Hepatitis C Virus Infection among Tuberculosis Patients in Egypt: Seroprevalence and Associated Risk Factors

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Received date: December 03, 2017; Accepted date: May 04, 2018; Published date: May 11, 2018

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Abstract

Background and study aim: Tuberculosis (TB) and hepatitis C virus (HCV) infection have emerged as major public health problems in Egypt. We aimed to determine the prevalence and risk factors for the HCV infection among patients with TB in Sohag and Qena governorates.

Patients and methods: A cross-sectional study was carried out at Sohag and Qena university hospitals. Hundred thirty five tuberculosis patients fulfilled the inclusion criteria. HCV infection was diagnosed in 21/135 (6.4%).

Results: Goza smoking (P value 0.01 Odd's Ratio 3.75, 95% confidence interval 0.24-0.44), history of operation (P value 0.001 ORs 7.67, 95% CI 0.165-0.263), presence of tattoos (P value 0.03 ORs 2.3, 95% CI 0.168-0.338), extra pulmonary tuberculosis (P value 0.001 ORs 3.5, 95% CI 2.341-3.384), low serum albumin (P value 0.002 ORs 1.5, 95% CI 0.068-0.317) were the main risk factors associated with HCV infection.

Conclusion: Universal screening for HCV infection in TB patients is highly recommended with an urgent need to detect HCV infection in high-risk groups to prevent future HCV transmission as well as morbidity and mortality associated with TB.

Keywords Hepatitis C virus; Tuberculosis; Extra pulmonary tuberculosis; Hepatocellular carcinoma

Introduction

Tuberculosis is the third most life-threatening disease in Egypt, after bilharziasis and hepatitis C. Despite this, in its 2007 Global Report, the World Health Organization (WHO) said Egypt had succeeded in achieving the global target in TB case detection and treatment success in 2007. Health officials in Egypt plan to eradicate TB by 2050. WHO, (2007) estimated that TB incidence rate in the general population of Egypt, was 25/100000, using sputum smear microscopy for AFB detection [1]. The World Health Organization had stated hepatitis C as a worldwide health problem, with approximately 3% of the world's populace (roughly 170-200 million people) infected with HCV. In Egypt the situation is relatively worse. The national prevalence rate of HCV antibody positivity has been assessed to be between 10-13%. The estimated adjusted national prevalence rate of chronic hepatitis C infection is 7.8% [2]. HCV Chronic infection is the leading cause of liver cirrhosis and liver malignancy in Egypt and, truly, one of the topmost five important causes of death. Egypt has a very high prevalence of HCV with high morbidity and mortality from cirrhosis and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has increased rates of HCV transmission due to injection therapy and inadequate infection control practices. Such as, tattooing, circumcision or other medical procedures done by non-medical persons are more common routes of infection in Egypt than somewhere else. Furthermore, household transmission, vertical transmission and sexual transmission are routes that are also under investigation [2]. HCV infects an estimated 170 million persons worldwide. The institution of blood screening measures in industrialized countries had reduced the hazard of hepatitis induced from blood transfusion to a least level, but transfusion-related transmission still occurs in developing countries that have not fully implemented blood screening procedures. Worldwide, new cases of HCV also remain to arise as a consequence of injection drug users (IDU) and through other ways of percutaneous or mucous-membrane contact [4].

In Egypt, the major route of transmission appears to be due to injection therapy and inadequate infection control practices. With such a high background prevalence rate, transmission of hepatitis C through other nonmedical routes has become more significant. Such as, tattooing, circumcision or other medical procedures done by non-medical persons are more common routes of infection in Egypt than somewhere else. Furthermore, household transmission, vertical transmission and sexual transmission are routes that are also under investigation [2]. HCV infects an estimated 170 million persons worldwide. The institution of blood screening measures in industrialized countries had reduced the hazard of hepatitis induced from blood transfusion to a least level, but transfusion-related transmission still occurs in developing countries that have not fully implemented blood screening procedures. Worldwide, new cases of HCV also remain to arise as a consequence of injection drug users (IDU) and through other ways of percutaneous or mucous-membrane contact [4].

