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Research Article

PREVALENCE AND EVALUATION OF SALMONELLOSIS AND BRUCELLOSIS IN CHRONIC HEPATITIS C VIRUS PATIENTS FROM EGYPT

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A B S T R A C T

Typhoid fever and brucellosis resulted in a significant morbidity and mortality in patients, particularly in endemic areas. These bacteria could invade the hepatic tissue and involved in a critical complications. The current study detected the seroprevalence and assessed the clinical changes of *Salmonella* or *Brucella* infection among the HCV infected patients. 185 chronically infected patients with HCV were serologically examined and some clinical parameters were detected. Overall seroprevalence of *Salmonella typhi* and *Brucella spp* infection was 22.16%, 1.62%, respectively. No significant difference was detected in the prevalence of *Salmonella typhi* or *Brucella spp* among HCV patients based on area, gender, age and HCV RNA load. Higher prevalence of *Salmonella typhi* was significantly detected among rural area residents. Liver cirrhosis demonstrated a high percentage of patients with co-infections of *Salmonella typhi* and chronic HCV compared to patients with chronic HCV mono-infection. Moreover, a significant increase in the level of ALT, AST and the relative lymphocyte count was detected in patients with concomitant *Salmonella typhi* and chronic HCV infections compared to patients with chronic HCV mono-infection. In conclusions, *Salmonella typhi* and *Brucella spp* infection is common among HCV patients in Egypt. Regular screening for these bacterial infections among HCV patients is highly recommended.

INTRODUCTION

Salmonellosis and Brucellosis caused by gram-negative bacteria belong to genus *Salmonella* and *Brucella*, respectively, which resulted in a significant morbidity and mortality in patients, particularly in endemic areas (Pappas *et al*., 2005; Kumar *et al*., 2008). Both infections are endemic in the developing countries, including Egypt and represent a critical public health problem. Salmonellosis and Brucellosis usually invade the gastrointestinal system, but both infections may manifest as various clinical syndromes (Ozaras *et al*., 2004; Pandit *et al*., 2008).

Many syndromes and major complications belong to these bacterial infections were reported. Typhoid fever that caused by *Salmonella* is characterized by constipation followed by diarrhea with fever, relative bradycardia, cough and headache (Singh, 2001). *Salmonella* infection can invade many parts of the abdomen, but it commonly invades spleen and the hepatobiliary system (Chaudhry *et al*., 2003).

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Critical complications such as liver cirrhosis, sickle cell disease, malignancies, renal failure and acute pancreatitis were recorded (Sarma and Narula, 1996; Khan *et al*., 2009). Moreover, *Salmonella* infection is a well-known cause of pyogenic liver abscess (Choi *et al*., 2006; Kumar *et al*., 2008).

Brucellosis infection resulted in fever, jaundice, hepatosplenomegaly, increase in liver enzymes and alkaline phosphatase (AAP, 2009). The *Brucella* organisms are mostly detected in reticuloendothelial tissues (Cervantes *et al*., 1982; Pappas *et al*., 2005). The largest organ of the reticuloendothelial system is the liver which plays an important role in the defense against Brucellosis (Albayrak and Albayrak 2011). Therefore, during the course of human Brucellosis hepatic tissue involvement, rare hepatic abscess and rare acute hepatitis, is usually reported (Ariza *et al*., 2001; Ozaras *et al*., 2004; Erdem *et al*., 2005; Kilicaslan *et al*., 2008; Zadeh *et al*., 2009).

Worldwide, liver transplantation, due to decompensated liver cirrhosis, or hepatocellular carcinoma (HCC) is commonly associated with the hepatitis that caused by HCV infection (El-Serag and Mason, 1999; Davis *et al*., 2003; Verna and Brown, 2006). The highest occurrence of HCV infection all over the world, about 15%, was recorded in Egypt (Fallahian and

Najafi, 2011; Guerra *et al*., 2012). Dual infections of Salmonellosis or Brucellosis infection and HCV have been previously recorded (Bashir *et al*., 2005; Abou El Azm *et al*., 2013). Patients with multiple infections of HCV and Salmonellosis or Brucellosis, may demonstrate worse clinical consequences in comparison with patients with HCV mono-infection. Hence, in this study a trail has been made to detect the seroprevalence of Salmonellosis or Brucellosis among the HCV patients. The current study was also assessing the biochemical and hematological changes during Salmonellosis or Brucellosis co-infection in the chronic HCV infected patients.

MATERIALS AND METHODS

Ethical statement

The present study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice and approved by the ethical committee of Faculty of Medicine, Al-Azhar University and Kafer El Shiekh Liver and Heart Institute, Egypt. The purpose and procedures involved in the present study were explained and written informed consent was obtained from all participants.

Study population

One hundred eighty five patients chronically infected with HCV from Kafer El Shiekh Liver and Heart Institute, Egypt during the period between February 2015 and March 2016 were enrolled in the present study. The study population included 82 females and 103 males, with age range 20-57 with a mean of (40.90 ±7.90) years.

In order to evaluate the hematological and biochemical alteration, the study population was divided into three groups. Group-I: 121 patients with chronic HCV infection without other bacterial infection. Group-II: 41 patients with concomitant *Salmonella typhi* and chronic HCV infections. Group-III: 3 patients with concomitant *Brucella spp* and chronic HCV infections.

Exclusion criteria

Patients with malignancy, including hepatocellular carcinoma (HCC) or renal, cardiopulmonary or autoimmune disorders and pregnant women were excluded from the study.

Detection of HCV antibodies and RNA

HCV antibodies were evaluated by EIA (COBAS-Amplicore, Germany). According to the manufacturer's instructions, HCV-RNA qualitative assessment by PCR was done using a commercial kit (Roche Diagnostic, Branchburg, NJ).

Serological analysis of Salmonella typhi and Brucella spp infection

In order to diagnose *Salmonella typhi*, widal test was performed by tube method according to manufacturer's instructions (Agappe Diagonistics, Switzerland).

The positivity cut-off point for tube agglutination reaction for both O and H antigens was defined as antibody titers >1:160. The agglutination test was performed on serial serum dilutions of 1/40 to 1/1280 by using *Brucella spp* antigen obtained from (Linear Chemicals, Barcelona, Spain). The serum agglutination test was considered positive when a titre of ≥ 1/160 was obtained.

Clinical, hematological and biochemical analysis

In patients, compensated cirrhosis was determined by Fibro-scan™ >12.5 kPa. Complete blood count (CBC) was determined using an automated hematology analyzer XP series (Sysmex, Japan). Direct, total bilirubin, albumin, fasting sugar creatinine, alanine transaminase (ALT), and aspartate transaminase (AST) were run on using ABX Pentra C400 clinical chemistry analyzer (Horiba ABX SAS, Montpellier, France). Antinuclear antibody (ANA) and alpha-fetoprotein (AFP) were determined using chemiluminescent immunoassay (Liaison, DiaSorin, Germany), Thyroid-stimulating hormone (TSH) was done using a commercial kit (Teco Diagnostics, *CA,* USA). International normalized ratio (INR) was done automatically using a commercial kit (Siemens Healthcare Diagnostic Inc., Germany).

Statistical analysis

For statistical analysis, the SPSS (IBM SPSS statistics for Windows, Armonk, NY) computer program was used.Binary logistic regression was used to assess significant differences of *Salmonella typhi* and *Brucella spp* infection rate in HCV-infected patients of different age, residences, and sex. Hematological and biochemical changes were evaluated by using an analysis of variance (ANOVA) test followed by post hoc analysis of group differences that was accomplished by the least significant differences (LSD) test; $p<0.05$ were considered to be statistically significant.

