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Original papers

Association of *Toxoplasma gondii* infection with cardiovascular diseases: a cross-sectional study among patients with heart failure diseases in Urmia, North-West of Iran

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ABSTRACT. Toxoplasmosis is a disease caused by the protozoan parasite *Toxoplasma gondii*. Infection with *T. gondii* is one of the most common parasitic diseases in humans and other warm-blooded animals with global distribution and generally, one-third of human populations are estimated to be contaminated with this parasite. The prevalence of infection varies according to age, geographical location and dietary habits. The socioeconomic losses caused by the disease can be costly for the community. Acquired toxoplasmosis is potentially associated with schizophrenia, Alzheimer's disease, driving accidents, self-injury and suicide. Also, unusual strains of parasite that are genetically different from the rest (atypical strains) are responsible for several cases of lethal acquired parasites in people with safe immunity, which highlights the potential danger of this parasite in public health. As there is no comprehensive study on the association between toxoplasmosis and cardiovascular diseases in Iran, therefore, current study aimed at assessing the relationship between cardiovascular disease and toxoplasmosis among cardiac patients at the Seyyed al-Shohada specialist Cardiology Centre, Urmia, Iran. This study investigated the seropositivity rate for anti-*Toxoplasma* IgG antibodies by ELISA in patients with cardiovascular diseases. So, 375 patients with cardiovascular diseases and 336 healthy volunteers were selected for this investigation. The seropositivity rate of anti-*Toxoplasma* IgG antibodies was significantly higher in cardiovascular patients (63.73%) than in healthy volunteers (37.64%) ($P<0.001$). Also, a positive association was observed between anti-*T. gondii* IgG antibody seropositivity and cat contact ($P\leq0.001$, OR: 5.178; 95% CI: 1.97–13.57), consumption of raw or undercooked meat ($P\leq0.001$, OR: 0.3; 95% CI: 0.15–0.61), and consumption of not boiled milk ($P\leq0.001$, OR: 0.26, 95% CI: 0.12–0.54). Our results indicate that *T. gondii* infection is associated with heart disease and suggest that heart disease might be related with a chronic infection. Risk factors associated with *T. gondii* exposure found in the present study may help design future prevention strategies against *T. gondii* infection.

Keywords: cardiovascular diseases, frequency, heart failure, toxoplasmosis

Introduction

Infection with *Toxoplasma gondii* is one of the most common parasitic diseases in humans and other warm-blooded animals with global spread [1,2]. This obligate intracellular parasite has an active form, tachyzoite, and two resistant forms, namely tissue cyst and oocyst [3]. In the life cycle of *T. gondii,* cat and other Felidae are definitive host, while birds, humans, and other mammals act as a non-sexual (intermediate) host [4–6]. Toxoplas - mosis has a global distribution and it is estimated

that one-third of human populations are infected with this parasite [7], varies from 30% to 50% in the Middle East [8]. The prevalence of infection can be influenced by age, geographical location, food habits, and economic and health conditions [9].

Extensive distribution of this parasite in the environment mainly results from the large number of intermediate hosts, the global abundance of cats as the definitive hosts, and diverse methods of parasite transmission including vertical transmission, oocyst-contaminated water and food, raw or crude meat containing live tissue cysts, organ transplants, and blood transfusion [10,11]. Mother's infection into the acute type, if occurred for the first time during the pregnancy, can cause the transmission of infection to the foetus [12]. In this case, the infection can be associated with a wide range of clinical signs, varying in severity, from asymptomatic infections to abortion or severe infections during infancy [11,13]. In acquired toxoplasmosis, symptoms of acute infection include high level of IgM antibody and positive IgG, as well as clinical symptoms. Increase in the antibody level for more than three weeks is also one of the symptoms of acute infection [14]. Acute stages typically involve various organs such as the brain, lymph nodes, liver, heart, and eyes [15]. In chronic infections, the level of IgG antibody is normally high, but the IgM has decreased to its normal level [11,16]. Latent toxoplasmosis can causes a variety of pathologies and has been linked to adverse effects on pregnancy [17]. Also, studies have affirmed that the contamination with *T. gondii* is a risk factor for schizophrenia [18] and personality profile is affected by latent toxoplasmosis [19].