Most patients with newly-acquired HCV infection do not present with an acute hepatic illness as most estimates suggest only 10-15% of cases are acutely jaundiced. In the remainder, the infection is either...
asymptomatic, or may present with mild constitutional symptoms (nausea, loss of appetite, fatigue, vague abdominal pain), with elevated liver enzyme which peaks below 1,000 IU/ml. As a result, few such cases come to medical attention or are tested for evidence of HCV infection [5]. HCV may have a major impact among patients with TB. Data from one study have proposed that co-infection with hepatitis C raises the threat of drug-induced hepatic toxicity with anti-TB drugs, and there was an even greater risk for drug-induced hepatotoxicity among those undergoing treatment for TB who had HCV infection [6]. No systematic research on HCV/TB co-infection is currently being undertaken. Therefore, the objectives of the present study were to estimate the prevalence and risk factors of HCV in TB patients.

Materials and Methods

Study population and enrolment procedures

From June to December 2016, patients with a clinical and documental diagnosis of tuberculosis either recently diagnosed or already on anti-tuberculous treatment who attended tuberculosis clinic at Sohag university hospital were invited to participate. The study was approved from the ethical committee of Qena faculty of medicine. Patients were recruited through physicians, who explained the study objectives and procedures, and obtained written informed consent from the patients. Clinical and epidemiological data were obtained in a confidential manner. Data obtained from the enrolled patients included information about demographics, medical history (hospitalizations, prior surgical procedures, blood transfusions, blood donations, vaccinations/injections by medical personnel, dental treatments), history of bilharziasis, tattoos, history of Intravenous drug users or other history of substance use. Participants were invited to receive HCV testing. A case-control study was performed to identify risk factors for HCV infection. Cases were defined as patients with TB and HCV-seropositive, and controls were patients with TB who were HCV-seronegative. One hundred thirty five TB patients were fulfilled the selection criteria of the study.

Inclusion criteria: age more than 15 years old, patients with all form of tuberculosis either pulmonary or extra pulmonary.

Exclusion criteria: Patients with abnormal baseline liver function test, drug induced hepatitis, and patients with chronic liver diseases were excluded by abdominal sonography, underlying malignancy and autoimmune disease.

Blood sample collection

10 ml blood samples were withdrawn from each subject into sodium citrate for prothrombin time and concentration and plain vacutainer for liver function test and PCR. Serum samples were separated from whole blood rapidly under aseptic sterile condition, aliquoted and immediately stored frozen at -70 °C until use. Liver function tests, anti-HCV antibodies were done for all patients. HCV-RNA by PCR for positive anti-HCV antibody cases. Liver function tests were performed on autoanayser Synchroinic CX 9 system Bechman coulter, Inc/USA.

Detection of Anti-HCV

It was performed using a second generation ELISA, and confirmatory tests were performed using recombinant immunoblot assay (RIBA) and HCV polymerase chain reaction (PCR) tests. Using ARCHITECT Kits (provided by Abbott laboratories). ARCHITECT anti HCV is a Chemiluminescent Microparticle Immunoassay (CMIA) for the quantitative detection of antibody to Hepatitis C virus (anti HCV) in human serum or plasma.

Biological principle of the procedure

ARCHITECT anti HCV is a two-step immunoassay which uses Chemiluminescent Micro particle Immunoassay (CMIA). In the first step, sample, recombinant HCV antigen coated paramagnetic micro particles and Assay Diluents are combined. Anti HCV present in the sample binds to the HCV coated micro particles. After washing, anti-human acridinium-labeled conjugate is added in the second step. Following another wash cycle, pre-Trigger and Trigger solutions are added to the reaction mixture. The resulting chemiluminescent reaction is measured as relative light units (RLUs).

A direct relationship exists between the amount of Anti-HCV in the sample and the RLUs detected by the ARCHITECT optical system. The presence or absence of Anti-HCV in the sample is determined by comparing the chemiluminescent signal in the reaction to the cutoff signal determined from a previous ARCHITECT Anti-HCV calibration .If the chemiluminescent signal in the sample is greater than or equal to the cutoff signal, the specimen is considered reactive for Anti HCV. Once ARCHITECT Anti-HCV is accepted and stored, all subsequent samples may be tested without further Calibration. ARCHITECT calculates the Anti-HCV Calibrator 1 Mean chemiluminescent signal from the three Calibrator 1 replicates and stores the result.

