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The Correlation Between *Toxoplasma Gondii* Infection and Schizophrenia: A Comparative Study With Family Members (Control Group)

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Background: *Toxoplasma gondii* (*T. gondii*), a protozoan parasite is well known for its neuroinvasiveness and persistent effects. This intracellular parasite leads to central nervous system congenital anomalies. Moreover, some delayed less serious neuropsychiatric squeals following *T. gondii* infection have been reported.

Objectives: To study the correlation between *T. gondii* infection and schizophrenia, family members of cases were considered as the control group in order to match the two groups in terms of socioeconomic, sanitary, housing conditions and other demographic risk factors described in the etiology of *T. gondii* infection.

Materials and Methods: A case-control study was performed on 152 patients with schizophrenia diagnosis living in Iran, and 152 individuals from the first relatives of each schizophrenic patient, as the control group. A questionnaire inquiring about socioeconomic status, dietary habits and clinical characteristics was filled for each individual. Blood samples were taken from subjects and evaluated for *T. gondii* immunoglobulin G (IgG) antibody. Sera with positive results for IgG were further tested for *T. gondii* immunoglobulin M (IgM) antibody.

Results: The prevalence of *T. gondii* antibody positive cases among patients showed differences between males and females. In the patient group, IgG was positive in 53.2% whereas, 41.4% of the control group had IgG positive ($P = 0.02$). Age at the time of diagnosis of schizophrenic patients with positive *T. gondii* IgG and IgM was significantly lower than other cases (34.2 ± 14.3 vs. 49.2 ± 11.7; $P = 0.01$). Patients with family members that had positive results for IgG ELISA test had higher probability for positive IgM seropositivity.

Conclusions: Our results supported the longstanding hypothesis of correlation between *T. gondii* infection and schizophrenia. We also considered this infection as a possible etiological factor in the development of schizophrenia.

*Keywords:*Schizophrenia; Toxoplasmosis; Communicable Diseases

1. Background

Schizophrenia is regarded as a psychotic disorder with unknown etiology, characterized as derangements in cognition with prevalence of 10 - 15 cases among 1000 individuals from normal population (1). Its median point of prevalence and lifetime prevalence estimates are 4.6 per 1000 and 4.0 per 1000 individuals, respectively (2). Genetic factors, environmental insults and their interactions are purposed etiologies in the disease development, however, genetics has proven to be the most important (3); this is supported by findings of twin, family and adoption studies (2). Recent evidences indicate a pathophysiological role for infectious agents. Previously, much attention was paid to infections during the prenatal period, whereas, more recent studies have suggested that infections during childhood and adulthood may also influence risk of disorders and alter associated neuromorphologic and neuropsychologic outcomes (4). *Toxoplasma gondii* (*T. gondii*) is an intracellular parasite, causing disruption in fetal brain development. Many studies have indicated that there is a relationship between the infection and schizophrenia as suggested by seropositivity to this microbe in affected patients (4).

2. Objectives

In this study, we aimed to evaluate the correlation be-

Implication for health policy/practice/research/medical education:
Our study supports the longstanding hypothesis of the correlation between *T. gondii* infection and schizophrenia. We also consider this infection as a possible etiological factor in the development of schizophrenia. Therefore long term follow up of schizophrenia-free individuals with positive serum antibody in future studies will result in the determination of the possibility of schizophrenia occurrence.

tween *T. gondii* infection and schizophrenia by conducting a comparative study between a patient and a control group selected from the first-degree family members of patients (residing together).

3. Materials and Methods

3.1. Study Design

This case-control study was carried out from July 2011 to July 2012, in Tehran, IR Iran. Informed consents were obtained from all participants or their guardians before initiating the study. Institutional Review Board approval was granted by the local Research Ethics Committee of Baqiyatallah University of Medical Sciences. Reference number of the local Ethics Committee approval was 27-90-04-01.

3.2. Participants

One hundred and ninety schizophrenic patients were recruited from schizophrenic patients referred to three referral and academic psychiatric hospitals of Tehran, IR Iran. The diagnosis was made by academic psychiatrists according to the DSM-IV-TR classification (5), through an interview. Schizophrenic patients, who had an available age and sex matched control first-degree family member living in a single household, were included and schizophrenic patients who had a positive history of ambient neurologic or ophthalmic diseases were excluded.

3.3. Clinical and Dietary Characteristics

Clinical data including age at diagnosis of schizophrenia, number of hospitalizations, family history of mood disorders or psychoses, blood transfusion and transplant history were recorded from patients' electronic dossiers. History of animal contact and cleaning up cat feces, history of foreign travel and dietary habits including types of consumed meat (pork, lamb, beef, goat, boar, chicken, turkey, rabbit, deer, squirrel, horse, sea food, snake and bird), consumption of raw or undercooked meat, unpasteurized dairy products, unrefined water, dried or cured meat (chorizo, ham, sausages or salami), unwashed raw vegetables and fruits, eating out and finally, contact with soil (gardening or agriculture) before disease onset were recorded. Dietary habits were obtained by a psychologist via an interview.

3.4. Serological Technique

In order to examine the relationship between the presence of immunoglobulin G (IgG) antibodies against *T. gondii* and schizophrenia, 5 ml sera from all studied individuals were collected and sent to the biochemical laboratory of Tehran University of Medical Sciences in less than an hour. The presence of *T. gondii* IgG was measured using ELISA kits (Euroimmune, Medizinische). The results were considered positive when concentration of the specific antibody was above 10 IU/ml. Blood samples of those with positive IgG test results, underwent further evaluation for immunoglobulin M (IgM) measurement using the ELISA kit (Euroimmune Medizinische).

3.5. Statistical Analysis

Data are expressed as mean ± SD, odds ratio (OR) and 95% confidence interval (95% CI). The Statistical Package of Social Science version 15.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. One-sample Kolmogrov-Smirnov test estimated whether data were normally distributed. The *T. gondii* infection and schizophrenia were considered as exposure and outcome of this study, respectively. Statistical significance was considered when $P \leq 0.05$. For comparison between the quantitative data of the two groups, independent-samples t-test was used and Chi-Square test and Fisher's exact test were used for comparison of qualitative measurements.

4. Results

Among 190 schizophrenic patients entered in the study, thirty patients were excluded due to a positive history of ambient neurologic or ophthalmologic diseases and eight patients refused the blood sampling during the study. The final set of the patient group contained data on an overall of 152 schizophrenic patients, 67 (44%) women and 85 (56%) men. The age range at the time of diagnosis of the patient group was 20-64 (median 32 years). The age range of healthy controls was 19-84 (median of 33.5 years). Other demographic data of the subjects are presented in Table 1.

Among patients, *T. gondii* IgG was positive in 81 cases (53.2%); while only 48 of them (31.5% of total case) were positive for IgM antibodies against *T. gondii*. Surprisingly, *T. gondii* IgG and IgM were positive in 89 (58.6%) and 30 (19.7%) individuals in the control group as determined by the ELISA test, respectively. Out of the total 81 patients with positive *T. gondii* IgG results, in only 28 (34.5%), the family member in the control group was concomitantly tested positive for *T. gondii* IgG. Among these 28 selected patients, 16 (51.7%) cases had positive test results for *T. gondii* IgM. Table 2 indicates results of *T. gondii* antibody tests.

Table 1. Comparison of Demographic Data Between 152 Cases With Schizophrenia and 152 Healthy Controls

	Patients	Controls	P value
Age at diagnosis, y, mean ± SD	32.7 ± 4.1	33.5 ± 10.5	0.53
Single patients, No. (%)	140 (92.1)	73 (48.0)	< 0.001 [a]
Illiterate patients, No. (%)	2 (1.3)	5 (3.2)	0.25
Employed patients, No. (%)	25 (16.4)	75 (49.3)	< 0.001 [a]

[a] P < 0.05

Age at the time of diagnosis of schizophrenic patients with positive *T. gondii* IgG and IgM was significantly lower than the other cases (34.2 ± 14.3 vs. 49.2 ± 11.7; P = 0.01).

Consumption of unwashed raw vegetables and fruits was 55.2% (84 cases) among schizophrenic patients and only 20.4% (31 individuals) in the control group, indicating a 35.2% difference (P < 0.001). Contact with soil (gardening or agriculture) was positive in 56.5% of patients (86 cases) and 30.3% of the control group (46 controls, P < 0.001). Similar significant findings were found for other clinical and dietary characteristics including history of previous foreign travel and any direct or indirect contact with animals (Table 3).

5. Discussion

T. gondii , a protozoan parasite usually infects humans through undercooked meat, cat feces, soil and water, is well known for its neuroinvasiveness and persistent effects (6-8). This intracellular parasite leads to central nervous system congenital anomalies. Moreover, some delayed less serious neuropsychiatric squeal following *T. gondii* infection have been reported (2). In this study we explored the relationship between serum antibodies (IgM and IgG) to *T. gondii* and the occurrence of schizophrenia. It has been estimated that *T. gondii* involves about one third of the human population in developed countries (9). In epidemiological studies, a variety of study models have been used to prove the correlation between Toxoplasma and schizophrenia (10-12). Also, models have been used to prove the correlation between latent toxoplasmosis and schizophrenia. Various studies have shown that patients with schizophrenia are more commonly infected by *T. gondii* compared to the general population (13-16). Some of these studies have also emphasized that *T. gondii* infection has an etiological role for a subgroup of cases with schizophrenia (17). A study conducted by Deibuhr and his colleagues on United State military personnel diagnosed with schizophrenia showed higher probability of seropositivity among these individuals compared to matched military service members free from schizophrenia (18).

In 2006, Wang et al. indicated that patients with first-episode schizophrenia have increased IgG antibodies to *T. gondii* compared to the controls, which were matched in terms of age and gender (19). Laursen et al. discovered that fetuses with *T. gondii* seropositive mothers are at a higher risk of developing schizophrenia in adulthood (20). In 2007, Hinze-Selch and colleagues presented the first controlled, age-adjusted, prospective, large study on *T. gondii* infection in psychiatric patients with schizophrenia and major depression. They reported that sero-frequency did not differ between the two groups, whereas sero-intensity differed (21). The same group of investigators reported that the diagnosis of a personality disorder increases the likelihood for sero-positivity to *T. gondii* in psychiatric patients (22). Brown et al. reported that titers of more than 1/128 maternal *T. gondii* IgG antibody are associated with increased risk of schizophrenia development in the offspring by more than two folds (23).

Table 2. ELISA Results for *T. gondii* Antibody Tests in 152 Cases With Schizophrenia and 152 Healthy Controls

	Positive in Patient Group, No. (%)	Positive in Control Group, No. (%)	P value	Odd Ratio (CI [a])
***T. gondii* IgG** [b]	81 (53.2)	63 (41.4)	0.03 a	1.612 (1.024-2.536)
T. gondii IgM [b]	48 (58.5)	30 (47.6)	0.01 a	1.877 (1.109-3.176)

[a] P < 0.05
[b] CI, confidence interval; IgG, immunoglobulin G; IgM, immunoglobulin M

Table 3. Clinical and Dietary Characteristics of Cases and Controls

	Patients, No. (%) (n = 152)	Controls, No. (%) (n = 152)	P value
Positive family history of mood disorder or psychosis	19 (12.5)	29 (19.1)	0.11
History of blood transfusion	15 (9.8)	17(11.2)	0.42
Previous foreign travel	40 (26.3)	27 (17.7)	0.048 [a]
Raw meat consumption	10 (6.5)	4 (2.6)	0.08
Unwashed raw vegetables or fruits	84 (55.2)	31 (20.4)	< 0.001 [a]
Contact with soil (gardening /agriculture)	86 (56.5)	46 (30.3)	< 0.001 [a]
Animal contacts	80 (52.6)	34 (22.3)	< 0.001 [a]
Cleaning up cat feces	65 (42.7)	28 (18.4)	< 0.001 [a]

[a] P <0.05

As described in a meta-analysis, the possibility of *T. gondii* seropositivity is 2.73 times higher in schizophrenic population compared to the normal population (OR = 2.73) (15). In an animal study, it was proven that *T. gondii* causes behavioral changes in rats (6). Moreover, as described in the literature, *T. gondii*, results in behavioral changes in intermediate hosts (24, 25).

To our knowledge, this is the first study in this field to include family members of patients from the same household as the control group, to match the patients in terms of unknown risk factors for developing the disorder and also genetics which is an established etiological factor in the development of schizophrenia apart from infection with *T. gondii* (3). We performed IgM ELISA tests on blood samples of those with positive IgG results. As described in the literature, positive IgG antibody test for *T. gondii* indicates the occurrence of a previous infection. Therefor only relying on IgG serology may lead to overlooking further seroconversion. Although IgG seropositivity is associated with chronic infection and is used for initial screening, measurement of IgM is more specific as it includes seroconversion prospectively. *T. gondii* sero-positivity (IgM and IgG) was significantly different between the two groups, both indicating higher incidence of *T. gondii* infection among patients. Subjects with positive results for IgG ELISA test and negative result for IgM ELISA were regarded to have latent toxoplasmosis, whereas IgM positive results indicated acute phase of infection.

There was a significant difference between the controls and patients in terms of animal contact (53%) and also in terms of cleaning up feces (43%) indicating higher probability for patients to be infected with the parasite compared to controls. A significant difference was observed in consumption of unwashed raw vegetables and fruits and soil contact, referring to the higher chance of being infected by *T. gondii* in patients. Similar to our findings, the hypothesis on the correlation between *T. gondii* infection and the occurrence of schizophrenia has called for global attention in the recent years (26). Genetics has proven to be the most important factor in schizophrenia, while infectious agents are also considered a culprit in development of the disease (3). This originates from the fact that schizophrenia is a chronic psychotic disease, similarly, *T. gondii* is capable of being latent in a variety of organs, especially the brain; considering the increased antibody seropositivity in schizophrenic patients, it is assumed that some cases of schizophrenia are strongly related to the infection. Little is known about the potential pathophysiological mechanism of action by which *T. gondii* infection leads to schizophrenia. However, dopamine is the main neurotransmitter involved in the pathogenesis of schizophrenia. Studies have proved that neurotransmitters, such as dopamine, are relevant to some psychological disorders which occur during *T. gondii* infection, and chronic infection leads to increased dopamine level in brain cells (27). Furthermore, *T. gondii* infection leads to an increase in gene expression of indolamine 2-3 di-oxygenase and kinorenin, leading to a decline of serotonine level and derangements in glutaminergic neurotransmission in mice neural cells (21, 28). