative cryptococcal antigen.

2) CT or MRI evidence of infarction, exudates, tuberculoma or hydrocephalus.

3) Evidence of extra CNS tuberculosis.

Presence of the essential criteria and any of the supportive criteria was considered TBM.

Presence of AFB in CSF or culture (BACTEC) and positive AFB PCR or IgM antibodies in CSF were considered definite TBM

Treatment protocol

Total treatment period was 18 months including intensive (4 drugs) and continuation phases (2 drugs) of 9 months each. The intensive phase comprised of isoniazid (5 mg/kg/day; maximum 300 mg/day), ethambutol (15–20 mg/kg/day, maximum of 800 mg/day), pyrazinamide (20–25 mg/kg/day with maximum of 1500 mg/day), and either rifampicin (10 mg/kg/day; maximum 450 mg/day) or levofloxacin (10 mg/kg/day with maximum of 500 mg). We conducted a randomized controlled trial to evaluate the efficacy and safety of levofloxacin and rifampicin in the patients with TBM. The continuation phase comprised daily similar doses of INH and ethambutol. The patients also received prednisolone 0.8 mg/kg with a maximum of 40 mg for 1 month then tapered within 3weeks.

Diagnosis of drug induced hepatitis

The following criteria were used for the diagnosis of DIH.

1. Normal Liver Function Test (LFT) prior to starting the anti-tubercular drugs.

2. No use of alcohol or other substance abuse for at least 10 days prior to starting ATT.

3. Patients receiving isoniazid, rifampicin or pyrazinamide in standard doses, alone or in combination for at least 3 days prior to the development of abnormal LFT.

4. While receiving ATT, there should be 5 times increase in ALT without symptoms or 3 times of normal (normal=40 IU/L) with symptoms and/or an increase in total bilirubin to >1.5 mg/dl (normal up to 1 mg/dl).

5. No other apparent cause for the elevation of LFT.

6. Removal of the medications should result in normalization or at least 50% improvement of the abnormal LFT3.

Evaluation

A detailed history including liver disease, alcoholism and malnutrition were enquired. Severity of meningitis was graded into stage I- meningitis only, stage II meningitis with focal neurologic signs Glasgow Coma Scale (GCS) score 11-14 and stage III- meningitis with altered sensorium (GCS score <11). The investigations included hemoglobin, LFT (serum ALT, bilirubin, albumin and alkaline phosphatase), serum creatinine, fasting and postprandial blood sugar, HIV serology, radiograph of chest, and abdominal ultrasonography. Hepatitis markers included IgM antibody against hepatitis A, C and E virus and HBsAg. Cranial CT scan and/or MRI were done in all. The patients with DIH received ethambutol and streptomycin till the LFT improved (serum bilirubin <1.5 mg/dl and ALT < 80 U/L). The patients on levofloxacin arm continued to receive it. The drugs were sequentially reintroduced starting with isoniazid followed by pyrazinamide and rifampicin. The pyrazinamide was introduced before rifampicin because of better CSF penetration. The LFT was repeated every 4th day for 2 weeks and then weekly for a month.

Exclusion

The patients with Hepatitis A, B, C, E and those having abdominal ultrasonographic evidence of chronic liver disease (CLD) or gall bladder disease were excluded.

Outcome

The patients were followed up at 3, 6 and 9 months. Death during this period was noted and the functional outcome was assessed using Barthel Index (BI) score. The functional outcome was categorized as poor (<12), partial (12-19) and complete (=20) [13].

Statistical analysis

The patients were categorized into those with DIH and those without. The demographic, clinical and laboratory parameters in the patients with and without DIH were compared using parametric and nonparametric tests. The variables having a p value of <0.1 on univariate analysis were included in the multivariate logistic regression analysis with Bonferroni correction. The role of DIH on the outcome and the contribution of AED to DIH were evaluated by Chi square/ Fisher exact test. The variables were considered significant if the two tailed p value was <0.05. All the statistical analysis was carried out using SPSS 16 version software.