Cardiovascular disease is the most common cause of mortality and responsible for about 30% of deaths worldwide [20]. Coronary artery disease is known to be the deadliest cardiovascular disease accounting for more than 50% of heart deaths [21]. As fatal toxoplasmosis has been reported in liver and bone marrow, haematopoietic stem cell transplant recipients, it has been reported as a significant human pathogen for heart transplantation [22]. In this situation, *Toxoplasma* cysts may be activated after being transplanted to a host with the weakened immune system [23]. For instance, in a case of cardiac transplantation, a severe fever was observed a few days after the transplantation, and in the development of his peripheral blood, infected neutrophils and in various parts of his heart, severe infection with the tachyzoite form were observed [24]. In cardiac transplant recipients, the diagnosis of freshly synthesized IgG antibodies by Western blot is valuable in case of positive donors [25]. Studies have shown that patients with chronic cardiovascular disease are often exposed to opportunistic infections such as toxoplasmosis, due to general body weakness and immunocompromised state. In a 2016 study in Mexico, a significant relationship was found between toxoplasmosis and chronic cardiovascular disease [26].

Undoubtedly, the socioeconomic losses caused by this disease along with the transformations that this parasite cause in the human body can be costly for the community in comparison to other diseases. Many research works have been conducted on *Toxoplasma* in different parts of Iran [8,27–29], but no comprehensive study has investigated the association of this disease with cardiovascular disease in Iran. So, the current work was designed to determine the frequency of toxoplasmosis in patients with various types of cardiovascular diseases.

Materials and Methods

Samples collection. This descriptive cross-sectional study was conducted in Seyyed al-Shohada Hospital (Urmia, West Azerbaijan, Iran) from March to June 2018. The group of patients included those who diagnosed as having one of the following chronic heart diseases: coronary artery disease, arrhythmia, myocardial infarction, and heart failure. Individuals with infectious diseases or immune deficiency at the same time as heart disease disease (such as any diagnosed microbial or viral diseases like liver hepatitis, tissue transplant recipients who took immunosuppressive drugs, HIV-positive persons, chemotherapy patients and so on) were excluded. Also, in the control group, those with chronic heart disease were eliminated from the study. After receiving consents, patients (n=375) with heart problems were assigned as the case group, and healthy volunteers (n=336) without heart disease, who were age (mean: 62.44±13.37) and sex matched to cardiac patients, were considered as the control group. Blood samples of both groups (3 ml) were collected and the sera kept at –20°C for ELISA testing. A questionnaire was also completed by the participants, and its information was used in data analysis.

Antibodies assay. The ELISA technique was used to assay IgG antibodies against *T. gondii* by

Table 1. Frequencies of the participants' demographic features

Feature	Frequency		
	Patients group (N/%)	Control group (N/%)	Total (N/%)
Gender			
Female	166 (44.26)	170 (50.44)	336 (49.19)
Male	209 (55.74)	167 (49.56)	376 (52.81)
Residence			
Urban	193 (51.46)	258 (76.64)	451 (64.23)
Rural	182 (48.54)	79 (23.36)	261 (35.77)
Ethnicity			
Fars	2 (0.53)	20 (5.97)	22 (3.08)
Arab	0	0	0
Lor	0	0	0
Kord	97 (25.94)	096 (28.57)	193 (27.1)
Turk	274 (73.26)	196 (58.33)	470 (66.01)
Other	2 (0.53)	23 (6.86)	25 (3.51)

using the commercial ELISA kit (Pishtaz Teb Co., Tehran, Iran) based on the manufacturer's instructions.

Statistical analysis. The statistical analysis of the data was performed with the chi-square test using the SPSS v.25.0 for Windows. Statistical probability of $P<0.05$ was considered significant.

Results

In the present study, 375 patients in the cardiac patients group and 336 healthy people in the control group were enrolled. Demographic information of the participants, including gender, age, occupation, educational and residential status, consumption of undercooked meat, consumption of raw vegetable, and method of washing raw vegetables, were collected by interviewing. According to the questionnaire data, 166 (44.26%) of participants were female and 209 (55.74%) were male, 193 (51.46%) lived in village, and 182 (48.54%) lived in city (Table 1).

