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Toxoplasma gondii Exposure and the Risk of Schizophrenia

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Background: Schizophrenia is a major psychiatric disorder with a deeply destructive pathophysiology. There are evidences to indicate that infectious agents such as *Toxoplasma gondii* may play some roles in etiology of the disorder.
Objectives: The current study aimed to determine the association between *T. gondii* exposure and the risk of schizophrenia.
Materials and Methods: *T. gondii* IgG antibodies of 100 patients with schizophrenia as well as 200 healthy volunteers were assessed. The subjects also completed demographic questionnaires. Data was analyzed using the chi-square and Fisher exact tests.
Results: The analyses confirmed the significant differences between healthy women and ones with schizophrenia (P = 0.001) as well as between males and females with schizophrenia (P = 0.009) in IgG positivity.
Conclusions: The present study supported the contamination with *T. gondii* as a risk factor for schizophrenia just in women.

Keywords: Toxoplasma gondii; Schizophrenia; Toxoplasmosis; Parasite; Enzyme-Linked Immunosorbent Assay; Iran

1. Background

Schizophrenia is a major psychiatric disorder with a deeply destructive pathophysiology, with effects on thought, perception, emotion, and behavior (1). It is a psychotic disorder with devastating consequences for patient, his or her family, and society at large (2); it is one of the most difficult syndromes in definition, etiology and treatment (3). Although it is known as a single disease, the symptomology, course, and outcome of this disease vary in different individuals (3). Its pathophysiology and etiology are complicated and unclear and the ambiguities in pathogenesis of the disorder underlie our inability to use prevention strategies or effective treatments (4). Effectiveness of the existing interventions in controlling the disorder is relative and about half of the cases are described as poor outcomes (2). Such defects could be a great barrier in the way of discharging patients from psychiatric hospitals and even putting them in the facilities cycle anticipated for this purpose by the psychiatrics community (1, 2).

The researches' clarifications of the existing ambiguities in etiology of schizophrenia continue in various areas. There are evidences to indicate that infectious agents may play some roles in etiology of the disorder; some of them have pointed to the role of *Toxoplasma gondii* infection (5-11). Infection with *T. gondii* is one of the most common parasitic infections in humans as well as other warm blooded vertebrates including birds, livestock, and marine mammals (12, 13). Humans commonly become infected by consumption of undercooked or raw meat containing tissue cysts or by accidentally ingesting oocytes presented on vegetables contaminated with cat faces (14), or consumption of contaminated drinking water (15).

After a short phase of acute toxoplasmosis, the infection becomes latent and gets encysted in the central nervous system and muscle tissues, probably for the whole life of the infected host (16, 17). The parasite has the ability to alter the behavior of its intermediate host to increase its transmission (3). Evidences suggest that the parasite affects the synthesis of neurotransmitters, especially dopamine, in infected individuals, which could lead to personality changes (18-22), psychotic symptoms (23), and in some cases neurological and psychiatric disorders (24). Infected rodents also have been found to experience behavioral changes and cognitive dysfunctions (21, 25). Besides the studies that directly indicated the association between *Toxoplasma* infection and increased incidence of schizophrenia, some indirect evidences also pointed to the role of *T. gondii* in etiology of schizophrenia (26, 27). Haloperidol (an antipsychotic drug) and valproic acid (a mood stabilizer), used in treatment of mental illnesses including schizophrenia, can prevent the development of *T. gondii*-associated behavioral and cognitive altera-

tions (28); in contrast, there are some results that challenge the plausibility of this association (29, 30).

In spite of the high prevalence of toxoplasmosis in Iran (31), few researches have been conducted in this field. Two studies regarding toxoplasmosis and schizophrenia have been carried out in Iran. Hamidinejat et al. (23) reported that the positivity rate of anti-*T. gondii* IgG antibodies among individuals with schizophrenia was significantly higher than that of healthy controls. Saraei-Sahnesaraei et al. (29), whereas, did not find any significant differences in seroprevalence of toxoplasmosis between individuals with schizophrenia and healthy controls. Due to the existence of conflicting results in general, and few conducted researches in Iran in particular, the present study was performed to evaluate *Toxoplasma* infection in patients with schizophrenia and compare it with healthy controls. More knowledge about the pathogenesis of the disorder would result in more effective prevention and treatment strategies.

2. Objectives

Studies in the world indicated different results regarding the association between *T. gondii* exposure and the risk of schizophrenia. The current study aimed to determine this association.