Results

There were 165 patients with TBM of whom 15 were excluded; 10 due to preexisting liver disease (hepatitis B in 1, nonalcoholic steatohepatitis in 1, septicemia in 4, HIV in 1, cryptogenic CLD in 1 and unidentified cause in 2) and 5 due to coexistent liver disease while on ATT (hepatitis A in 1, hepatitis E in 2, hepatitis C in 1 and cryptogenic cirrhosis in 1). The results of the present study therefore are therefore based on 150 patients.

Demographic and clinical details

The patients' age ranged between 3 and 90 (median 28.5) years. Eight (5.3%) patients were below 13 years of age. Seventy-two (48%) were females and 98 (65.3%) belonged to the rural areas. Eight (5.33%) patients smoked and 13 (8.7%) took alcohol occasionally and none consumed alcohol 10 days prior to the illness. The majority (106, 70.7%) of the patients had severe meningitis; stage III in 34 (22.7%) and stage II in 72 (48%).

Spectrum of DIH

Out of 150 patients, 65 (43.3%) developed DIH after a median duration of 22 (3–210) days; isolated raised ALT in 17 and bilirubin in 3 patients, both ALT and bilirubin in 21. The liver dysfunction appeared in the first week of ATT in 11, second week in 14 and after the 2nd week in 38 patients (Figure 1).

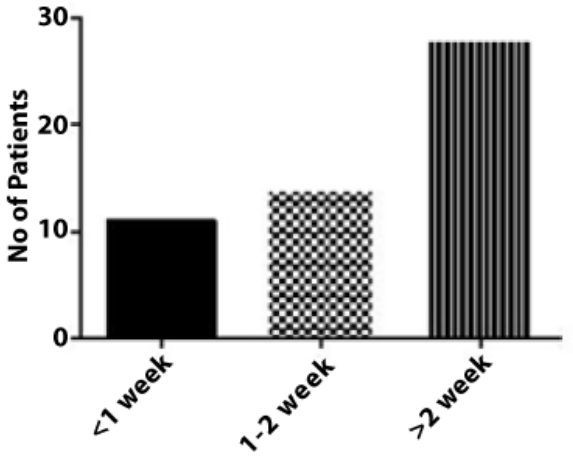

Figure 1: No.of Patients vs weeks.

Hundred patients were on rifampicin and 50 on levofloxacin in addition to isoniazid, pyrazinamide and ethambutol. DIH was insignificantly more frequent in rifampicin group (46%) compared to levofloxacin (38%) (P=0.35). On discontinuing the hepatotoxic drugs, the liver functions improved in the first week in 19, second week in 8 and after the second week in 27 patients (median 13, range 3–90 days). In 7 patients, in spite of withdrawal of RHZ the liver function did not improve and all these patients died. DIH resulted in repeated interruption in treatment in 18 patients; twice in 10, thrice in 5, 4 times in 2 and 5 times in one. Comparison of early (less than 2 weeks) and late (2 weeks or more) reversibility of DIH did not reveal significant difference in age, duration of illness, stage of TBM, serum albumin, hemoglobin, alcohol intake and vegetarianism (Table 1).

Predictors of DIH

On comparing the demographic and clinical variables in the patients with and without DIH, no significant difference was found with respect to age (31.6+17.1 versus 34.7+18.7 P=0.30), gender (female- 27 versus 45; P=0.17), alcohol consumption (6 versus 7; P=0.85), vegetarianism (18 versus 20; P=0.58) and stage of TBM (P=0.16). Out of 34 patients with stage III meningitis 19 had hepatotoxicity and 15 did not. GCS score was also not significantly related to hepatotoxicity (11.98+3.16 versus 12.89+2.48; P=0.10) (Table 2).