As shown in Table 2, about 239 out of 375 (63.73%) cases in the patient group and 127 out of 336 (37.64%) healthy volunteers (the control group) were found to be positive for *T. gondii*-specific IgG antibodies.

The percentage of anti-*T. gondii* IgG-positive individuals in the patient group with heart failure and heart diseases was observed to be significantly greater than that of healthy volunteers ($P<0.001$). In this study, we investigated the relationship of anti-*T. gondii* IgG antibody seropositivity with age and gender (Table 3) and some other risk factors, including residence (city or village), soil contact, cat contact, consumption of unwashed vegetables, type of drinking water consumed, history of allergy, special diseases, and blood transfusion. Our observations and the significance of each risk factor are illustrated in Table 4.

Discussion

Toxoplasmosis emerges as a life-threatening risk in situations of immunodeficiency [30,31]. However, very little information is available on the sero-epidemiology of *T. gondii* infection in patients with heart diseases. The present study was performed to investigate the association of *T. gondii* infection with patients suffering from heart diseases attending in a

Table 2. Analysis of anti-*Toxoplasma gondii* IgG antibodies in cardiac patients group and control group

	Patients' group N (%)	Healthy N (%)	Sig	OR	CI_{95}
IgG-positive	239/375 (63.73)	127/336 (37.79)	<0.001	2.91	2.14-3.94

Sig: significance; OR: odd ratio; CI_{95}: confidence interval.

Table 3. Distribution of latent toxoplasmosis according to age and gender in cardiac patients group and healthy controls

Gender	Patients group N (%)	Healthy N (%)	Sig	OR	CI_{95}
Male	134/209 (64.11)	66/167 (39.52)	<0.001	2.81	1.85-4.27
Female	105/166 (63.25)	62/170 (36.47)	<0.001	2.99	1.92-4.67

Sig: significance; OR: odd ratio; CI_{95}: confidence interval.

cardiovascular centre in Urmia City, Iran.

In this study, we found 63.73% seroprevalence of anti-*T. gondii* IgG antibodies in patients suffering from heart disease, while in controls, the seroprevalence was 37.64% (the seroprevalence of *T. gondii* infection in a general population in Urmia City has been reported to be 45.12% [32]. In line with these findings, Yazar et al. [31] have found that the seropositivity rate for anti-*Toxoplasma* IgG and IgM antibodies in patients with chronic heart failure was significantly greater than the healthy volunteers, i.e. 68% and 36%, respectively. These observations indicate that patients with heart diseases represent a risk group for *T. gondii* infection.

In searching the factors associated with *T. gondii* exposure in patients, we observed a positive association between seropositivity and soil contact (the test results were positive for 64.97% of people who came in contact with the soil while this rate was 40% in people without soil contact (P<0.001)), cat touch (66% among those who had a cat at home compared to 27.27% without contact with a cat (P<0.001)), consumption of raw or undercooked meat (the test results were positive for 82.81% of people who ate raw or undercooked meat while this rate was 59.8% in people who cooked the meat well and then consumed it (P<0.001)), and consumption of raw milk (85% among those with raw milk consumption compared to 59.68% among people who boil milk before consumption (P<0.001). In contrast, such association was not detected in residential area (urban or rural; P=0.4) and also in purified or unrefined drinking water (P=0.6). These two recent results were far from our expectation because we anticipated that the subjects with rural residence have behaviours that might favour *Toxoplasma gondii* exposure. However, some of these results agree with those obtained by Alvarado-Esquivel et al. [26]. In their case-control study, there was not any positive correlation between *T. gondii* infection and undercooked meat consumption among 400 patients suffering from heart diseases attending in a public hospital in Durango City, Mexico (P=0.13).