3. Materials and Methods

This study was carried out during 2011-2012. It consisted of 100 patients (65 males and 35 females) with a mean age of 36.39 years old (SD = 10.28, range: 20-65) who attended Golestan Educational Hospital in Ahvaz, Iran, and were diagnosed with schizophrenia disorder, as well as 200 healthy volunteers including 96 males and 104 females, 18 to 52 years old (mean age of 25.04), who had no history of schizophrenia disorder. The participants were divided into five groups based on their ages (< 20, 20-29, 30-39, 40-49, and > 50 years old).

The patients' diagnoses were made through the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV-TR) by at least two psychiatrists. The subjects of two groups were not immune-deficient and did not have any other major psychiatric disorder or neurological disease. They did not have any clinical symptoms of acute toxoplasmosis. All the subjects or their legal guardians gave informed consents before participation in the study and completed the questionnaire to provide demographic data about ethnicity, gender, age, level of education, marital status and employment. The study was approved by the ethical committee of the university.

3.1. Serological Test for Toxoplasmosis

A 5-*mL* blood sample was taken from each subject for serological analysis. The blood samples were centrifuged at 3000 rpm for 20 minutes to procure clear supernatants. The sera were kept at -20°C until the analysis (32). The IgG antibodies in two case and control groups were measured by ELISA technique (Torch-IgG, Trinity Biotech Company, USA) according to the manufacturer's instructions.

3.2. Statistical Tests

Data were analyzed using chi-square and Fisher's exact tests. The odds ratios (OR) with 95 confidence intervals (95 CI) were also determined. The probability level of 0.05 was accepted as statistically significant. Statistical analyses were carried out using SPSS version 16.

4. Results

In this study, the seroprevalence of anti-*T. gondii* IgG antibodies were evaluated in 300 subjects. Latent toxoplasmosis was diagnosed in 87 (29) subjects and 213 (71) participants were toxoplasma-negative. Among the seropositive subjects, 45.97 (n = 40) were female and 54.02 (n = 47) were male. Frequencies of the participants' demographic features are listed in Table 1.

Table 1. Frequencies of the Participants' Demographic Features [a]

Feature	Frequency		
	Patients Group	Control Group	Total
Toxoplasma gondii			
Positive	34 (34)	53 (26.5)	87 (29)
Negative	66 (66)	147 (73.5)	213 (71)
Gender			
Female	35 (35)	104 (52)	139 (46.3)
Male	65 (65)	96 (48)	161 (53.7)
Residence			
Urban	76 (76)	163 (81.5)	220 (80)
Rural	24 (24)	37 (18.5)	55 (20)
Marital status			
Single	64 (64)	144 (72)	208 (69.3)
Married	27 (27)	56 (28)	81 (27.2)
Divorced/widowed	9 (9)	0	9 (3)
Level of education			
Grade school	70 (70)	23 (11.5)	93 (31)
12 years/High school	19 (19)	20 (10)	39 (13)
University degree	11 (11)	157 (78.5)	168 (56)
Ethnicity			
Fars	18 (24)	72 (36)	90 (32.49)
Arab	39 (39)	57 (28.5)	96 (33.12)
Lor	40 (40)	46 (23)	86 (24.6)
Other	3 (6)	25 (8)	28 (6.3)
Age, y			
< 20	0	21 (10.5)	21 (7)
20-29	31 (31)	85 (42.5)	116 (38.7)
30-39	35 (35)	50 (25)	85 (28.3)
40-49	23 (23)	23 (11.5)	46 (15.3)
> 50	11 (11)	21 (10.5)	32 (10.7)

[a] Data are presented as No. (%).

Table 2. Analysis of Anti-*Toxoplasma gondii* IgG Antibodies in Patients With Schizophrenia and Control Group [a]

	Patients Group, No. (%)	Healthy Individuals, No. (%)	Sig. [b]	OR	CI 95
Gender					
Male	16/65 (26.61)	31/96 (32.2)	0.3	0.68	0.33-1.39
Female	18/35 (51.42)	22/104 (21.1)	0.001	3.94	1.75-8.89

[a] Abbreviations: CI, confidence interval; OR, odds ratio.
[b] Significance.

The difference in seropositivity between the patients and the control group was also analyzed separately for men and women. As seen in Table 2, no significant difference was found between the IgG levels of male patients in the two groups (P = 0.3). However, the difference between the female patients and the female control group in prevalence of *T. gondii* infection was statistically significant (P < 0.001).

