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Short Communication

Development of Rheumatoid Arthritis by Toxoplasmosis in Iranian Patients

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ABSTRACT

Background: *Toxoplasma gondii* (*T. gondii*) is an intracellular protozoan parasite capable of infecting approximately one-third of the world human population. In this study, the seroprevalence of *Toxoplasma gondii (T. gondii)* antibodies in Iranian patients with rheumatoid arthritis was investigated, given the lack of information on the magnitude of toxoplasmosis in these patients.

Methods: The serum was collected from patients with rheumatoid arthritis (n = 93) and a healthy control group (n = 93) from central parts of Iran to investigate the prevalence of anti-*T. gondii* IgG and IgM antibodies.

Results: Anti-*T. gondii* IgG was detected among 76 of 93 patients with rheumatoid arthritis (81.72%) versus 37 of 93 healthy control group (39.80%), and it was higher among patients with rheumatoid arthritis than controls. The seroprevalence of anti-*T. gondii* IgM was significantly higher in patients with rheumatoid arthritis (36 of 93; 38.70%) compared to the healthy control group (2 of 93; 2.1%). Demographic variables (age and sex) did not have significant correlations in patients with rheumatoid arthritis who were positive for *T. gondii* infection.

Conclusion: The findings of the present study provide efficient evidence that confirm the association between toxoplasmosis and development of rheumatoid arthritis, suggesting that *Toxoplasma* may contribute to the rheumatoid arthritis pathogenesis.

Keywords: *Toxoplasma gondii*, Autoimmunity, Rheumatoid arthritis, Iran, Immune system

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Introduction

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan parasite capable of infecting approximately one-third of the world human population and a wide range of warm-blooded animals (1-3). In the human population, the infection has a worldwide distribution, and its seroprevalence can vary depending on geographical and socioeconomic conditions such as health-related practices, kitchen habits, and host susceptibility (4-6). In the life cycle of these pathogens, tachyzoites are responsible for the acute phase and clinical manifestations of toxoplasmosis, while bradyzoites cause the chronic phase of the disease (7-9). *T. gondii* is capable of causing long-term chronic infection in the host. In 80% of the cases, toxoplasmosis is asymptomatic or show mild symptoms such as fever or transient lymphadenopathy (10). Whereas, in immunocompromised or immunodeficient individuals, toxoplasmosis symptoms are severe and life-threatening (11). Toxoplasmosis can be diagnosed by detecting the parasite in biological samples, detecting specific antibodies, or performing molecular tests (12-14). Treatment of this infection remains problematic as many drugs may produce severe side effects, besides, there is a possibility of relapse at any time of disease (15). Currently, no effective human vaccine against *T. gondii* has yet been developed (16).

Systemic rheumatoid diseases are a series of autoimmune disorders that mainly affect the joints and connective tissue. However, other tissues and organs such as arteries, kidneys, skin, brain, etc. may also be affected. The prototype of these diseases is Lupus, a systemic and severe disorder. Other diseases in this group include rheumatoid arthritis (RA), Sjogren's syndrome, systemic sclerosis, and mixed connective tissue disease (MCTD). The etiology of these diseases is not yet fully understood, but the role of genetics, infections, environmental factors, and hormones in the development of these disorders has been established (17, 18). The diagnosis of systemic RA is usually based on clinical and laboratory criteria. Laboratory diagnosis depends on the detection of specific autoantibodies in the serum of patients. These autoantibodies are usually produced during the pathogenesis process and their increase is an indicator of the presence, and in some cases, the severity of the disease (19, 20).

The cause of autoimmune diseases remains largely unclear, but some of the factors that cause these diseases include genetic abnormalities and infections (21). Infections have a known role in the development and progression of autoimmune diseases. Among them, the role of viruses and bacteria on the pathogenicity of autoimmune diseases has been substantially proven in recent years (22-24). Parasitic infections have various effects on the immune system and can modulate it or control autoimmune diseases. These factors may also underlie clinical manifestations in some rheumatoid conditions. *T. gondii* is a widespread parasite and has recently been shown to be associated with autoimmunity (25, 26). Despite the evidence for the role of helminth infections and some protozoa, such as *Trypanosoma cruzi* in autoimmunity development, the association between parasitic infections and autoimmune diseases remains largely unclear. In particular, there is limited information on the effects of *T. gondii* on autoimmune diseases (19, 20, 27, 28). Primary or secondary infection with *T. gondii* may alter the immune response to autoimmune diseases (29). On the other hand, the prevalence of toxoplasmosis in patients with systemic RA in Iran has not been studied until the time of writing of this article. In this case-control study, the serological evidence of *T. gondii* in patients with RA and healthy controls was investigated to determine the relationship between *T. gondii* infection and RA.

