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Asian Pacific Journal of Tropical Disease

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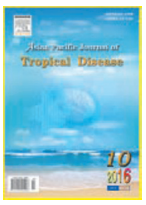

Parasitological research doi: 10.1016/S2222-1808(16)61133-7

The current status of *Toxoplasma gondii* infection among Egyptian rheumatoid arthritis patients

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ARTICLE INFO

Article history:
Received 25 Aug 2016
Received in revised form 31 Aug 2016
Accepted
Available online

Keywords:
Toxoplasma gondii
Autoimmune diseases
Rheumatoid arthritis
ELISA

ABSTRACT

Objective: To ascertain a relationship between *Toxoplasma gondii* (*T. gondii*) infection and rheumatoid arthritis (RA) disease among Egyptian patients.

Methods: One hundred RA patients and 50 healthy subjects participated in this study. The patients were classified into three groups, namely GI, G2 and G3. Patients in G1 were recently diagnosed with RA with the disease duration of less than one year (prior treatment); G2 included RA patients receiving anti-tumor necrosis factor agents and RA patients in G3 received disease modifying anti-rheumatic drugs (methotrexate, antimalarial, corticosteroids). Serum samples of all participants were examined for the presence of anti-*Toxoplasma* immunoglobulin G *(*IgG) antibodies and positive samples were further analyzed for anti-*Toxoplasma* IgM antibodies to detect the possibility of reactivation of latent toxoplasmosis. Also, the association between *Toxoplasma* seropositivity and clinical, laboratory and radiological features of these patients were determined.

Results: There was a significantly higher percentage of *T. gondii* IgG positivity in RA patients (54%) than in the controls (32%). At the same time, 20.40% of *T. gondii* IgG positive patients had anti-*T. gondii* IgM antibodies with a statistically significant difference as comparing to *T. gondii* IgG positive controls. Out of *T. gondii* seropositive patients, 20.37% had a lower IgG level with a mean titer of (65.3 ± 17.7) IU/mL, 46.29% had moderate level with a mean titer of (184.2 ± 60.0) IU/mL and 33.33% had higher level with a mean titer of (404.3 ± 50.0) IU/mL. A positive correlation was found between disease activity and *Toxoplasma* seropositivity. *T. gondii* seropositive RA patients had longer disease duration, longer time morning stiffness, higher numbers of tender and swollen joints and also increase in disease severity markers (erythrocyte sedimentation rate, C-reactive protein, disease activity score 28, anti-cyclic citrullinated peptide anti-bodies, rheumatoid factor) than *T. gondii* seronegative patients. As regards radiological findings, Larsen score was found significantly higher in *T. gondii* seropositive RA patients.

Conclusions: The positive correlation between *T. gondii* infection and RA disease among Egyptian patients indicated the need to improve awareness of this parasitic infection and its management in this risk group.

1. Introduction

Toxoplasmosis is a parasitic disease caused by *Toxoplasma gondii* (*T. gondii*), an intracellular protozoan parasite. The infection is acquired by oral ingestion of the contaminated water or foods with *T. gondii* excreted in cat feces or undercooked meat containing tissue cysts. In addition, this infection can be transmitted through the placenta, organ transplantation and blood transfusion[1]. *T. gondii* infection in immunocompetent individuals is mostly asymptomatic or can be manifested as lymphadenopathy and is usually followed by a lifelong latent infection that may be reactivated as a result of immune disorders inducing serious complications[2]. The prevalence of latent toxoplasmosis ranges from 20% to 80% among different populations, which depends on various sociological and environmental factors including hygienic standards, living habits and the number of cats in the environment, moisture and latitude[3].

Rheumatoid arthritis (RA) is a complex autoimmune disease affecting 1%–2% of the general worldwide population and more prevalent in females at late childbearing years of age[4]. The

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The study protocol was performed according to the Helsinki declaration and approved by the Research Ethics Committee, Faculty of Medicine, Benha University, Egypt. Informed written consent was obtained from all participants.

The journal implements double-blind peer review practiced by specially invited international editorial board members.

etiopathogenesis of RA is multifactorial resulting from a complex interaction between genetic and environmental factors that can trigger the immune response[5]. This disease is characterized by an inflammatory synovitis, usually involving peripheral joints in a symmetric distribution causing cartilage damage, bone erosions and changes in joint integrity[6]. The patients may have a mild oligoarticular illness of brief duration with minimal joint damage. However, the most will progress to poly-arthritis with marked impairment[7].