Parameter	Early reversibility	Late reversibility	P value
Age in years	29.04+14.85	33.03+17.88	.341
Alcoholic	3	2	.639
Severity			
Stage 1	3	8	.221
Stage 2	15	13	
Stage 3	9	6	
Duration of illness (days)	94.74+102.5	65.96+59.6	.219
Hemoglobin gm/dl	11.74+1.68	11.4+2.24	.521
S. albumin gm/dl	3.42+0.62	3.40+0.46	.914
Peak bilirubin mg/dl	1.85+1.15	2.66+2.46	.127
Peak ALT IU/L	214.4+143	315.4+232.7	.060

Table 1: The relationship of early (<2 weeks) and late (≥ 2 weeks) reversibility of drug induced hepatitis (DIH) with various clinical and biochemical parameters.

Parameter	Total	Hepatotoxicity present N=65	No hepatotoxicity N=85	P value
Mean age (Yrs)	150	31.6+17.1	34.7 ± 18.7	0.30
Female	72	27	45	0.17
Alcohol intake	13	6	7	0.85
Smoking	8	4	4	0.70
Vegetarian diet	38	18	20	0.58
Stage				
Stage I	44	15	29	0.16
Stage II	72	31	41	
Stage III	34	19	15	
CSF pressure mmH2O	52	247.4+135.6	174.6+93	0.03
GCS score	150	11.98+3.16	12.89 ± 2.48	0.10

Extra CNS TB	40	14	26	0.21
Duration (days)	146	77.9+82.8	74.4 ± 84.3	0.80
Diabetes	14	5	9	0.55
Hemoglobin gm/dl	150	11.4+2	11.5 ± 1.5	0.57
S. Protein gm/dl	148	6.4+0.80	6.7 ± 0.98	0.02
S. Albumin gm/dl	150	3.3 ± 0.67	3.7 ± 0.61	0.002
S. calcium (total) mg/dl	146	8.67 ± 1.03	8.61 ± 0.69	0.72
S. calcium (ionic) mg/dl	143	4.54 ± 0.54	4.50 ± 0.52	0.66
Seizure	64	36	28	0.006
Hepatotoxicity after AED				
Enzyme inducers	30	21	9	0.006
Non enzyme inducers	22	7	15	
Treatment Protocol				
HRZE	100	46	54	0.35
HLZE	50	19	31	
MRI findings				
Tuberculoma	86	39	47	0.66
Exudate	69	35	34	0.11
Hydrocephalus	63	30	33	0.36
Infarct	65	31	34	0.40

Table 2: Predictors of drug induced hepatitis (DIH) in patients with tuberculous meningitis; GCS=Glasgow Coma Scale, CNS=Central Nervous System, CSF=Cerebrospinal Fluid, AED=Antiepileptic Drugs, HRZE=Isoniazide, Rifampicin, Pyrazinamide, Ethambutol, HLZE=Isoniazid, Levofloxacin, Pyrazinamide, Ethambutol.