Detection of HCV RNA in serum by RT-PCR

RNA extraction was performed by the kit supplied by QIAGEN (VIRAL RNA Mini Kit) lot No.11233766.

Principle

The kit combines the selective binding properties of silica gel-based membrane with speed of microspin technology and is ideally suited for simultaneous processing of multiple samples. The sample is first lysed under highly denaturing conditions to inactivate RNAase and to ensure isolation of intact viral RNA. Buffering conditions are then adjusted to give optimum binding of RNA to the QIAamp membrane then the sample is loaded onto QIAamp spin column. The RNA binds to the membrane and contaminants are efficiently washed away into two step using two different wash buffers High-quality RNA is eluded in special RNAase free buffer.

Sample

Serum, heparinized plasma Reagents: AVL buffer, RNA carrier, Buffer AW1 concentrate, Buffer AW2 concentrate, AVE buffer, QIAamp spin column, Ethanol (96-100%). Microcentrifuge tubes (1.5 ml). Sterile RNase free pipette tips with aerosol barrier.

Statistical analysis

Variables were presented as frequencies. Chi-square test was utilized to compare proportions. Student’s t-test or a Mann-Whitney U-test was used to compare continuous variables. Association of risk factors with HCV were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). ORs were manually calculated by multiplying cases with exposure (risk factor) and controls without exposure divided by controls with exposure multiplied with cases without exposure. ORs
either higher or lower than one may indicate the association. Calculation of confidence interval was done by linear regression analysis. Statistical analyses were conducted using SPSS version 11.0 software package.

Results

One hundred thirty five tuberculosis patients fulfilled the inclusion criteria, 78 patients were below 30 year (58%), only 3 patients were positive for HCV (14.3%) while 57 patients were above 30 year (42%), 18 patient were positive for HCV (85.7%) and HCV infection was positive in female patient’s more than male patients without statistical significance P value 0.2, (ORs 1.56, 95% CI 0.328-0.413). HCV infection was diagnosed in 21/135 (6.4%). Goza smokers, history of operation, blood transfusion, presence of tattoos, extra pulmonary tuberculosis were the main risk factors associated with HCV infection as shown in Table 1 with significant p values and ORs more than one and (95% confidence interval 0.240-0.448, 0.165-0.263, 0.103-0.362, 0.168-0.338, 2.341-3.384 respectively) (Table 2) revealed that most extra pulmonary tuberculosis was TB lymphadenitis 30 cases (22.2%) while 6 cases (28.6%) were positive for HCV infection, followed by pleural effusion 24 (17.8%) case while 3 cases (14.3%) were HCV infection positive and 15 case with Pott’s disease while 9 cases (42.9%) were HCV positive with statistically significant difference P value was 0.004 and (ORs 3.5, 95% CI 2.341-3.384). Among 45 (33%) pulmonary tuberculosis patients 30 with bilateral chest X- ray lesion (22.2%) and 15 patient with unilateral lesion (13.2%). HCV infection was positive in 3 patients (14.3) with bilateral pulmonary lesion and all patients with unilateral pulmonary lesion were negative for HCV with significant P value 0.02 (ORs 0.5 and 95% CI 0.675-1.626). Low serum albumin level was found in 8 patients (5.9%) 5 of them were positive for HCV infection (23.8%) with statistically significant P value 0.002 and (ORs 11.56, 95% CI 0.068-0.317).

