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Original Article

Is there any role of latent toxoplasmosis in schizophrenia disease?

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Abstract

Background: A large number of studies have hypothesized that *Toxoplasma gondii* is a potentially relevant etiological factor in some cases of schizophrenia. By contrast, some studies have disproved this association. The aim of this study was to investigate whether latent toxoplasmosis has any role in schizophrenia disease. Additionally, the association between *T. gondii* and subtypes of schizophrenia, and the impacts of toxoplasmosis on psychopathology were examined in the study.
Methods: A total of 85 patients with schizophrenia and 60 healthy volunteers were included in this prospective study. Immunoglobulin G (IgG) antibody to *T. gondii* was examined by enzyme-linked immune-sorbent assay method.
Results: Seropositivity rates were 43.5% for the patients with schizophrenia and 43.3% for the healthy controls (odds ratio: 1.008, 95% confidence interval: 0.517–1.964, $p = 0.981$).There was no significant difference in *T. gondii* IgG positivity between the schizophrenia and control groups with respect to sex and age. The difference in seroprevalence of *T. gondii* IgG antibodies among the schizophrenia subtypes was not statistically significant ($p = 0.934$). No significant difference was found in Positive and Negative Syndrome Subscales between *Toxoplasma*-infected and *Toxoplasma*-free patients.
Conclusion: In the study area with a high prevalence of *T. gondii*, no association between toxoplasmosis and schizophrenia was detected. These findings showed that toxoplasmosis has no role in the risk of schizophrenia disease.

Keywords: schizophrenia; *Toxoplasma gondii*; toxoplasmosis

1. Introduction

Schizophrenia is a serious neuropsychiatric disorder that is thought to have multiple etiologies. Family studies have indicated that genetic factors have a key role in etiopathogenesis of schizophrenia.[1] By contrast, epidemiologic studies have indicated that environmental exposures, such as winter–spring birth, urban birth, and peri- and postnatal infections, are risk factors for the disease developing in later life.[2] In researches on infectious agents, it has been hypothesized that *Toxoplasma gondii* is a potentially relevant etiological factor in some cases of schizophrenia.[3–5]

T. gondii that commonly infects humans and animals is an obligate intracellular protozoan parasite. Humans are mainly infected by consumption of undercooked meat containing tissue cysts or by ingestion of food and water contaminated with oocysts from infected cat feces. Furthermore, *T. gondii* can be transmitted by maternofetal transmission that can cause congenital toxoplasmosis, blood transfusion, and solid organ or hematopoietic cell transplantation.[6,7] After ingestion, sporozoites and bradyzoites released from oocysts and cysts invade intestinal cells and are converted to tachyzoites.[8]

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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Actively proliferating tachyzoites or trophozoites are usually seen in cells of different tissues in the acute phases of infection. Within weeks or months, tachyzoites disappear, and the resting bradyzoites in tissue cysts appear in various tissues, mainly in the brain and muscle.[9,10] These cysts may remain throughout the life of the host. If the host becomes immunosuppressed, the infection can be reactivated.[11]

Both *in vitro* neuropathologic studies of *T. gondii* in cell cultures and postmortem studies on the brains of schizophrenic patients have shown many glial abnormalities, especially in astrocytes. The fact that patients with schizophrenia have abnormal neurotransmitters, especially dopamine, glutamate, and gamma aminobutyric acid (GABA), is well known. Animal studies of *T. gondii* have demonstrated that this organism can lead to altered behavior and affect dopamine, norepinephrine, and other neurotransmitters.[2,12] Recent studies have indicated that the genome of *T. gondii* has two genes encoding tyrosine hydroxylase; this enzyme affects dopamine biosynthesis.[1]

In the literature, there are numerous studies to indicate that schizophrenia disease is associated with toxoplasmosis. However, some studies have disproved this association. This study investigated whether latent toxoplasmosis has any role in schizophrenia disease, by analyzing *T. gondii* immunoglobulin G (IgG) antibodies. In addition, the association between *T. gondii* and subtypes of schizophrenia, and the impacts of toxoplasmosis on psychopathology were examined in the study.

2. Methods

2.1. Patients

This prospective study was conducted in Elazig Mental Health Hospital, Elazig, Turkey. A total of 85 patients with schizophrenia and 60 healthy volunteers were included in the study. Clinical diagnosis was confirmed through the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR. The Positive and Negative Syndrome Scale is a medical scale, which is used for measuring symptoms of patients with schizophrenia. Patients with histories of head trauma, brain surgery, meningitis, encephalitis, mental retardation, alcoholism, substance abuse, and immunodeficiency disease were excluded from the study.