Of the 100 patients, anti-*T. gondii* IgG antibodies were present in 31.3 (21/67) of those with paranoid type schizophrenia, 42.8 (3/7) of cases with catatonic type, 33.3 (6/18) of undifferentiated type and 33.3 (1/3) of patients with residual type. None of the patients with the disorganized type was seropositive. The difference in infection rate among the subtypes was not statistically significant (P = 0.5). Serological analyses also confirmed no significant increase in IgG levels in patients with first-episode schizophrenia disorders (13/30) compared with those with recurrent episodes (18/67) (P > 0.05). The prevalence of *T. gondii* infection in patients was analyzed with respect of gender and residential area. The seroprevalence of anti-*T. gondii* IgG antibodies in male and female patients with schizophrenia disorder was 26.6 and 51.4, respectively. The difference between male and female patients was statistically significant (P = 0.009) (Table 3).

The prevalence of *T. gondii* infection in patients living in urban and rural areas was 28.07 and 22.2, respectively; the difference was not significant (P = 0.7). The seroprevalence of *T. gondii* infection in the five age groups was 0, 32.2, 40, 26, and 36.3, respectively; in the healthy individuals it was 33.3, 24.7, 24, 30.4, and 28.5, respectively. The differences in infection rate among the age subgroups were not statistically significant (P > 0.05). Comparing the seroprevalence adjusted by age, the differences between patients and healthy participants were not significant in any of the age subgroups (Table 4).

5. Discussion

The present study was conducted to evaluate the association between *Toxoplasma* infection and schizophrenia disorder. Most of studies conducted in various parts of the world compared males and females together with the other groups. Here, we compared samples of males and females separately. This provided more clarity in the research, as gender is removed as a potential confound. The analyses confirmed significant differences between female healthy controls and female patients with schizophrenia disorder (P = 0.001), and between male and female patients with schizophrenia disorder (P = 0.009) in IgG positivity. However, there was no significant difference in prevalence of anti-*T. gondii* IgG antibody between male and female individuals in the healthy group.

Table 3. Distribution of Latent Toxoplasmosis in Clinical Course in the Schizophrenia Group [a,b]

	Patients Group [a]		Sig. [c]	OR	CI
	Male	Female			
IgG-positive	16/65 (26.6)	18/35 (51.4)	0.009	0.3	0.12-0.73

[a] Abbreviations: CI, confidence interval; OR, odds ratio.
[b] Data are presented as No. (%).
[c] Significance.

Table 4. Distribution of Latent Toxoplasmosis According to Age in Patients With Schizophrenia and Healthy Controls [a]

	Patients Group, No. (%)	Healthy Individuals, No. (%)	Sig. [b]	OR	CI 95
Age, y					
< 20	0 (0)	7/21 (33.3)			
20-29	10/31 (32.2)	21/85 (24.7)	0.4	1.45	0.59-3.5
30-39	14/35 (40)	12/50 (24)	0.1	2.1	0.82-5.3
40-49	6/23 (26.08)	7/23 (30.4)	1	0.8	0.22-2.9
> 50	4/11 (36.3)	6/21 (28.5)	0.7	1.4	0.3-6.7

[a] Abbreviations: CI, confidence interval; OR, odds ratio.
[b] Significance.

Sex-determined changes in kinetics and quantities of cytokine production during *Toxoplasma* infection may in part explain these sex differences. As shown in animal studies, higher levels of interferon-gamma (IFNg) are produced by spleens of male mice than those of female mice in the early stages of *Toxoplasma* infection. Rapid responses to *T. gondii* infection with high levels of IFNg and tumor-necrosis factor-alpha help male mice to control parasite multiplication. Interleukin-10 may also be of importance in down-regulation of the parasite. Higher cyst burdens in female mice may be caused by the inability to respond as quickly as their male counterparts in terms of IFNg production (33).

Our findings were in contrast with the investigation conducted by Xiao et al. (30), which demonstrated that seroprevalence of anti-*T. gondii* IgG was not significantly different between males and females with psychiatric disorders including schizophrenia disorder. According to the literature research, the intervention studies (28, 34) and some direct studies (5-11, 23) support the link between toxoplasmosis and schizophrenia. However, results of the researches conducted by Saraei-Sahnesaraei et al. (29) and Xiao et al. (30) showed no correlation between *T. gondii* infection and schizophrenia.