The association between microbiological infections (bacterial, viral and parasite) and autoimmune disease has been shown in several studies. These infections are believed to act as triggers inducing or promoting autoimmune disease in genetically predisposed individuals by molecular mimicry, epitope spreading, or bystander activation[5,8,9]. Toxoplasmosis is considered as a major health problem in patients with systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis, autoimmune thyroid diseases and inflammatory bowel disease[10-12] and also its association with RA has been studied by several authors[7,8,13]. To ascertain a relationship between *T. gondii* infection and RA, this study was conducted to determine *T. gondii* positivity among Egyptian RA patients and its correlation with their clinical, laboratory and radiological findings.

2. Materials and methods

2.1. RA patients and controls

One hundred patients from the outpatient and inpatient clinics of the Rheumatology and Rehabilitation Department of Benha University Hospitals during the period from June 2015 to May 2016 were enrolled in this study. Seventy patients were female and thirty were male. The ages of the patients ranged form 30 to 58 years with a mean age of (43.1 ± 4.8) years. All of them were subjected to full history taking, clinical examination and they met the classification criteria of the American College of Rheumatology/European League against Rheumatism for RA classification[14]. The patients were divided into three groups, G1, G2 and G3. G1 included 25 recently diagnosed RA patients with disease duration of less than one year (prior treatment). G2 included 25 RA patients receiving anti-tumor necrosis factor (TNF) agents (infliximab, etanercept and adalimumab) and G3 was formed by 50 RA patients receiving disease modifying anti-rheumatic drugs (DMARDS), methotrexate, antimalarial, corticosteroids.

Fifty control subjects from the general population of Benha City, Egypt were also enrolled in the study. They were 34 females and 16 males with a mean age of (40.3 ± 1.9) years (ranged from 29–57 years) and and were compatible with both sex and age of patients ($P > 0.5$).

2.2. Investigations

2.2.1. Laboratory investigations

All patients were investigated for erythrocyte sedimentation rate (ESR) by Westergren method[15], C-reactive protein (CRP) and rheumatoid factor (RF) by latex agglutination tests (Leaner Chemicals Co., Spain), anti-cyclic citrullinated peptide antibodies (anti-CCP) by ELISA (Euro Diagnostica, Co., Sweden).

2.2.2. Assessment of the disease activity score 28 (DAS28)

DAS28 is an index calculated after the examination of 28 swollen and tender joints involving hands, arms and knees. The DAS28 ranges from 1 to 9 where a low score (< 3.2) indicates a low disease activity, a moderate score (3.2–5.1) indicates moderate disease activity and a high score (> 5.1) indicates high disease activity[16].

2.2.3. Radiological examination

Plain X-ray (P–A views) on hands, wrists and feet were obtained and scored by Larsen score[17] that was applied for proximal interphalangeal joints (2–5), metacarpophalangeal joints (2–5) in each hand, four quadrants in both wrists and metatarso-phalangeal joints (2–5) in each foot. The grading scale ranged from 0 to 5 where 0 was intact bony outlines and normal joint space, 1 was erosion (diameter < 1 mm), 2 referred to one or several small erosions (diameter > 1 mm); 3 indicated marked erosion, 4 was severe erosion (usually no joint space left and the original bony outlines were only partly preserved) and 5 was mutilating changes (the original bony outlines have been destroyed). Then, the score was summed up giving a maximum score of 160 when all joints were fully destroyed.

2.2.4. Determination of the anti-T. gondii antibodies positivity

Serum samples of all participants were analyzed for anti-*Toxoplasma* IgG antibodies using commercially enzyme immunoassay, *Toxoplasma* IgG kit, (DRG International Inc., USA). Anti-*T. gondii* IgG antibody levels were expressed as IU/mL, and a result equal or greater than 32 IU/mL was considered positive. Low IgG antibody level was less than 100 IU/mL, moderate level was 100–300 IU/mL while the high level was more than 300 IU/mL. Additionally, positive samples for anti-*T. gondii* IgG antibodies were further analyzed for anti-*T.gondii* immunoglobulin M (IgM) antibodies by the commercially enzyme immunoassay, *Toxoplasma* IgM kit, (DRG International Inc., USA). The tests were performed following the manufacturer's instructions.

2.3. Statistical analysis

Statistical analysis was carried out by SPSS software (statistical package for social science) (version 16, SPSS, Inc., USA). Qualitative data were expressed in numbers and percents and quantitative data were expressed as mean and standard deviation. The collected data were analyzed using *Chi*-square test, and student's *t*-test for significance differences. $P < 0.05$ was considered statistically significant.

2.4. Ethical considerations

The study was approved by the Research Ethics Committee,