The control group consisted from 60 healthy volunteers who had no history of schizophrenia or psychiatric disorder. The healthy volunteers comprised health care workers who shared the same environment and ate the same food as the patients. A questionnaire was administered to all individuals participating in the study, which included information on their age, sex, medical history, family history, dietary habits (especially about consuming uncooked/undercooked meat, milk, or eggs), and close contact with cats or dogs up to the participant's age of 15 years. This study was approved by the Firat University Ethical Committee.

2.2. Serological analysis

Blood samples were taken from all participants of this study, under sterile conditions. The samples were centrifuged at 200*g*, and the sera were stored at −20°C until serological examination. The commercial enzyme-linked immune-sorbent assay kits (Vircell, Granada, Spain) were used for detection of *T. gondii* IgG. All samples were analyzed on the Triturus system (Grıfols, Parets del Valles, Spain) according to the manufacturer's instructions. *T. gondii* IgG was measured by the semiquantitative ELISA method. A sample was considered negative if *T. gondii* IgG level was under 10 IU/mL, and values of above 10 IU/mL were also considered positive.

2.3. Statistical analysis

Statistical analyses were performed using SSPS version 21 (SPSS Inc., Chicago, IL, USA). Visual (histograms) and analytical (Kolmogorov–Simirnov/Shapiro–Wilk's test) methods were used to test the normality of distributions of continuous variables. The Student *t* test or Mann–Whitney *U* test, where appropriate, was used to compare parameters between the groups. The Chi-square test or Fisher exact test, where appropriate, was used for categorical comparisons of nominal values in different groups. A p value <0.05 was considered statistically significant.

3. Results

Demographic properties of the participants are summarized in Table 1. There were no statistically significant differences between patients with schizophrenia and controls with respect to age and sex.

The seroprevalence of *T. gondii* IgG antibodies was detected in 43.5% of patients with schizophrenia and 43.3% of healthy controls. As shown in Table 2, there were no statistically significant differences in *T. gondii* IgG positivity between the schizophrenia and control groups.

There were also no significant differences in *T. gondii* IgG positivity between the schizophrenia and control groups with

Table 1
Demographic characteristics of patients with schizophrenia and healthy controls.

Characteristics		Patients with schizophrenia *n* (%)	Healthy controls *n* (%)	*p*
Number of participants		85	60	
Age (mean ± SD)		41.73 ± 12.07	40.45 ± 9.49	0.494
Sex	Male	46 (54.1)	31 (51.7)	0.771
	Female	39 (45.9)	29 (48.3)	
Age group (y)	<30	17 (20)	6 (10)	0.027
	30–39	18 (21.2)	26 (43.3)	
	40–49	30 (35.3)	15 (25)	
	≥50	20 (23.5)	13 (21.7)	
Cat contact history		50 (58.8)	8 (13.3)	<0.001
Dog contact history		46 (54.1)	8 (13.3)	<0.001
Consumption of uncooked meat, milk, chicken eggs		64 (75.3)	21 (35)	<0.001
Schizophrenia history in family		10 (11.8)	0	0.006

SD = standard deviation.

Table 2
Seroprevalence of *Toxoplasma gondii* IgG antibodies in the study populations.

		Patients with schizophrenia		Healthy controls		χ^2	p	OR	CI_{95}
		IgG positive, *n* (%)	IgG negative, *n* (%)	IgG positive, *n* (%)	IgG negative, *n* (%)				
Overall		37 (43.5)	48 (56.5)	26 (43.3)	34 (56.7)	0.001	0.981	1.008	0.517–1.964
Sex	Male	19 (41.3)	27 (58.7)	13 (41.9)	18 (58.1)	0.003	0.956	0.974	0.387–2.454
	Female	18 (46.2)	21 (53.8)	13 (44.8)	16 (55.2)	0.012	0.914	1.055	0.402–2.770
Age group (y)	<30	5 (29.4)	12 (70.6)	1 (16.7)	5 (83.3)	[a]	>0.99	2.083	0.191–22.670
	30–39	4 (22.2)	14 (77.8)	10 (38.5)	16 (61.5)	1.293	0.256	0.457	0.117–1.787
	40–49	13 (43.3)	17 (56.7)	9 (60)	6 (40)	1.112	0.292	0.510	0.145–1.798
	≥50	15 (75)	5 (25)	6 (46.2)	7 (53.8)	[a]	0.142	3.500	0.791–15.495