However, seizures were commoner in the DIH group compared to those without DIH (36 versus 28; P=0.006). Among the 64 patients with seizures, 8 patients did not receive AED because of drug induced seizure or a single episode of seizure. Of the 56 patients who received AED, 4 patients had liver dysfunction before AED was started. Among the remaining 52 patients, 30 patients received enzyme inducing antiepileptic drugs (carbamazepine and phenytoin) and 22 patients received non enzyme inducing antiepileptic drugs (levetiracetam, pregabalin, sodium valproate and clobazam). Patients who received enzyme inducing antiepileptic drugs were more frequently associated with DIH (21 versus 9) compared to those who received non enzyme inducing antiepileptic drugs (7 versus 15; P=0.006). In the DIH group, serum albumin (3.33+0.67 gm/dl) and serum protein (6.38+0.80 gm/dl) were significantly lower than the non DIH group; 3.66+0.61 gm/dl (P=0.002) and 6.72+0.98 gm/dl (P=0.02), respectively. Hypoalbuminemia was present in 59 patients and 35 of them had hepatotoxicity; whereas out of 91 patients with normal serum albumin only 3 patients had hepatotoxicity (P=0.002). The MRI findings such as exudates, hydrocephalous, tuberculoma and infarctions were not related to DIH. The CSF opening pressure was higher in DIH group compared to those without (247.4+135.6 versus 174.6+93 mm of H_2O; P=0.03). On multivariate analysis, serum albumin (OR1.4, 95%CI 1.30-13.26, P=0.02) and seizures (OR 1.65, 95% CI 1.54-17.53, P=0.01) were significantly related to DIH after adjustment of the other variables. The relative risk of hepatotoxicity in the presence of seizure was 1.6 (95% CI 1.18-2.44; P<0.01) and that of hypoalbuminemia 1.8 (95%CI 1.25-2.58; P<0.01). Death and disability at 3, 6 and 9 months were not related to DIH. 15/63 (23.8%) patients in the hepatitis group died, whereas 25/80 (31.2%) patients in the non hepatitis group died (P=0.32). At 3 months, 12 patients had poor, 14 partial and 22 complete recovery in the DIH group whereas these were 8, 11 and 33, respectively in the non DIH group (P=0.20). The BI score at 3 months in the DIH group was however significantly lower (14.2+7.2) compared to the non DIH group (17+5.6; P=0.04). At 6 months, 7 had poor, 11 partial and 23 had complete recovery in the DIH group whereas these were 4, 8, and 29 in the non DIH group respectively (P=0.37). The BI score was significantly worse in DIH (15.9+6.1) compared to non DIH group (18.3+3.7; P=0.03). At 9 months, 5 had poor, 9 partial and 22 had complete recovery in the DIH group whereas these were 1, 7, and 24 in the non DIH group, respectively (P=0.25). The BI score was not significantly different in DIH (16.8+5.8) group compared to non DIH group (18.6+3; P=0.11) (Figure 2).

Discussion

In the present study, 43% of TBM patients had ATT associated hepatotoxicity and was related to hypoalbuminemia and seizure. The

frequency of DIH in the present study is higher than the reported literature. The incidence of clinical hepatitis following ATT has been reported in 8%-19.8% from Asia [10,11,14,15]. Meta-analysis of 14 studies from the western countries however reported low incidence of DIH (4.3%) following ATT [3]. The majority of these studies however included patients with pulmonary tuberculosis. The higher incidence of DIH in the Asian countries compared to the Western may be due to the prevalence of infections, infestations and under-nutrition and may have a genetic basis. The patients with extra-pulmonary tuberculosis have greater risk of DIH which has been attributed to subclinical hepatic involvement [16]. The present study included patients with tuberculosis meningitis, and 40 of whom had extra CNS involvement. The majority of them had severe meningitis; 26.7% of them had associated extra CNS tuberculosis suggesting heavy disease burden. The relationship of disease burden and DIH has been reported in pulmonary tuberculosis [17]. In our study, malnutrition, seizure and enzyme inducing antiepileptic drugs were significantly related to DIH. Malnutrition is a commonly reported risk factor for DIH [18-21]. We were not able to evaluate the body mass index because the patients with stage II and stage III meningitis had focal deficit and altered sensorium as we did not have special weighing facility. Low serum albumin was therefore taken as a surrogate marker of malnutrition. The association of low serum albumin with DIH has also been reported in pulmonary tuberculosis [22]. In malnourished state, glutathione depletion renders the patient vulnerable to oxidative liver injury and slows hepatic metabolism of drugs [4]. Drug metabolism including acetylation pathways have been reported to derange in protein energy malnutrition [23]. The patients with DIH in our study had higher frequency of seizures and those on enzyme inducing antiepileptic drugs developed significantly higher incidence of DIH compared to nonenzyme inducing antiepileptic drugs. In our study, 21 out of 30 patients developed hepatotoxicity after starting enzyme inducing antiepileptic drugs. In these patients, enzyme inducing antiepileptic drugs contributed to hepatotoxicity in association with ATT. This was in sharp contrast to nonenzyme inducing antiepileptic drugs in which only 7 out of 22 patients developed heptotoxicity.

