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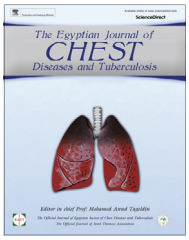

ORIGINAL ARTICLE

Prevalence of hepatitis C virus in patients with tuberculosis and its impact in the incidence of anti-tuberculosis drugs induced hepatotoxicity

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KEYWORDS

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Abstract *Background:* The prevalence of hepatitis C virus (HCV) infection among patients with tuberculosis (TB) has not been extensively investigated, and very limited data on rates of HCV co-infection among patients with TB exists. Hepatotoxicity is the major adverse effect of three of the first line anti-TB agents: isoniazid (INH), rifampin (RIF), and pyrazinamide (PZA). Chronic liver disease raises a risk of hepatotoxicity during anti-tuberculosis treatment, up to three to five times more than TB patients who do not have viral infection.

Aim: To assess the prevalence of HCV infection in patients with tuberculosis and its impact in the incidence of anti-tuberculosis drug induced hepatotoxicity (DIH).

Subjects and methods: The prevalence of HCV in patients with newly diagnosed pulmonary or extrapulmonary tuberculosis was estimated using polymerase chain reaction (PCR). Then patients were classified into 2 groups: group I (patients with HCV-TB coinfections) and group II (HCV-seronegative tuberculous patients). Baseline and monthly measuring liver transaminases was done before and following the start of 1st line anti-tuberculosis therapy.

Results: The prevalence of HCV in patients with TB was 17.02%. Regarding DIH, in group I; 6 (40%) cases showed transient transaminase elevations and 6 (40%) cases developed DIH. In group II; 11 (20.75%) cases developed transient transaminase elevations and only 2 (3.78%) cases developed DIH, and there was a highly significant difference (<0.01) between both groups. Regarding the severity of DIH, in group I; 4 cases were mild, one case was moderate and one case was severe. While in group II, no cases was with severe DIH. The risk factors for developing DIH during anti-tuberculosis therapy were; age $\geqslant 40$, high baselines transaminases, ALP and total bilirubin,

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and low BMI. Most cases of DIH occurred during the 1st 4 weeks of starting anti-tuberculosis therapy (66.7% and 50% in group I and group II, respectively).

Conclusions: Tuberculosis and hepatitis C virus co-infection is common, and elevation of liver functions during anti-tuberculosis therapy is not uncommon. HCV-positive patients with tuberculosis should be closely monitored during treatment especially if they had elevated baseline liver functions, old age and with low BMI. Monitoring should include the whole period of treatment, especially the 1st 2 months.

Introduction

Tuberculosis remains a leading health problem in both developing and developed countries [1]. The World Health Organization (WHO) estimates that there were 8.6 million new cases of TB globally in 2012 and 1.3 million deaths [2]. Hepatitis C virus is a well-known agent of liver diseases, including chronic hepatitis, cirrhosis and hepatocellular carcinoma [3,4]. Hepatitis C virus has a positive sense single-stranded RNA genome that presents a high degree of genetic heterogeneity. HCV strains are classified into six genotypes (1–6), each comprising multiple subtypes (designated a, b, c, etc.) [5,6]. A seventh genotype (subtype 7a) was recently discovered [7]. Hepatitis C virus infection is a global public health problem. Hepatitis C virus affects over 200 million people, with an estimated HCV prevalence of 2.2% globally. It has been estimated that HCV accounts for 27% of cirrhosis and 25% of hepatocellular carcinoma cases worldwide. Global and region-specific estimates of HCV prevalence vary greatly, but the highest prevalence (15–20%) has been reported from Egypt [8–9]. HCV is characterized by a high degree of genetic heterogeneity [10]. Globally, the prevalence of HCV infection among patients with TB has not been extensively investigated, and very limited data on rates of HCV co-infection among patients with TB exists [11]. Hepatotoxicity is the major adverse effect of three of the first line anti-TB agents: isoniazid, rifampin, and pyrazinamide [12]. Chronic liver disease raises a risk of hepatotoxicity during anti-tuberculosis treatment, up to three to five times more than TB patients who do not have viral infection [13]. Similarly, fourteen fold increase in the risk of anti-TB hepatotoxicity has been reported in HIV and HCV co-infected patients [14]. Patients with increased susceptibility to the hepatotoxic effects of first-line treatment regimens represent special populations and need to be identified prior to therapy initiation and monitored more carefully. Although three of the first-line drugs, rifampin, pyrazinamide, and isoniazid are known to be hepatotoxic [15–20], the patient characteristics that confer greater risk of treatment-associated liver injury are poorly understood. Older age, concurrent or chronic alcohol use, hepatitis C, hepatitis B, and HIV virus infection have been found to increase the risk of DIH [21–23]. Until definitive studies are conducted, caution suggests that patient populations should be screened for the above-mentioned characteristics and monitored carefully following the initiation of therapy [24].