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>All patients (135)</th>
<th>Negative HCV (114)</th>
<th>Positive HCV (21)</th>
<th>P value</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 30 yr</td>
<td>78</td>
<td>58</td>
<td>75</td>
<td>66.8</td>
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<tr>
<td>Age &gt; 30 yr</td>
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<td>42</td>
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<tr>
<td>Sex: Male</td>
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<td>37</td>
<td>32.5</td>
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<tr>
<td>Sex: Female</td>
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<td>66</td>
<td>77</td>
<td>67.5</td>
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<tr>
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<td>9</td>
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<td>21</td>
<td>19</td>
<td>16.7</td>
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<td>26.7</td>
<td>30</td>
<td>26.3</td>
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<tr>
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<td>32</td>
<td>28</td>
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<td>15</td>
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<td>Blood transfusion</td>
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<td>8.9</td>
<td>6</td>
<td>4.5</td>
<td>6</td>
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<tr>
<td>Tattooing</td>
<td>18</td>
<td>14</td>
<td>12</td>
<td>10.5</td>
<td>6</td>
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<td>2.2</td>
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<td>1</td>
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<td>5.2</td>
<td>4</td>
<td>3.5</td>
<td>3</td>
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<td>33</td>
<td>42</td>
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<td>72</td>
<td>63.2</td>
<td>18</td>
</tr>
<tr>
<td>Relapse patients</td>
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<td>4.4</td>
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Table 1: Demographic and clinical features of TB patients according to HCV infection

<table>
<thead>
<tr>
<th>Clinical features of TB patients</th>
<th>Hepatitis C negative cases</th>
<th>Hepatitis C positive cases</th>
<th>P value</th>
<th>Odds ratio</th>
</tr>
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<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>21</td>
<td>18.4</td>
<td>3</td>
<td>14.3</td>
</tr>
<tr>
<td>Peritonitis&amp; ascits</td>
<td>18</td>
<td>15.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>24</td>
<td>21.1</td>
<td>6</td>
<td>28.6</td>
</tr>
</tbody>
</table>

Discussion

Chronic viral infection may increase the risk for development of accelerated lung destruction [7]. Chronic HCV infection is also associated with both direct and indirect effects on pulmonary tissue [8]. Tuberculosis and viral hepatitis are two of the commonest co-infections [9]. Studies concerning TB-HCV co-infection are limited, especially for detection of TB infection in HCV patients, but there were few studies described the diagnosis of HCV in TB patients. Our study revealed that 21/135 (6.4%) of tuberculous patients were HCV sero-positive this is in comparison with other Studies Richards et al. [10] declared that HCV co-infection was common among patients infected with TB. Kuniholm et al. [11] determined the prevalence of HCV antibodies among TB infected individuals to be (12%).

The prevalence in those under age 30 was approximately (14.3%), while in those above 30 year was (85.7%). This is attributed to most common way for transmission and persistence of HCV in middle and old age to tartar emetic injection by nondisposable syringe for Bilharziasis and demonstrating the continued presence of significant hepatitis C transmission in modern-day Egypt and this is consistent with Mohamed [2]. There were very high rates of HCV co-infection (nearly one in four) among persons with TB in Georgia. While HIV infection is uncommon in Georgia, recent reports have suggested that HCV is much more prevalent. Among 552 blood donors, 7.8% had positive serology for HCV [12]. The findings from this study suggest that patients with TB may have among the highest prevalence of HCV infection in Georgia, second only to injection drug users (58.2%).

While in our study HCV co-infection among patients with TB in Sohag governorate (nearly one in six) and HIV is uncommon as all studied patients were negative for HIV as done routine for all TB patients. HCV infection more prevalent in TB patients than HIV so universal screening for it as HIV is highly recommended.

Different risk factors were detected in our study, extra pulmonary TB (18/23), history of previous operation (15/23) followed by Goza smoker (9/23). This is inconsistent with Richards et al. [10] and Weissenbacher et al. [13,14] who stated that use of injected drugs (13/15) was by far the main risk factor associated with hepatitis infection. As its common habits in these countries but in our locality Goza smokers are common habits and infection via operation (transfusion-related transmission) is common procedures. This is consistent with studies done at Egypt stated that invasive medical procedures, previously reported to be associated with HCV infection in Egypt.