The possible reason for different findings obtained from the studies of *T. gondii* and schizophrenia may be related to *T. gondii* genotypes. This protozoan has genotypes that are different in terms of virulence, and geographical replication of *T. gondii* genotypes may be different; distinct neuropathogenic potentials have been found in different genotypes of *T. gondii* (35). In contrast with some previous studies (7, 29), in our study, the proportion of seropositive subjects was not significantly different between the first-episode patients (43.3) and those in the next episodes (26.8). In the research of Hamidinejat (23), the prevalence of anti-*T. gondii* IgG antibodies in first-episode patients with schizophrenia disorder was not significantly different from the control group. No significant differences were detected between the subtypes of schizophrenia disorder in the present research.

We also did not find significant difference in seroprevalence of anti-*T. gondii* IgG between individuals living in urban and rural areas. Based on this result, residential area has no effect on the risk of the toxoplasmosis. In the research of Xiao et al. individuals living in urban and rural areas in the northern part of China, similarly, did not have significant difference in the infection rate (30). In contrast, Yuksel et al. and Kolbekova et al. reported an association between residences in a small town/village and toxoplasmosis (6, 36). In the current study, the differences in latent toxoplasmosis were not statistically significant among the five age subgroups, as well as the healthy group. There were not significant differences between the patients' group compared with the healthy controls in anti-toxoplasmosis IgG antibodies in each different age subgroups. Xiao et al (30) also found that the differences in infection rates among age groups (< 20, 20-29, 30-39, 40-49, and > 50 years) were not statistically significant.

In conclusion, the present study supported the contamination with *T. gondii* as a risk factor for schizophrenia disorder just in females. It is suggested to study larger samples and conduct better controlled studies in further investigations to determine the precise relationship between these two disorders. Our study also suggests assessing the influence of different parasite genotypes on increased risk of schizophrenia disorder.

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References

1. Sadock BJ, Kaplan HI, Sadock VA. *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry.*Philadelphia: Wolter Kluwer/Lippincott Williams & Wilkins; 2007.
2. Sadock BJ, Sadock VA, Ruiz P, Kaplan HI. *Kaplan and Sadock's Comprehensive Textbook of Psychiatry.*Philadelphia: Wolters Kluwer Health; 2009.
3. Fittipaldi KE. *Toxoplasma gondii as an etiological agent of schizophrenia.*: Hofstra University; 2008.
4. Freedman R. Schizophrenia. *N Engl J Med.* 2003;**349**(18):1738–49.
5. Mahmoud SS, Hasan MS. Seroprevalence of toxoplasmosis among schizophrenic patients. *Yemeni J Med Sci.* 2009;**1**(3):1–7.
6. Yuksel P, Kocazeybek B, Alpay N, Babur C, Bayar R, Karaköse AR, et al. Establishing the Role of Latent Toxoplasmosis in the Ethiopathogenesis of Schizophrenia. *Int J Infect Dis.* 2008;**12**.
7. Niebuhr DW, Millikan AM, Cowan DN, Yolken R, Li Y, Weber NS. Selected infectious agents and risk of schizophrenia among U.S. military personnel. *Am J Psychiatry.* 2008;**165**(1):99–106.
8. Hinze-Selch D, Daubener W, Eggert L, Erdag S, Stoltenberg R, Wilms S. A controlled prospective study of toxoplasma gondii infection in individuals with schizophrenia: beyond seroprevalence. *Schizophr Bull.* 2007;**33**(3):782–8.
9. Mortensen PB, Norgaard-Pedersen B, Waltoft BL, Sorensen TL, Hougaard D, Torrey EF, et al. Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biol Psychiatry.* 2007;**61**(5):688–93.
10. Cetinkaya Z, Yazar S, Gecici O, Namli MN. Anti-Toxoplasma gondii antibodies in patients with schizophrenia--preliminary findings in a Turkish sample. *Schizophr Bull.* 2007;**33**(3):789–91.
11. Brown AS, Schaefer CA, Quesenberry CP, Jr, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry.* 2005;**162**(4):767–73.
12. Suzuki Y. Host resistance in the brain against Toxoplasma gondii. *J Infect Dis.* 2002;**185 Suppl 1**:S58–65.
13. Dubey JP. Toxoplasma gondii infections in chickens (Gallus domesticus): prevalence, clinical disease, diagnosis and public health significance. *Zoonoses Public Health.* 2010;**57**(1):60–73.
14. Kijlstra A, Jongert E. Control of the risk of human toxoplasmosis transmitted by meat. *Int J Parasitol.* 2008;**38**(12):1359–70.
15. Herrmann DC, Pantchev N, Vrhovec MG, Barutzki D, Wilking H, Frohlich A, et al. Atypical Toxoplasma gondii genotypes identified in oocysts shed by cats in Germany. *Int J Parasitol.* 2010;**40**(3):285–92.
16. Dubey JP, Jones JL. Toxoplasma gondii infection in humans and animals in the United States. *Int J Parasitol.* 2008;**38**(11):1257–78.