CI = confidence interval; IgG = immunoglobulin G; OR = odds ratio.
[a] Fisher's exact test was performed.

respect to sex. The seroprevalence of *T. gondii* IgG antibodies in male and female patients with schizophrenia was 41.3% and 46.2%, respectively ($p = 0.653$). The participants were categorized into four groups based on their age, and no significant differences in the seroprevalence of *T. gondii* were seen between the schizophrenia group and healthy controls with respect to age groups (Table 2). However, the odds ratio (OR) was detected to be 3.5 for participants aged >50 years.

In Table 3, the patients with schizophrenia were categorized according to schizophrenia subtypes. The difference in the seroprevalence of *T. gondii* IgG antibodies among schizophrenia subtypes was not statistically significant.

The effect of toxoplasmosis on psychopathology was investigated in patients with schizophrenia. No significant difference was found in Positive and Negative Syndrome Subscales between *Toxoplasma*-infected and *Toxoplasma*-free patients (Table 4).

Table 3
Seroprevalence of *Toxoplasma gondii* IgG antibodies in the schizophrenia subtypes.

Schizophrenia subtypes		*T. gondii* IgG		p
		Positive	Negative	
Paranoid	Count	15	16	0.934
	% within schizophrenia subtypes	48.4	51.6	
	% within *T. gondii* IgG	40.5	33.3	
Disorganized	Count	5	7	
	% within schizophrenia subtypes	41.7	58.3	
	% within *T. gondii* IgG	13.5	14.6	
Catatonic	Count	0	1	
	% within schizophrenia subtypes	0.0	100.0	
	% within *T. gondii* IgG	0.0	2.1	
Undifferentiated	Count	2	3	
	% within schizophrenia subtypes	40.0	60.0	
	% within *T. gondii* IgG	5.4	6.3	
Residual	Count	10	15	
	% within schizophrenia subtypes	40.0	60.0	
	% within *T. gondii* IgG	27.0	31.3	
Simple schizophrenia	Count	5	6	
	% within schizophrenia subtypes	45.5	54.5	
	% within *T. gondii* IgG	13.5	12.5	

IgG = immunoglobulin G.

Table 4
PANSS subscales in *Toxoplasma*-infected and *Toxoplasma*-free patients.

PANSS	*T. gondii* IgG positive Mean ± SD	*T. gondii* IgG negative Mean ± SD	p
Positive subscale score	17.60 ± 10.08	22.02 ± 13.23	0.136
Negative subscale score	29.82 ± 8.95	29.20 ± 8.68	0.753
General psychopathology subscale score	36.88 ± 14.21	36.28 ± 14.61	0.907
PANSS	84.41 ± 22.64	87.50 ± 24.76	0.569

IgG = immunoglobulin G; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation.

4. Discussion

In this prospective study, no significant difference was found in the seroprevalence of *T. gondii* between patients with schizophrenia and healthy controls (OR: 1.008, 95% confidence interval: 0.517–1.964, $p = 0.981$). Patients and control individuals had the similar prevalence of toxoplasmosis. In this region, raw meatball consumption and village life are mostly common. Therefore, the prevalence of *T. gondii* antibodies in the general population is high. The high seroprevalence in both the schizophrenia and the control group could be due to the high prevalence of *T. gondii* in the general population in Elazig. Therefore, the prevalence of *T. gondii* antibodies in the patients with schizophrenia in this study may be less apparent. These results were consistent with some studies. Tanyüksel et al[13] from Ankara, Turkey, did not find any significant differences in seropositivity to *T. gondii* between patients with the first episode of schizophrenia and control individuals. In another study published in 2014, anti-*Toxoplasma* antibodies were detected in 34% of patients with schizophrenia and 47.39% of healthy controls.[14]