RESULTS

Salmonella typhi and *Brucella spp.* infection among HCV patients from Egypt was summarized in Table 1. The prevalence of *Salmonella typhi* and *Brucella spp* was 22.16%, 1.62%, respectively. Although, high prevalence of *Salmonella typhi* and *Brucella spp* 24.51%, 1.96% was recorded in Kafr-elshikh province compared to Gharbiya province 19.28%, 1.20%, respectively, no significant difference was observed among the patients from Kafr-elshikh province when compared to Gharbiya province.

Table 1 Seroprevalence of *Salmonella typhi* and *Brucella spp.* infection among HCV infected patients from Egypt

Regions	Total	*Salmonella*	*Brucella*
Kafr-elshikh	102	25 (24.51%)	2 (1.96%)
Gharbiya	83	16 (19.28%)	1 (1.20%)
Total	185	41 (22.16%)	3 (1.62%)

Prevalence of *Salmonella &Brucell* is not significantly different according to region ($p>0.05$, logistic regression test).

To further understand the epidemiology of *Salmonella typhi* and *Brucella spp* in the present study, the prevalence's of *Salmonella typhi* and *Brucella spp* on the basis of the age, gender, and residence were evaluated (Table 2). Based on residence, the *Salmonella typhi* prevalence was significantly higher ($p < 0.05$) among rural area residents, 30.34 %, than urban area residents, 14.58%. On the other hand, the *Brucella spp* prevalence was highly detected only among urban area residents, 2.08% compared to rural area residents 1.12%. No significant difference was detected in the prevalence of *Salmonella typhi* and *Brucella spp* among HCV patients based on gender and age.

Characteristics of cirrhosis, HCV RNA load and some biochemical data of the study population were shown in Table 3.

Table 2 Seroprevalence of *Salmonella typhi* and *Brucella spp.* infection among HCV infected patients according to sex, residence and age

Characteristics	Total	*Salmonella*	*Brucella*
Age			
40 year or less	84	19 (22.62 %)	1 (1.19%)
More than 40	101	22 (21.78 %)	2 (1.98%)
Sex			
Male	103	20 (19.42%)	1 (0.97%)
Female	82	21 (25.61%)	2 (2.44%)
Residence			
Urban	96	14 (14.58%)	2 (2.08%)
Rural	89	27 (30.34%)*	1 (1.12%)

* Prevalence of *Salmonella* is significantly different ($p < 0.05$, logistic regression test).

Table 3 Characteristics of cirrhosis, HCV RNA load and biochemical data of the study population

Parameter	Group I (HCV)	Group II (HCV+ *Salmonella*)	Group III (HCV+ *Brucella*)
Cirrhotic Liver	16(13.22%)	8(19.51%)	0 (0.00%)
HCV RNA (10^5 IU/ml)	19.69±2.44	20.38±3.46	7.41±2.69
AFP (ng/dl)	12.45±3.17	9.75±2.32	22.03±8.52
TSH (µlU/ml)	1.54±0.09	1.57±0.20	2.09±0.3
Glucose (mg/dl)	113.11±5.67	104.00±7.28	94.67±5.9
INR	1.08±0.01	1.08±0.01	1.16±0.12
ANA (Negative/Positive)	185(100%)/0(0%)	185(100%)/0(0%)	185(100%)/0(0%)

Data are expressed as: mean ± standard error (STE) or number (% among study population).

Higher percentage of cirrhotic liver was recorded in patients with concomitant *Salmonella typhi* and chronic HCV infections compared to those patients with chronic HCV mono-infection. Although no significant difference was detected at the level of HCV RNA load, the lower level was observed in patients with concomitant *Brucella spp* and chronic HCV infections than those patients with chronic HCV mono-infection. No significant differences were detected at the levels of TSH, ANA, glucose and INR among the study populations. AFP levels in patients with concomitant *Brucella spp* and chronic HCV infections showed higher levels than those patients with chronic HCV mono-infection or those patients with concomitant *Salmonella typhi* and chronic HCV infections.

Liver, kidney function and hematological findings of the study population were illustrated in Tables 4 and 5. Significant ($p < 0.05$) increase in the levels of *ALT* and *AST* was detected in patients with concomitant *Salmonella typhi* and chronic HCV infections as compared to those patients with chronic HCV mono-infection or those patients with concomitant *Brucella spp* and chronic HCV infections.

Table 4 Liver & kidney function findings of different groups

	Study population		
	Group I (HCV)	Group II (HCV+ *Salmonella*)	Group III (HCV+ *Brucella*)
Creatinine (mg/dl)	0.74±0.01	0.73±0.02	0.67±0.07
Direct-Bil (g/dl)	0.39±0.04	0.37±0.06	0.50±0.30
T-Bil (mg/dl)	1.01±0.06	1.01±0.11	1.23±0.49
Albumin(g/dl)	3.94±0.04	3.99±0.07	4.16±0.49
ALT (U/L)	61.88±4.20	78.78±9.55*	49.67±10.27
AST (U/L)	55.58±3.66	71.46±7.87*	53.00±17.61

Data are expressed as: mean ± standard error (STE). *$p<0.05$ indicate significant difference compared to patients with chronic HCV mono-infection.

No significant differences were determined on the levels of albumin, total bilirubin, direct bilirubin or creatinine (Table 4). On the level of hematological findings, significant increase ($p < 0.05$) was detected at the level of the relative lymphocyte countin patients with concomitant *Salmonella typhi* and chronic HCV infections compared to those patients with chronic HCV mono-infection or those patients with concomitant *Brucella spp* and chronic HCV infections. No significant changes were demonstrated on the levels of the other examined hematological parameters (Table 5).

Table 5 Hematological findings of different groups

	Study population		
	Group I (HCV)	Group II (HCV+ *Salmonella*)	Group III (HCV+ *Brucella*)
RBCs $\times 10^6$	4.83±0.09	4.82±0.15	4.43±0.39
PCV (%)	41.35±0.39	41.56±0.01	38.67±0.01
Hb (g/dl)	13.63±0.15	13.59±0.28	12.43±0.59
MCV (%)	83.69±0.55	84.74±0.97	83.07±4.94
MCH (%)	27.64±0.26	27.78±0.48	27.43±1.56
MCHC (%)	32.99±0.18	32.74±0.31	32.77±0.30
Platelets $\times 10^3$	185.31±7.38	173.4±12.06	174.67±54.67
WBCs $\times 10^3$	6.62±0.19	6.47±0.29	5.57±0.59
Lym (%)	36.97±0.01	40.73±0.02*	37.67±0.01
Mon (%)	10.96±0.003	11.24±0.01	8.67±0.01
Neu (%)	51.40±0.01	48.27±0.01	53.67±0.01

Data are expressed as: mean ± standard error (STE). *$p<0.05$ indicate significant difference compared to patients with chronic HCV mono-infection.

DISCUSSION

Salmonella typhi and *Brucella spp* prevalence in 185 HCV infected patients from Kafr-elshikh and Gharbiya provinces were serologically determined. *Salmonella typhi* and *Brucella spp* prevalence was 22.16%, and 1.62%, respectively. According to the province, no significant differences were detected among HCV infected patients. *Salmonella typhi* or *Brucellaspp* co-existence with HCV have been previously recorded (Bashir *et al*., 2005; Abou El Azm *et al*., 2013). Bashir *et al*. (2005) detected observable *Salmonella typhi* positivity 33.8%, 7.7% and 3.1% using serology, PCR and blood culture, respectively, among HCV patients from Pakistan with history of blood contact. The previous report detected 35%, 12.5% and 7.5% *Salmonella typhi* positivity among HCV patients without a history of blood contact using serology, PCR and blood culture, respectively (Bashir *et al*., 2005). Higher prevalence 13.3% was recorded for *Brucella* and HCV co-infection among Egyptian patients in the period from November 2008 to December 2011 (Abou El Azm *et al*., 2013). Moreover, *Brucella* and hepatitis A or hepatitis D virus co-infection was demonstrated in Turkey (Bektaş *et al*., 2014; Suvak *et al*., 2017).