Aim of the work

The aim of this work was to assess the prevalence of HCV infection in patients with TB and its impact on the incidence of anti-tuberculosis therapy induced hepatotoxicity.

Subjects and methods

This study included 94 patients with newly diagnosed pulmonary or extrapulmonary TB admitted to Chest Department, Menoufiya University Hospitals, from February 2013 to February 2014. At the baseline visit 10 ml of blood was drawn to test for HCV antibodies, HBV antibodies and liver enzymes; ALT, AST, alkaline phosphatase (ALP), total bilirubin and albumin (ALB). In cases with HCV antibodies seropositive, they were sent for doing PCR. The prevalence of HCV in patients with TB was estimated. The following patients were excluded: patients with abnormal baseline aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels $\geqslant 120$ IU/L; with underlying malignancy; patients with chronic liver disease; patients started anti-tuberculosis therapy; and patients who were unavailable for 6 months follow up. Included patients started anti-tuberculosis treatment that included an intensive phase of four drugs isoniazid, rifampicin, pyrazinamide, and ethambutol for two months, followed by a continuation phase of RIF and INH for four months using WHO dosing recommendations [25]. Monthly follow-up visit included measuring ALT, and AST levels were done. Patients were encouraged to return at any time if new symptoms arose during therapy. DIH was defined when liver transaminase levels were >120 IU/L. If the AST/ALT levels were <200 IU/L, the DIH was defined as mild. AST/ALT levels of 200–500 IU/L indicated moderate hepatotoxicity, and AST/ALT levels $\geqslant 500$ IU/L were considered to indicate severe hepatotoxicity [26].

Transient transaminase elevation was diagnosed if AST/ALT levels were increased but were still less than three times the upper normal limit (120 IU/L) and resolved spontaneously despite continued anti-TB medications [27]. Patients exhibiting mild increases in liver transaminase levels, but without clinical symptoms, were carefully observed with no changes in treatment. In the case of a patient who exhibited symptoms suggesting DIH, who also showed markedly increased liver transaminase levels ($\geqslant 3$ times their normal values), all hepatotoxic drugs were stopped. These drugs were then replaced with non-hepatotoxic drugs, such as ethambutol, quinolones, and aminoglycosides. After liver transaminase normalization, the hepatotoxic drugs were reintroduced. RIF therapy was reintroduced first, at progressively increasing dosages, and then INH therapy was restarted. The targeted treatment regimen usually included INH, RIF, and ethambutol, without pyrazinamide. If symptoms recurred or liver transaminase levels increased during the reintroduction of therapy with hepatotoxic drugs, the offending drug was withdrawn, and non-hepatotoxic drug therapy was maintained [28].

Anti-HCV antibody assay: the test was done using the Architect anti HCV kit (Abbott, Germany). Principle: The test

was done using a two steps immunoassay based on the chemiluminescent assay. In the first step; sample, recombinant HCV antigen coated paramagnetic microparticles and assay diluent were combined. Anti-HCV antibodies (if present) bound to the antigen coating the microparticles. Second step included a washing step followed by addition of anti-human acridinium-labeled conjugate. After another washing step, pre-trigger and trigger solutions were added. The resulting chemi-luminescent reaction was measured by the Architect i* system optics as relative light units which was proportional to the amount of anti-HCV Ab in the sample. PCR: HCV RNA detection: Real time quantitative reverse transcriptase PCR: RNA was extracted using Promega RNA extraction kit (Abbott).

Then real time quantitation of HCV RNA PCR was done using Abbott m 2000rt instrument system, Abbott Molocula Inc., Des. Plaines 1L60018, Singapore.

