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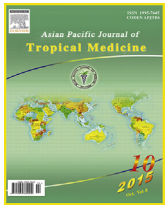

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Is toxoplasmosis a potential risk factor for liver cirrhosis?

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ABSTRACT

Objective: To document *Toxoplasma gondii* (*T. gondii*) antibody status in patients with liver disease, blood samples were taken from 180 hepatic patients and 180 healthy controls.

Methods: *Toxoplasma* IgG antibody was detected using enzyme-linked immunosorbent assay and histopathological assessment of liver biopsy METAVIR score was applied.

Results: Anti-*T. gondii* IgG antibodies were found in 32.8% of patients and in 22.2% of controls (P = 0.02). *Toxoplasma* seropositivity was significantly associated with lymphadenopathy, history of blood transfusion and reflex impairment in patients. Chronic hepatitis C virus (HCV) and chronic HCV-related cirrhosis groups compared to chronic HBV and chronic HBV-related cirrhosis groups expressed significantly higher prevalence of *T. gondii* seropositivity (odds ratio (OR) = 4; 95% confidence interval (CI): 1.3–12.6; P = 0.013, OR = 4.8; 95% CI: 1.5–14.9; P = 0.006, respectively). Within the chronic HCV group, *T. gondii* seropositivity significantly associated disease evolution as regards to METAVIR histopathological system for fibrosis and inflammation (OR = 19.4; 95% CI: 2.3–165.2; P = 0.0008, OR = 0.29; 95% CI: 0.1–0.8; P = 0.01, respectively). Albumin, international normalized ratio (INR) and platelets count were the laboratory parameters significantly altered in *Toxoplasma*-positive chronic HCV patients (P = 0.001, 0.03, 0.04, respectively). Child-Pugh scoring for cirrhosis in chronic HCV group placed the majority of seropositive patient in class C with significant statistical difference compared to Child A reference group (OR = 0.08; 95% CI: 0.01–0.5; P = 0.003).

Conclusions: *Toxoplasma* seropositivity was high in patients with cirrhosis and associated higher grades of inflammation and necrosis signifying disease evolution, suggesting that cirrhotic patients may thus form a risk group for toxoplasmosis.

1. Introduction

Toxoplasmosis is a parasitic zoonosis with the highest human incidence [1]. Seroprevalence of *Toxoplasma* infection among immunocompromised patients is high and reactivation of latent infections in them can be life-threatening [2]. During chronic toxoplasmosis, both $CD4^+$ and $CD8^+$ T lymphocytes are required to prevent reactivation of toxoplasmosis. Thus, depletion of T cells in the setting of chronic infection as in depressed cellular immunity states, leads to reactivation of latent infection [3]. Cirrhosis is considered an immunocompromised state that leads to a variety of infections, which then account for an approximate 30% mortality [4].

Hepatic involvement in toxoplasmosis does exist but it may go unnoticed as infection spreads to the liver early in course of infection and may not induce laboratory or clinical alterations [5]. Granulomatous hepatitis [5], hepatomegaly, abnormal liver function tests [6], cholestatic jaundice [7], cirrhosis [8] as well as liver dysfunction in liver and kidney transplant recipients [9] are the usually reported consequences. Hepatitis in *Toxoplasma* infection varies between 11% and 89% depending on the virulence of the strain [10].

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are hepatotropic viruses affecting about 600 million individuals

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worldwide. Severe liver diseases, such as liver cirrhosis and hepatocellular carcinoma are usual consequences of chronic infections resulting in 1 million deaths per year [11]. *Toxoplasma* and hepatitis viruses are intracellular pathogens that both stimulate polarised immune responses involving Th1 cytokine profiles (pro-inflammatory mediators) such as IL-12, IFN-γ and nitric oxide [12]. In developing countries, co-infection by more than one pathogen is widespread and it remains an underestimated risk factor for infection although it can play a critical role in the infection outcome via effects on the host immune response or by inducing changes in host physiology [13].

Globally, the prevalence of latent *Toxoplasma* infection among patients with hepatitis B and C viruses as well as cirrhotic patients has not been extensively investigated, and the effect of co-infections with these pathogens on the progression of liver disease needs to be clarified especially in Egypt where all of these pathogens are reported with high prevalence rates. The paucity of information motivated us to undertake this study to determine the prevalence of latent *Toxoplasma* infection among chronic viral hepatitis as well as cirrhotic patients compared to controls not complaining of liver disease and to explore the effects of co-infection on the course of liver disease within these patient groups.