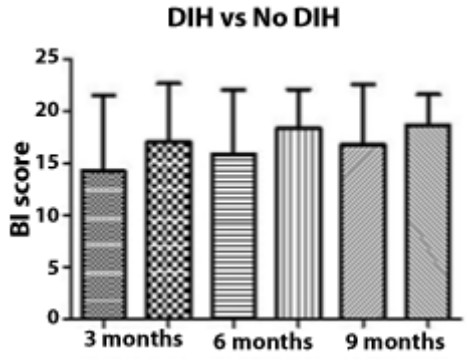

Figure 2: DIH vs No DIH.

The incidence of hepatitis in our study correlated with raised intracranial pressure. The higher incidence of hepatitis in our study may be because of stress response secondary to severe disease with raised intracranial pressure. Raised intracranial pressure induces stress and results in hepatic blood flow changes [24]. It also effects hypothalamopituitary adrenal axis and sympathetic over activity in liver inflammation [25]. Studies have also documented increased incidence of liver dysfunction in stroke [26]. Cholestasis is associated with deep coma. In our study also DIH has a borderline significance with low GCS score. Age has been reported as an important determinant of DIH. Hepatotoxicity was present in 22%-33% patients older than 35 years whereas it was present in 8%-17% only below 35 years of age [18]. In our study, the age of the patients ranged between 3 and 90 years; only 34.7% patients were above the age of 35 years. The lack of relationship of age and DIH may be due to higher number of younger patients. Our results are in agreement with Shakya et al. [20] in which higher frequency of DIH was found in the younger patients. The role of gender in DIH is controversial [22,27,28]. Coexisting liver disease and alcohol consumption have been reported to be associated with DIH but were not found in our study. We have excluded preexisting hepatitis and other co-morbidities such as nonalcoholic steatohepatitis and CLD. The liver dysfunction improves after a few days (median 15 days) of withdrawal of ATT [4]. In our study, the liver functions normalized by a median of 13 days. On comparing the demographic and clinical features in the patients whose liver functions normalized within 2 weeks with those who took longer time, there was no difference. DIH was not associated with higher mortality but was associated with poor outcome at 3 and 6 months which may be attributed to interruption of hepatotoxic ATT. In our earlier study also DIH was a poor predictor of 6 month outcome [29]. DIH however was not associated with poor outcome at 9 months. This indicates that once the patient recovers from DIH, it does not adversely influence the long term outcome. The predictors of mortality in TBM are severity of meningitis, focal deficit, brain herniation, seizures, stroke and secondary infections. DIH may not be a direct cause of mortality except in rare cases of fulminant hepatic failure [30]. Delay in starting treatment and time needed for DIH to manifest (13 days after starting ATT) may be responsible for lack of statistical significance of DIH with morality. We were able to restore ATT fully in 60% and partially in 40% patients. After DIH, we introduced isoniazid first, pyrazinamide next and finally rifampicin. This was in contrast to the recommendation of American Thoracic Society which recommends isoniazid, rifampicin and pyrazinamide in that order [31]. We preferred pyrazinamide over rifampicin because of its 100% CSF penetration and bactericidal effect [32]. The limitation of our study is unconventional choice of ATT regimen. World Health Organization recommends 2 months RHZE followed by 4months HR for extra pulmonary tuberculosis including TBM [33] some experts recommend longer treatment for TBM [34-36]. We have used levofloxacin as an alternative to rifampicin in about one-third patients. There are studies showing better CSF penetration of fluroquinolones compared to rifampicin in the patients with tuberculosis [37-40]. Fluroquinolone does not have hepatotoxicity. In our study DIH was insignificantly lower in the patients with levofloxacin (38%) compared to those with rifampicin (46%). To evaluate the safety and efficacy of levofloxacin in TBM however needs a separate study. It can be concluded that DIH is commoner in TBM than other forms of tuberculosis, and is related to low serum albumin and seizures. Nonenzyme inducer may be preferred antiepileptic drugs in TBM.

Acknowledgement

We acknowledge Rakesh Kumar Nigam and Deepak Kumar Anand for secretarial help.

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