Statistical methodology [29]

Data collected were tabulated and analyzed by SPSS (statistical package for the social science software) statistical package version 11 on an IBM compatible computer. Two types of statistics were done:

1. *Descriptive statistics:* Quantitative data are expressed to measure the central tendency of data and diversion around the mean, mean (x) and standard deviation (SD). Qualitative data were expressed in number and percentage.
2. *Analytic statistics:* Students T test was used for the comparison of two quantitative variables, Mann Whitney test was used to compare between two groups of quantitative data not normally distributed; and chi-square (χ^2) tests were used to compare categorical outcomes.
   - P value > 0.05 was considered statistically non-significant.
   - P value $\leqslant 0.05$ was considered statistically significant.
   - P value $\leqslant 0.001$ was considered statistically highly significant.

Results

This study included 94 patients with newly diagnosed tuberculosis (70 cases were pulmonary, 20 cases were pleural, and 4 cases of TB lymphadenopathy). 18 cases were HCV antibodies seropositive but using PCR, HCV was confirmed in 16 cases (2 false positive cases) and the prevalence of HCV in patients with tuberculosis was 17.02%. The patients were classified into 2 groups: group I (patients with HCV-TB co-infection) and group II (TB patients without HCV infection). 3 cases (2 cases were HCV negative with PCR and one case was HCV and HBV co-infection) were excluded from group I before starting anti-tuberculosis drugs, while 25 cases (5 cases of HBV seropositive, 3 patients with malignancy, 3 cases with history of chronic liver disease, 8 cases could not be followed up for 6 months, and 6 cases started anti-TB drugs), were excluded from group II. Table 1 shows that there was no significant difference between the 2 studied groups regarding gender, but there was significant difference regarding age (p value < 0.05) as patients of group I were older than those of group II. Regarding baseline liver function tests, Table 1 shows that group I had a higher baseline levels of ALT, AST, bilirubin and ALP and there was a highly significant difference (< 0.01) between both groups regarding ALT, AST and ALP, and a significant difference regarding total bilirubin (< 0.05) while there was a non-significant difference regarding albumin although it was higher in group II than group I. Regarding DIH, Table 2 shows that in group I; 6 (40%) cases showed transient transaminase elevations and 6 (40%) cases developed DIH. In group II; 11 (20.75%) cases developed transient transaminase elevations and only 2 (3.78%) cases developed DIH, and there was a highly significant difference (< 0.01) between both groups. Regarding the severity of DIH, Table 3 shows that in group I; 4 cases were mild, one case was moderate and one case was severe. While in group II; one case was mild and one case was moderate DIH with no cases of severe DIH. Table 4 shows that the risk factors for developing DIH during anti-tuberculosis therapy were; age more than 40, high baselines transaminases, ALP and total bilirubin, and low BMI. While Table 5 shows that most cases of DIH occurred during the 1st 4 weeks of starting anti-tuberculosis therapy (66.7% and 50% in group I and group II, respectively).

Discussion

This study included 94 patients with newly diagnosed TB (70 cases were pulmonary, 20 cases were pleural, and 4 cases of TB lymphadenopathy) admitted to the Chest Department, Menoufiya University Hospitals, from February 2013 to March 2014. Regarding the prevalence of HCV in patients

Table 1 Baseline characteristics of the studied groups.

	Group I (n = 15)	Group II (n = 53)	Student test	P-Value
Age	55.6 ± 17.3	47.2 ± 13.3	2.01	0.048 < 0.05 S
Sex				
Male	11	30	Chi square	0.273 NS
Female	4	23	1.20	
Baseline ALT	45.6 ± 13	31 ± 11.9	4.10	< 0.001 HS
Baseline AST	49.12 ± 14.7	33 ± 10.3	4.83	< 0.001 HS
Baseline ALB	3.2 ± 1.7	3.4 ± 1.49	0.44	0.658
Baseline ALP	105 ± 30.34	89.34 ± 19	2.43	0.017 < 0.05 S
Baseline total bilirubin	1 ± 0.15	0.9 ± 0.11	2.85	0.0058 < 0.01 HS

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALB, albumin; S, significant difference; HS, highly significant difference; NS, non-significant difference.

Table 2 Comparisons between both groups regarding DIH.

DIH	Group I (n = 15)	Group II (n = 53)	Chi square	P-Value
No	3 (20%)	40 (75.47%)	20.46	<0.001 HS
Transient	6 (40%)	11 (20.75%)		
DIH	6 (40%)	2 (3.78%)		

HS, highly significant difference; DIH, drug induced hepatotoxicity.

Table 3 Degree of severity of DIH.

DIH	Group I	Group II	Chi square	P-Value
Mild	4	1	1.07	0.586 NS
Moderate	1	1		
Severe	1	0		
Total	6	2		

NS, non-significant difference; DIH, drug induced hepatotoxicity.

Table 5 Timing of DIH.

Timing	Group I	Group II
⩽4 wk	4	1
4–8 wk	1	1
8–12 wk	1	0
12–16 wk	0	0
16–20 wk	0	0
20–24 wk	0	0

DIH, drug induced hepatotoxicity; Wk, weak.

with TB; 18 cases were HCV antibodies seropositive but using PCR, HCV was confirmed in 16 cases (prevalence was 17.02%). In Egypt nearly 10% had chronic HCV infection; overall, an estimated 6 million Egyptians had chronic HCV infection in 2008. Prevalence of chronic HCV infection in Egypt is 10–12% [30]. Prevalence rate of HCV among TB patients varies internationally. Many Results of HCV prevalence (7.5%) was documented by Reis et al. [31], whereas in Thailand, a study revealed very high prevalence for HCV (31%) [32]. Another study conducted in Georgia, Richards et al. [12] found that 22% were HCV seropositive, Kuniholm et al. [33] revealed 12% HCV positives, Wang et al. [34] showed HCV 6.7%, Khalil et al. [35] reported HCV co-infections in TB were 28 (27.45%). In the study of Akhtar et al. [36] prevalence of HCV was 9.1% using ELISA technique in TB patient. In the study of Badawy et al. [37] who studied Hundred thirty-five tuberculosis patients with tuberculosis either pulmonary or extra pulmonary, they found that HCV infection was diagnosed in 21/135 (prevalence was 6.4%). This variation among results may be due to the use of conventional and different techniques including ELISA, PCR, and recombinant immunoblot assay (RIBA). The patients were classified into 2 groups: group I (patients with HCV-TB co-infection) and group II (HCV-negative tuberculous patients). There was no significant difference between the 2 studied groups regarding gender, but there was significant difference regarding age (p value <0.05) as patients of group I were older than those of group II. Regarding baseline liver function tests, group I had a higher baseline levels of ALT, AST, bilirubin and ALP and there was highly significant difference (<0.01) between both groups regarding ALT, AST and ALP, and a significant difference regarding total bilirubin (<0.05) while there was non-significant difference regarding albumin although its levels were lower in group I than group II. Regarding DIH, in group I; 6 (40%) cases showed transient transaminase elevations and 6 (40%) cases developed DIH. In group II; 11 (20.75%) cases developed transient transaminase elevations and only 2 (3.78%) cases developed DIH,

Table 4 Risk factors for DIH.

Factor	DIH (n = 8)	No-HIH (n = 60)	Mann Whitney U	p-Value
Age ⩾ 40	60.62 ± 14.34	48.26 ± 7.54	3.85	<0.001
Sex				
Male	6	39	Chi square	0.574
Female	2	21	0.32	
Baseline ALT	45.33 ± 15.81	30 ± 8.67	4.21	<0.001
Baseline AST	49.25 ± 16.22	33 ± 9.13	4.27	<0.001
Baseline albumin	3.10 ± 1.52	3.4 ± 0.91	0.80	0.424
Baseline ALP	106.78 ± 11.34	88.65 ± 22.75	2.21	0.031
Smoking				
+ve	5	32	Chi square	0.624
−ve	3	28		
BMI	18.78 ± 2.34	24.89 ± 4.54	3.72	<0.001
Alcohol intake				
+ve	1	1	Chi square	0.088
−ve	7	59	2.90	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; ALB: albumin; S: significant difference; HS: highly significant difference; NS: non-significant difference; DIH: drug induced hepatotoxicity.