Our study revealed that Goza smoker and tattoos were risk factors for HCV infection with (P value 0.01, 0.03, odds ratio 3.75, 3.40 and 95% Confidence interval 0.240-0.448, 0.168-0.338 respectively), this is consistent with Richards et al. [10] who found significant risk factors of prior incarceration and receipt of a tattoo (odds 2.6, 95% CI 1.2-5.6), a common practice in Georgia and other former Soviet republic prisons, as well as history of an STI and age between 26 and 45 years. While our findings are inconsistent with study done by Ahmed et al. [15,16] who stated that inhabitants who had tattoos, smoked goza pipes, were shaved by a community barber, or had their ears pierced were not at greater risk for anti-HCV than those that did not. "Sharing a water pipe mouthpiece poses a serious risk of transmission of communicable diseases, including tuberculosis and hepatitis". This statement is wrong attributed to researchers [17] who are not the authors of studies on such risks. "Generally speaking, the risks are not clearly established because of a non-rigorous methodology (simultaneous use of other products e.g., qat, cigarettes, bids, etc), strongly neglected hygiene, current profile and remote and recent career of smokers not specified, etc.) Diseases such as Hepatitis C and B and HIV can, theoretically, be transmitted through oral-oral contact, if both people involved have sores in their mouth, allowing blood-to-blood contact. But this is a theoretical and extremely difficult possibility. You’d be hard-pressed to find a single documented case of this in the literature. When you have a hookah mouth-piece passing between people, it’s being exposed to air in between users, which greatly decreases the likelihood of a virus surviving to infect you. Outside of their ideal environment of human blood, these viruses do not survive; that’s why they are only transmitted through acts of extreme body-fluid commingling.

HCV infects an estimated 170 million persons worldwide [4]. IDU is a major mechanism for the transmission of HCV, and many reports have noted a high prevalence of HCV infection among injection drug users. The institution of blood screening measures in industrialized countries has reduced the risk of transfusion-associated hepatitis to a minimal level, but transfusion-related transmission still occurs in developing countries that have not fully implemented blood screening procedures. IDU would be very rare or nonexistent in our locality.

Although IDU has been identified as a risk factor for infection in a small, metropolitan study of risk factors for HCV in Cairo [18], IDU

Table 2: Relationship between Hepatitis C positive cases and clinical features of TB patients

<table>
<thead>
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<th>Table 2: Relationship between Hepatitis C positive cases and clinical features of TB patients</th>
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<tbody>
<tr>
<td>Poti's disease</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>5.3</td>
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<tr>
<td>9</td>
</tr>
<tr>
<td>42.9</td>
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<td>0.004</td>
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</table>

Although IDU has been identified as a risk factor for infection in a small, metropolitan study of risk factors for HCV in Cairo [18], IDU
was denied (and believed not present) in another rural Egyptian village in the Nile Delta [19]. There are only 3 cases with a history of IDU with negative HCV infection in our study.

However, there may have been under reporting of this behavior due to fear of the potential consequences, given that IDU is illegal in Egypt. A report by Ungo et al. [14] suggested that HCV or HIV co-infection increased the risk of antituberculosis drug-induced hepatotoxicity.

Since therapy for schistosomiasis was the major cause of the extensive distribution of HCV in Egypt, we suppose that HCV epidemic may be a possible reason for the emergence and recurrence of TB infection in HCV patients, due to its impact on the immune system, in addition to delay in TB diagnosis. Further studies are needed to assess the impact of the high prevalence of HCV infection on prevalence, diagnosis and treatment outcomes of TB, especially in high risk populations as Egypt where HCV is the major epidemic. Egypt is in need of additional training programs, funding facilities and research in order to fight the hepatitis C epidemic.

Conclusion

Presence of HCV co-infection among patients with TB in Sohag has the potential to have a major impact upon TB management, treatment and control. Further studies will be needed to assess the impact of the high prevalence of HCV co-infection on the treatment outcomes of those with TB, including tolerability and risk of anti-tuberculosis drug-induced hepatotoxicity. In conclusion, the results of this study suggest an urgent need to detect HCV infection in high-risk groups to prevent future HCV transmission as well as morbidity and mortality associated with TB. Collaboration between TB and HCV programs seems to be the best approach to decrease the incidence of these diseases, especially in high-prevalence HCV settings. There are strong recommendations for universal screening of persons with TB for HCV infection as there are for HIV testing. Serologic screening of tuberculosis patients for HCV and HIV to identify patients in need of intensive monitoring during anti-tuberculosis therapy may reduce risk of hepatotoxicity and mortality.

References