It is hypothesized that patients with *T. gondii* infection have a high risk for heart disease, which is caused by the presence of cysts in the heart muscle. The interaction of *T. gondii* within skeletal muscle cells has recently been described [33]. However, as far as our knowledge, the interaction of *T. gondii* within heart muscle cells has not been investigated, and in fact, it is still unclear that how *T. gondii* may affect the function of heart muscle [26]. The probability is that heart disease is related with a chronic infection with *T. gondii*. Other possible reason can be that with increasing age and consequently reducing muscle powers and catching diseases such as high blood pressure, diabetes, etc., heart muscles of individuals with *Toxoplasma* tissue cysts can more prone to cardiovascular problems compared to those with negative antibody levels for *T. gondii*.

Given that there were only a limited number of each type of heart disease among our participants, it was difficult to determine the seroprevalence of toxoplasmosis among any type of heart failures and the influences of parasite on the function of heart cells.

Our results indicate that *Toxoplasma gondii* infection is associated with heart disease and suggest that heart disease might be related with a chronic infection. The results warrant for further research to determine the epidemiological impact of *T. gondii* exposure on heart diseases. The association of *T. gondii* infection with alcohol consumption deserves further research. Risk factors associated with *T. gondii* exposure found in the present study may help design future prevention strategies against *T. gondii* infection.

Ethical issues. The study was approved by the Ethics Committee of Urmia University of Medical Sciences, Urmia, Iran (IR.UMSU.REC.1396.362),

Conflict of interest statement. Authors declare that they have no conflict of interest.

Table 4. Sociodemographic and risk factors associated with *Toxoplasma gondii* seropositivity in cardiac patients' group and healthy controls

Characteristic	Cardiac patients (N= 375)					Controls (N = 336)					Total (N = 711)				
	number tested (%)	number positive (%)	OR	CI	*P* value	number tested (%)	number positive (%)	OR	CI	*P* value	number tested (%)	number positive (%)	OR	CI	*P* value
Residence area															
Urban	193 (51.4)	124 (64.24)	1.04	0.68-1.59	0.4	267 (79.22)	96 (37.5)	1.17	0.66-2.06	0.3	449 (64.2)	220 (53.69)	0.78	0.57-1.06	0.6
Rural	182 (48.5)	115 (63.18)				70 (20.88)	23 (33.82)				250 (35.7)	138 (55.2)			
Cat at home															
Yes	353 (94.13)	233 (66)	5.178	1.97-13.57	<0.001	261 (77.44)	87 (35.8)	0.85	0.41-1.47	0.3	596 (86.5)	320 (53.69)	2.01	1.28-3.16	0.002
No	22 (5.87)	6 (27.27)				76 (22.55)	28 (39.43)				93 (13.49)	34 (36.55)			
Consumption of raw/undercooked meat															
Yes	311 (82.93)	186 (59.8)	0.3	0.15-0.61	<0.001	317 (94.06)	117 (38.11)	1.72	0.6-4.91	0.2	618 (88.15)	303 (49.02)	0.41	0.25-0.68	<0.001
No	64 (17.06)	53 (82.81)				20 (5.93)	5 (4.20)				83 (11.84)	58 (69.87)			
Exposure to soil															
Yes	354 (94.65)	230 (64.97)	2.782	1.1- 6.98	0.02	258 (76.56)	85 (33.59)	0.5	0.3-0.84	0.007	607 (89.09)	315 (51.89)	1.17	0.76-1.79	0.2
No	20 (5.34)	8 (40)				79 (23.44)	39 (52)				98 (13.9)	47 (47.95)			
Drinking water															
Purified	369 (98.4)	235 (63.68)	0.8	0.15-4.85	0.6	332 (98.51)	119 (36.50)	0.14	0.01-1.3	0.06	695 (98.44)	354 (50.93)	.389	0.1-1.4	0.1
Unpurified	6 (1.6)	4 (66.66)				5 (1.49)	4 (80)				11 (1.66)	8 (72.72)			
Milk															
Boiled	315 (84)	188 (59.68)	0.26	0.12-0.54	<0.001	249 (73.96)	96 (38.62)	1.28	0.75-2.18	0.2	568 (79.42)	288 (50.72)	0.84	0.58-1.22	0.2
Raw	60 (16)	51 (85)				88 (26.03)	29 (32.92)				147 (20.57)	81 (54.92l)			

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