The findings of the present study have shown inconsistency with other studies that have reported that seropositivity to *T. gondii* infection was significantly higher in patients with schizophrenia compared with that in healthy controls. The results of the study that was carried out by Çetinkaya et al[9] in the same hospital in Elazig in 2007 are noteworthy. The authors found that the seropositivity rate for *T. gondii* IgG antibodies in

patients with schizophrenia (66%) was significantly higher than that in healthy volunteers (22%) or patients with depressive disorder (24%). However, in this area, the prevalence of *T. gondii* antibodies in the general population is higher. Several studies have evaluated the prevalence of *T. gondii* antibodies in the general population in Elazig. In a study, the prevalence of *T. gondii* was 41%, whereas in another study it was found to be 31%.[15,16] Additionally, the seropositivity rate of the healthy group in the present study was 43.3%. The seropositivity rates in these studies were higher than that for healthy controls in the study conducted by Çetinkaya et al.[9] Yuksel et al[2] from Istanbul, Turkey, found that *T. gondii* seropositivity rate was 61% in patients with schizophrenia, 37% in patients with anxiety and depression, and 45% in healthy controls. The authors have suggested that toxoplasmosis does not have a direct effect on the risk of schizophrenia in Turkey.

Male and female patients with schizophrenia did not show any significant differences in the *T. gondii* IgG positivity rate. Similar results were also reported in numerous studies.[2,17] By contrast, higher seropositivity in schizophrenic women than in schizophrenic man was also indicated by Khademvatan et al.[14] In the present study, seroprevalence of *T. gondii* was not significantly different between the schizophrenia group and healthy controls with respect to age groups. However, the OR was detected as 3.5 in the >50-year age group. Similarly, in the study of Yuksel et al[2] for the 51−65-year age group, anti-*Toxoplasma* IgG was significantly more prevalent in the schizophrenia group compared with healthy controls (OR: 3.08). The authors have interpreted that the age range of 51−65 years was a risk factor.

Regarding the subtypes of schizophrenia, in this study, no association between toxoplasmosis and subtypes of schizophrenia was determined. Similarly, another study also reported that there was no statistically significant difference in the prevalence of toxoplasmosis among subtypes of schizophrenia.[14]

Positive symptoms reflect an excess or distortion of the individual's normal functions, are not present in people in the normal population, and are mainly present during the acute stage of schizophrenia. Negative symptoms are characterized by the elimination or absence of normal behavior, and may appear months and years before the onset of positive symptoms.[18] Holub et al[19] indicated that schizophrenic psychopathology correlated negatively with the concentration of *T. gondii* IgG antibodies in *Toxoplasma*-infected patients. In addition, the authors have interpreted their findings as a cumulative effect of latent toxoplasmosis on individual psychopathology. Similar to the results of our study, Park et al[17] found that there were no significant differences in positive subscale, negative subscale, and general psychopathology subscale scores between patients seronegative and seropositive for *T. gondii*. For detecting a possible association between the severity of symptoms and *T. gondii* further studies are needed.

Despite many studies having been conducted to reveal the association between toxoplasmosis and schizophrenia, it is still controversial whether *T. gondii* plays an etiological role in schizophrenia disease. In geographic areas with a low prevalence of *T. gondii* antibodies, the higher prevalence of *T. gondii* antibodies in patients with schizophrenia may be more apparent. By contrast, in geographic areas with a high prevalence of *T. gondii* antibodies, the increase in seropositivity of patients with schizophrenia may be less apparent. Therefore, in areas with a high prevalence of *T. gondii*, it would be difficult to reveal the association between toxoplasmosis and schizophrenia. By contrast, although the people of countries such as France, Brazil, and Ethiopia have a high prevalence of *T. gondii* antibodies, the prevalence of schizophrenia in these countries has not been reported unusually high rates.[1] In Turkey, the prevalence of schizophrenia has been estimated to be as high as 8.9/1000.[20]

The main limitation of this study was the number of patients seropositive for *T. gondii.* Although there were 85 patients with schizophrenia in the study, the number of patients seropositive for *T. gondii* ($n = 37$) was small. Therefore, to compare the clinical symptoms of seropositive and seronegative schizophrenia patients further studies are need. Another limitation was that the distribution of individuals across age groups was not homogeneous.

In conclusion, in the study area with a high prevalence of *T. gondii*, no association between toxoplasmosis and schizophrenia was detected. In such areas, it is difficult to establish whether *T. gondii* has an etiological role in schizophrenia disease. To find out whether there is an association between toxoplasmosis and schizophrenia, more studies should be conducted, especially in areas with a high prevalence of *T. gondii*. Furthermore, future research should determine the serotype of the prevailing strains of *Toxoplasma* in schizophrenic patients and general population, and focus on the timing of infection.

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