2. Materials and methods

2.1. Participants

A comparative cross-sectional study was performed at Mansoura University Hospital, Egypt, during the period May 2013 and January 2014. One hundred and eighty patients with chronic HCV or chronic HBV, who attended the Tropical Medicine Department [67 females and 113 males, with mean age ±SD of (50.14 ± 12.60) years], participated in the study. Exclusion criteria included patients with schistosomiasis, heart failure, diabetes mellitus, hypertension, hyperlipidemia, peripheral vascular disease, hematological and neoplastic disorders. None of patients had received anticoagulant medications, non-steroidal anti-inflammatory drugs or oral contraceptive drugs before hospital admission. Patient groups were matched regarding age, gender and residence with 180 healthy controls [70 females and 110 males with mean age ± SD of (48.0 ± 7.5) years].

Patients were divided into 4 groups: Group I;: chronic HCV (n = 75 patients); Group II: chronic HCV-related cirrhosis (n = 45 patients); Group III: chronic HBV (n = 36 patients); Group IV: chronic HBV-related cirrhosis (n = 24 patients).

2.2. Ethical aspects

This study was approved by the Ethical Committee of Mansoura University. All participants were acquainted with the study and gave informed consent to participate in it after fully explaining the aim of the study to them. The study was conducted in accordance with the guidelines of the Helsinki Declaration.

2.3. Laboratory tests

Five mL of venous blood were withdrawn from patients and control participants and were divided into 3 aliquots: the first aliquot was used for liver function tests [ALT, AST, ALP, serum albumin, bilirubin, international normalized ratio (INR)], CBC and indirect haemagglutination test (IHA) for schistosomiasis to detect prior schistosomal infection, while the second was used for serum HBV surface antigen (HBs Ag) and HCV detection by PCR, and the third was analyzed for anti-*Toxoplasma* IgG antibody detection, using commercial *Toxoplama* IgG detection kit (DS-EIA-Anti-Toxo-G-Fast, DSI, Italy).

For *Toxoplasma* antibody testing, blood samples were processed immediately by centrifugation at 4000 rpm for 5 min after which they were kept at −20 °C until analysis. Anti-*Toxoplasma gondii* (*T. gondii*) IgG antibody levels were expressed as international units (IU)/mL, and a result greater than 15.95 IU/mL was considered positive. All tests were performed following the instructions of the manufacturer.

2.4. Histopathology of percutaneous ultrasound guided liver biopsy

Liver biopsies were analysed after paraffin embedding. Five μm sections were obtained from chronic HCV group, for hematoxylin and eosin (H&E) and Masson's trichrome staining. Each liver tissue sample was diagnosed on the basis of the presence of at least 10 complete portal tracts, which has long been considered the ‘gold standard’ to determine liver histology, disease activity and liver fibrosis [14]. The degree of histologic hepatic fibrosis and inflammation was scored using the METAVIR scoring system [15]. Based on the degree of lymphocyte infiltration and hepatocyte necrosis, the level of inflammation was classified from A0 to A3, with a higher score indicating more severe inflammation. Fibrosis was graded from F0 to F4 as follows: F0: no fibrosis, F1: portal fibrosis without septa, F2: portal fibrosis with rare septa, F3: numerous septa without cirrhosis, and F4: cirrhosis. Steatosis was quantified as the percentage of hepatocytes that contained fat droplets and classified into three groups: <5%, 5%–30% and >30% [16]. Liver biopsy was assessed by a pathologist blinded to clinical and laboratory data. All demographic and laboratory data were collected at the time of the liver biopsy.

2.5. Statistical analysis

To test for normal distribution, frequency of data was plotted against normal distribution curve. All data were parametric as most of the quantitative data showed normal distribution using Kolmogrov–smirnov test to test for normality. Frequency, mean, standard deviation were used to describe data. *Chi*-square test was used to test for association between *Toxoplasma* infection and sociodemographic and clinical characteristics. A student's t-test was used to compare the means between groups. A P value < 0.05 was considered statistically significant. These tests were run on an IBM compatible personal computer using the Statistical Package for Social Scientists for windows Ver. 20 (SPSS Inc., Chicago, IL, USA).

3. Results

Anti-*T. gondii* IgG antibodies were found in 59 (32.8%) of 180 patients and in 40 (22.2%) of 180 controls (P = 0.02). Of the anti-*T. gondii* IgG positive patients, 23 (39%) had IgG levels

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