Materials and Methods

Study population and sample collection

The subjects of this case-control study included 93 patients who referred from several autoimmune diseases centers in the central parts of Iran including Isfahan, Yazd, Chaharmahal and Bakhtiari, and Kohgiluyeh and Boyer-Ahmad provinces from September 2018 to June 2019. Also, 93 volunteers were selected and evaluated as the healthy control group in the same socioeconomic status with the patient group. Patients and control subjects were from the same geographical area. The control group was selected from the subjects who did not have any complaint and disease when they came for a routine checkup. Data related to the prevalence of toxoplasmosis including patient's residence, educational level, contact with animals or who had jobs involving them, and keeping of house cats, were collected through a predesigned questionnaire. All personal data of patients were recorded (Table 1). Informed satisfaction was obtained from the participants and the confidentiality of the participants' information was assured.

Table 1. Demographic characteristics of patients with rheumatoid arthritis as the case group and healthy control group and seroprevalence of *Toxoplasma gondii* infection

Variables	Patients with Arthritis (n = 93)						Control Subjects (n=93)					
	IgG			IgM			IgG			IgM		
	No. Tested	No. Positive (%)	P-value	No. Tested	No. Positive (%)	P-value	No. Tested	No. Positive (%)	P-value	No. Tested	No. Positive (%)	P-value
Age group (years)			0.46			0.13			0.72			0.59
<20	3	2 (2.6)		3	3 (8.33)		5	3 (6.5)		5	1 (50.0)	
21-30	17	13 (17.1)		17	6 (16.7)		9	2 (4.3)		9	0 (0.00)	
31-40	38	31 (40.8)		38	15 (41.7)		22	12 (26.1)		22	0 (0.00)	
41-50	13	12 (15.8)		13	4 (11.1)		17	8 (17.4)		17	0 (0.00)	
51-60	17	14 (18.4)		17	7 (19.4)		18	11 (24.0)		18	0 (0.00)	
>60	5	4 (5.3)		5	1 (2.8)		22	10 (21.8)		22	1 (50.0)	
Gender			0.80			0.40			0.56			0.59
Male	18	14 (18.4)		18	9 (25)		12	5 (10.9)		12	0 (0.00)	
Female	75	62 (81.6)		75	27 (75)		81	41 (89.1)		81	2 (100)	
Total	93	76 (81.7)		93	36 (38.7)		93	46 (48.4)		93	2 (2.1)	

$P < 0.05$ was considered statistically significant.

Serological evaluation for arthritis

Blood samples (5 ml) were taken from each subject, and sera were obtained from the collected blood. All patients were examined for reactive arthritis by serological tests. Based on the American College of Rheumatology (ACR, 2010), reactive arthritis was diagnosed by serologic tests for infection agents, C-reactive protein (CRP), and rheumatoid factor (RF) using latex agglutination tests. Also, erythrocyte sedimentation rate (ESR), complete blood count (CBC), and anti-cyclic citrullinated peptide antibodies (anti-CCP) were measured using ELISA method in this experiment (Axis Shield Diagnostics, Dundee, UK). To detect the antinuclear antibody (ANA), indirect immunofluorescence technique on HEp-2 cells ANA kit (Euroimmune AG Company, Germany) was applied (17). All tests were performed according to the kit manufacturers' instructions.

Determination of anti-*T. gondii* antibodies positivity

To determine the anti-*T. gondii* antibodies, the rest serum samples were transported to the Department of Parasitology and Mycology, Iran University of Medical Sciences (Tehran, Iran) and stored in aliquots frozen at -20°C until further analysis and screening for toxoplasmosis. The obtained sera were tested for IgG and IgM Anti-*T. gondii* antibodies using a commercial ELISA kit (Vircell, Granada, Spain), according to the manufacturers' instructions. The results were considered positive when the OD = 450 index was equal or higher than the cut-off value in ELISA.

Statistical analysis

SPSS software version 19 (SPSS Inc., Chicago, IL) was used for statistical analysis. A descriptive analysis was performed to evaluate the frequency of the variables and *T. gondii* antibodies. The data were statistically analyzed using Chi-square and student's t-tests for significance differences. In the present experiment, $P < 0.05$ was considered statistically significant.