17. Miller CM, Boulter NR, Ikin RJ, Smith NC. The immunobiology of the innate response to Toxoplasma gondii. *Int J Parasitol.* 2009;**39**(1):23–39.
18. Flegr J, Zitkova S, Kodym P, Frynta D. Induction of changes in human behaviour by the parasitic protozoan Toxoplasma gondii. *Parasitology.* 1996;**113 (Pt 1)**:49–54.
19. Flegr J, Havlicek J. Changes in the personality profile of young women with latent toxoplasmosis. *Folia Parasitol (Praha).* 1999;**46**(1):22–8.
20. Flegr J, Kodym P, Tolarova V. Correlation of duration of latent Toxoplasma gondii infection with personality changes in women. *Biol Psychol.* 2000;**53**(1):57–68.
21. Falagas ME, Rizos M, Bliziotis IA, Rellos K, Kasiakou SK, Michalopoulos A. Toxicity after prolonged (more than four weeks) administration of intravenous colistin. *BMC Infect Dis.* 2005;**5**:1.
22. Khademvatan S, Khajeddin N, Saki J, Izadi-Mazidi S. Effect of toxoplasmosis on personality profiles of Iranian men and women. *S Afr J Sci.* 2013;**109**(1-2):1–4.
23. Hamidinejat H, Ghorbanpoor M, Hosseini H, Alavi SM, Nabavi L, Jalali MH, et al. Toxoplasma gondii infection in first-episode and inpatient individuals with schizophrenia. *Int J Infect Dis.* 2010;**14**(11):e978–81.
24. Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite Toxoplasma gondii increases dopamine metabolism. *PLoS One.* 2011;**6**(9).
25. Webster JP. The effect of Toxoplasma gondii on animal behavior: playing cat and mouse. *Schizophr Bull.* 2007;**33**(3):752–6.
26. Torrey EF, Yolken RH. Toxoplasma gondii and schizophrenia. *Emerg Infect Dis.* 2003;**9**(11):1375–80.
27. Fuller Torrey E, Rawlings R, Yolken RH. The antecedents of psychoses: a case-control study of selected risk factors. *Schizophr Res.* 2000;**46**(1):17–23.
28. Webster JP, Lamberton PH, Donnelly CA, Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer and anti-parasite medication on Toxoplasma gondii's ability to alter host behaviour. *Proc Biol Sci.* 2006;**273**(1589):1023–30.
29. Saraei-Sahnesaraei M, Shamloo F, Jahani Hashemi H, Khabbaz F, Alizadeh S. Relation between Toxoplasma gondii infections and schizophrenia. *IJPCP.* 2009;**15**(1):3–9.
30. Xiao Y, Yin J, Jiang N, Xiang M, Hao L, Lu H, et al. Seroepidemiology of human Toxoplasma gondii infection in China. *BMC Infect Dis.* 2010;**10**:4.
31. Saeedi M, Veghari GR, Marjani A. Seroepidemiologic evaluation of anti-toxoplasma antibodies among women in north of Iran. *Pak J Biol Sci.* 2007;**10**(14):2359–62.
32. Ahmad MS, Maqbool A, Mahmood-ul-Hassan M, Mushtaq-ul-Hassan M, Anjum AA. Prevalence of toxoplasma gondii antibodies in human beings and commensal rodents trapped from Lahore, Pakistan. *J Anim Plant Sci.* 2012;**22**:51–3.
33. Roberts CW, Cruickshank SM, Alexander J. Sex-determined resistance to Toxoplasma gondii is associated with temporal differences in cytokine production. *Infect Immun.* 1995;**63**(7):2549–55.
34. Jones-Brando L, Torrey EF, Yolken R. Drugs used in the treatment of schizophrenia and bipolar disorder inhibit the replication of Toxoplasma gondii. *Schizophr Res.* 2003;**62**(3):237–44.
35. Darde ML. Genetic analysis of the diversity in Toxoplasma gondii. *Ann Ist Super Sanita.* 2004;**40**(1):57–63.
36. Kolbekova P, Kourbatova E, Novotna M, Kodym P, Flegr J. New and old risk-factors for Toxoplasma gondii infection: prospective cross-sectional study among military personnel in the Czech Republic. *Clin Microbiol Infect.* 2007;**13**(10):1012–7.