and there was a highly significant difference (<0.01) between both groups. Regarding the severity of DIH, in group I; 4 cases were mild, one case was moderate and one case was severe. While in group II; one case was mild and one case was moderate DIH with no cases of severe DIH. The present study is an agreement with that of Ungo et al. [13] who investigated the association of HCV infection and the development of DIH during anti-TB treatment. DIH, which was defined as a liver transaminase level $\geqslant 120$ IU/L, occurred more frequently in HCV-seropositive and HIV-seronegative patients (7 of 29 patients, 24%) than in HCV-seronegative and HIV-seronegative patients (3 of 55, 5%). Also the study of Kwon [26] included >50 HCV-seropositive patients, and revealed that the elevation of liver enzyme levels during standard therapy for TB was more common in HCV-seropositive patients (41%) than in the control subjects (20%) and DIH occurred more frequently in HCV-seropositive patients (13%) than in control subjects (4%). Sadaphal et al. [22] evaluated the risk of DIH in a cohort of 146 injection drug users, 95% of whom were HCV seropositive, who were treated with isoniazid for latent TB infection. In their study, an increase in liver transaminase values to more than three times the upper limit of normal occurred in 22% of patients. Fernandez-Villar et al. [38] also studied the risk of DIH among 415 drug users, 52% of whom were HCV seropositive, with isoniazid treatment for latent TB infection. The presence of HCV antibodies was associated with DIH (16 of 214 HCV-seropositive patients [7.5%] vs 4 of 201 control subjects [2%]) [38]. In study of Lomtadze et al. [39], 18.8% of subjects with a normal baseline ALT level developed DIH during the treatment, indicating an important increase from baseline ALT level during the six months of anti-TB therapy, while among patients with HCV co-infection, 43.8% developed hepatotoxicity, nearly double the proportion of chronic hepatitis patients with incident hepatotoxicity reported by Park et al. in Korea [40]. In the study of Sun et al. [41], abnormal liver function tests at baseline and liver cirrhosis were identified as independent risk factors for the development of hepatitis during anti-tuberculosis treatment. Teleman et al. [42] also showed that patients with abnormal baseline transaminase were at risk for the development of hepatitis during treatment, and Cho et al. [43] demonstrated that patients with liver cirrhosis have an insignificantly higher incidence of hepatitis than those without liver disease (27% vs. 10%, $p = 0.079$). Prior studies have demonstrated that transient elevation of AST/ALT (1–3 times higher than ULN) was observed in 26% of HBV carriers and 28% of HCV carriers [44]. Shakya et al. [45] reported that 38% and 40% of patients undergoing anti-tuberculosis treatment had ALT and AST levels two times higher than the pretreatment level. In the study of Sun et al. [41], they found that 50% and 40% of the patients without hepatitis had elevated AST and ALT level higher than ULN, and 19% and 15% had elevated AST and ALT levels >2 times ULN. The risk factors for developing DIH during anti-tuberculosis therapy were; age more than 40, high baselines transaminases, ALP and total bilirubin, and low BMI. Makhlouf et al. [46] who studied 26 TB patients of pulmonary and extrapulmonary TB associated with liver cirrhosis or viral hepatitis in addition to 46 TB patients without liver disease as controls, by univariate analysis, liver diseased patients with anti-TB-DIH had lower body mass index ($P < 0.049$) and lower serum albumin ($P = 0.008$). Using multivariate regression analysis proved that lower serum albumin was independent predictors of anti-TB-DIH ($P < 0.018$) in liver diseased patients while the presence of other co-morbid diseases was the only risk factor in patients without liver disease ($P < 0.024$). Regarding the timing of DIH; in the present work most cases of DIH occurred during the 1st 4 weeks of starting anti-tuberculosis therapy (66.7% and 50% in group I and group II, respectively) which is in agreement with the study of Makhlouf et al. [46], who found that Anti-TB-DIH developed within 15–60 days from the onset of therapy.

Conclusion

Tuberculosis and hepatitis C virus co-infection is common, and elevation of liver functions during anti-tuberculosis therapy is not uncommon. Serologic screening of patients with tuberculosis for HCV to identify patients in need of intensive monitoring during anti-tuberculosis therapy may reduce the risk of DIH. HCV seropositive patients with tuberculosis should be closely monitored during treatment especially if they had elevated baseline liver functions, old age and with low BMI. Monitoring should include the whole period of treatment, especially the 1st 2 months.

Conflict of interest

We have no conflict of interest.

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