In the current study, the prevalence of *Brucella spp* was increased amongurban area residents without significant difference. In contrast, higher prevalence of *Salmonella typhi* was significantly detected among rural area residents. In regard to gender and age, no significant difference was detected in the prevalence of *Salmonella typhi* or *Brucella spp* among chronically HCVinfected patients. Previous studies observed higher prevalence of *Salmonella typhi* more than 80% in rural and semi-urban communities in Nigeria and Bangladesh (Rahman *et al*., 2011; Umegbolu, 2017). Makita *et al*., (2010) reported that the risk of purchasing raw milk infected with *Brucella* in urban areas was the main reason of infection. Although previous studies have been considered the

age as the main risk factor for *Salmonella* and *Brucella* infection, these studies come in agreement with the current study on the level of gender as a non-significant risk factor for these bacterial infections (Al-Sekait, 2000;Younus *et al*., 2006; Malaeb *et al*., 2016).

Although, model for end-stage liver disease (MELD) scores of the cirrhotic patients infected with hepatitis D virus was associated with active *Brucella* infection (Suvak *et al*., 2017), the current study, did not detect any relation between *Brucella* infection and liver cirrhosis among HCV patients. This observation might be rendered to the low prevalence of *Brucella* among HCV infected patients. On the other hand, this study demonstrated a higher percentage of liver cirrhosis at patient with co-infection of *Salmonella typhi* and chronic HCV infected patients than those with chronic HCV mono-infection. No significant difference was detected at the level of HCV RNA load dual infection of *Salmonella typhi* or *Brucella spp* and chronic HCV compared to patients with chronic HCV mono-infection. Previous study demonstrated that hepatic failure was associated with *Salmonella* infection (Khan *et al*., 2006). Moreover, non-typhoid *Salmonella* were detected in patients with advanced stage of liver cirrhosis (Hsu *et al*., 2005; Lin *et al*., 2016).

While other studies, comes into disagreement about ALT and AST levels during *Brucella* infection (Ozturk-Engin *et al*., 2014; Denk and Ozden 2015; Erdem *et al*., 2017), the current study did not record any significant difference in patients co-infected with *Brucella spp* and HCV when compared to HCV mono-infected patients. In contrast, the current study detected a significant increase in the level of ALT and AST in patients with dual infection of *Salmonella typhi* and chronic HCV compared to patients with chronic HCV mono-infection.The association between *Salmonella typhi* infection and abnormal liver function tests such as ALT and AST was recorded (Arif *et al*., 1990; Albayrak *et al*., 2011). Moreover, previous studies detected higher activities of AST and ALT during chronic HCV infection (Herrine 2002, Missiha *et al*. 2008). The recorded higher serum ALT and AST levels in *Salmonella typhi* and HCV co-infected patients when compared to the HCV mono-infected patients suggested a synergistic effect of *Salmonella typhi* co-infection on liver tissue injury. In the present study, a significant increase in the level of the relative lymphocyte counts was detected in patients with dual infection of *Salmonella typhi* and chronic HCV compared to patients with chronic HCV mono-infection. Several studies demonstrated that the lymphocyte counts were significantly increased in *Salmonella typhi*-infected patients compared to those in *Salmonella typhi*-negative patients (Giri, 1993; Ifeanyi, 2014; de Jong *et al*., 2017).

In conclusion, the present study indicated that *Salmonella typhi* and *Brucella spp* infection is common among HCV patients in Egypt. Regular screening for *Salmonella typhi* and *Brucella spp* among HCV patients is highly recommended. Treatment and prevention of such kinds of bacterial infection are necessary in endemic countries.

Conflict of interest

The authors declare that they have no competing interests.

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