Results

A total of 186 individuals (93 patients with RA and 93 healthy controls) were tested for anti-*T. gondii* IgG and IgM antibodies from September 2018 to June 2019. Out of 93 patients

with RA, 76 patients (81.72%) were detected positive for anti-*T. gondii* IgG antibodies, and also, 37 of 93 healthy controls (39.80%) were found positive for this antibody; as a result, a significant difference was seen between these two cases and healthy controls (P = 0.001). Regarding anti-*T. gondii* IgM antibodies, 36 patients with RA (38.70%) and 2 healthy controls (2.1%) were positive; thus, a statistically significant difference was seen between the study groups (P = 0.001). The details of both patients with RA and healthy controls, including age distribution and sex are illustrated in Table 1.

Patients with RA who were seropositive for anti-*T. gondii* antibodies were found to have higher disease severity variables including CRP (30.2 mg/L), anti-CCP (501 U/ml), ESR (41 mm/h), and RF (249 U/ml). In contrast, patients with RA seronegative had lower disease severity variables of CRP (20.1 mg/L), anti-CCP (299.8 U/ml), ESR (33 mm/h), and RF (199 U/ml). The mean age of RA patients with anti-*T. gondii* IgG and IgM antibodies was 38.12 years (± 13.37). Conversely, the mean age of healthy controls was 45.47 years (±15.50).

The results showed no significant differences between male (n = 14; 18.4%) and female (n = 62; 81.6%) in patients with RA who were positive for *T. gondii* infection (P = 0.709). Besides, no statistically significant relationship was found between being infected by *Toxoplasma* and any of the study tested variables (sex and age). The findings also showed the highest seroprevalence in people aged 31-40 years and the lowest one in those with an age under 20 years, but there were no statistically significant differences among distinct age groups (IgG: P = 0.462; IgM: P = 0.13) (Table 1).

Discussion

Rheumatoid arthritis (RA) is one of the major autoimmune diseases with unclear etiology which is likely to tangle the intricate interaction between both genes and the environment (25). The association between infectious diseases such as parasitic infections and RA remains unclear despite growing evidence on the role of protozoan parasites like *Trypanosoma* spp. or helminths (27). Especially, there is a very limited registered document on the distinct effects of *T. gondii* on arthritis. Since *T. gondii* infection is progressively being reported in individuals with RA, but its epidemiology and impact have been unclear. In the present study, it was speculated that anti-*T. gondii* IgG and IgM antibodies have an essential role as a major cofactor in the setting of human autoimmune inflammatory disease such as RA. The presence of chronic or acute *T. gondii* infection is characterized by the presence of positive IgG and IgM antibodies, respectively. Therefore, the prevalence of *T. gondii* infection in 93 patients with RA from central parts of Iran was investigated from September 2018 to June 2019. For this purpose, the serum level of anti-*T. gondii* antibodies (IgG and IgM) in patients with RA was quantified against an equal number of healthy controls. Here, a high level of anti-*T. gondii* IgG and IgM antibodies in patients with RA was found, which suggests the possible role of *T. gondii* infection in the pathogenesis of this autoimmune disease. The findings of the present study support the data of other studies that showed a high prevalence of anti-*T. gondii* IgG antibodies in patients with RA as well as other autoimmune diseases (25, 27). The correlation between toxoplasmosis and RA has been reported in other studies in Tunisia (58.4%), Iraq (54.0%), Egypt (54.0% and 76.7%), and Europe (63.0%) (20, 25, 30-32). The present study showed a high prevalence of anti-*T. gondii* IgM antibodies in patients with RA, which is not consistent with the results of studies by El-Henaw et al. (2017) and Tian et al. (2017) (31, 33) that reported no anti-*T.gondii* IgM in patients with RA (31, 33).

Moreover, distinct disease severity variables such as CRP, anti-CCP, ESR, and RF were analyzed in patients with RA who were seropositive for anti-*T. gondii* antibodies. The serum levels of disease severity variables (CRP, anti-CCP, ESR and RF) were high in anti-*T. gondii* IgG and IgM seropositive patients, but no significant differences were seen when compared to seronegative patients, suggesting the plausible role of *T. gondii* in acute or chronic inflammation, which is consistent with the results reported by Fischer et al. (2013) (25).

T. gondii infection triggers various pathological processes in different people, which can finally result in RA. Different hypotheses have been described the high prevalence of toxoplasmosis in individuals with chronic autoimmune diseases (23). On the other hand, *T. gondii* infection may be involved in the development of distinct chronic diseases. Immunosuppressive drugs that are used in the treatment of autoimmune diseases can increase the susceptibility of patients to several chronic

infections such as toxoplasmosis (4,23). Studies have shown that *T. gondii* infection is involved in autoimmunity as a hidden and potential element. For instance, toxoplasmosis in mice induced severe inflammation of small intestine which was similar to the chronic form of Crohn's disease, proposing the potential role of *T. gondii* infection in triggering various autoimmune bowel disorders (31, 34). Moreover, a study has shown the high seroprevalence of *T. gondii* infection in patients with Crohn's disease compared to the control group (35). Another example of the relationship between *Toxoplasma* and autoimmune diseases is *T. gondii*-induced retinitis, when autoantibodies production against retina was increased (36).

T. gondii parasite leads in an intense and persistent cellular response due to T-helper 1 (Th1), which is characterized by the induction of several pro-inflammatory cytokines including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-12 (IL-12) (20, 37). These immune system cytokines and various immunological mechanisms protect the infected host's cells against swift replication of parasite, and also, major pathological changes (20). An increased risk of toxoplasmosis in patients with RA maybe because of the intense immunological variation through adaptive cellular immunity, which is vital for the rapid control of intracellular parasites like *Toxoplasma* (33). Immunosuppressive therapies such as TNF-α inhibitors, which are utilized in the treatment of RA, induce reactivation of latent toxoplasmosis in patients with RA and intense its tendency to get new opportunistic infections (33). Moreover, studies have shown that IL-17 involved in RA pathogenesis (38). Surprisingly, in patients with toxoplasmosis, the level of IL-17 is significantly increased (39).

Another immune system mechanism that helps for autoimmune inflammation in *T. gondii* infection is the activation of toll-like receptors (TLRs), which results in the expansion of host autoantibodies. In mammals, a total of 13 TLRs has been found, which identify several classes of pathogens, and importantly, induce different types of host immune responses (25). By acting as a major ligand for TLRs, *Toxoplasma* could be involved in distinct inflammatory responses. The signaling pathway of TLR11 has been described as an essential factor in the recognition of intracellular pathogens like *Toxoplasma* parasite (25). Other studies have shown that TLR2, TLR4, and TLR9 acted major functions in the mammalian host defense against *Toxoplasma* tachyzoites via activation of glycosylphosphatidylinositol (GPI)-anchored proteins on the parasite surface (40-42). A study has shown that the highest levels of IL-33 were found in RA patients with *Toxoplasma* infection compared with control groups. IL-33 has pathogenic roles in possibly inflammatory conditions such as RA and other diseases (43).

Although there was no positive evidence of a statistically significant relationship between being infected by *Toxoplasma* and sex or age, the data of the present study demonstrated the highest seroprevalence in patients aged 31 to 40 years. Other age groups including young and elderly people may be more plausible to interact with a feline (cats) than individuals within other age groups, and importantly, they have no efficient immunity to suppress and control parasitic opportunistic infections like *T. gondii* (29, 33). Several experiments have shown a significant relationship between age and seropositivity of *Toxoplasma* reported in older patients with RA (25, 33). In the present study, no significant differences were seen between male and female, which is consistent with the results of other studies (25, 33).

Previous studies have found a statistically significant relationship between contact with felines/cats and *Toxoplasma* seropositivity. They showed that contacting or living with cats is directly associated with an increased risk of being infected by cats' *T. gondii* infection (44, 45). Cats are the major host of *Toxoplasma* parasite and can transmit toxoplasmosis to humans (33). In Iran, cats as a very popular domestic pet have received less attention in terms of their major role in the contamination of the various environments with parasite oocysts. It is crucial to inform the medical professionals and the general public about the importance of toxoplasmosis as a main risk factor in transmitting *T. gondii* infection to patients with different autoimmune diseases in particular RA.

Conclusion

According to the results, a high level of anti-*T. gondii* IgG and IgM antibodies was found for the first time in the sera of Iranian patients with rheumatoid arthritis, suggesting a possible association between opportunistic *T. gondii* infection and rheumatoid arthritis. *T. gondii* might deviate immune system responses leading to autoimmune diseases like rheumatoid arthritis. In other words, reduced host defense in

response to toxoplasmosis was accompanied by an increased risk of rheumatoid arthritis. Future large-scale studies are needed to confirm the findings of his study and precisely clarify the major role of *Toxoplasma* in rheumatoid arthritis. Importantly, patients with rheumatoid arthritis appear to be at a higher risk of *Toxoplasma* infection, therefore, an urgent need for regular screening and follow-up for this infection should be considered. Collectively, the results of this study should inform health policy makers on the possible risk of *Toxoplasma* infection in patients with rheumatoid arthritis.

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Conflict of interests

The authors declare that they have no competing interests.

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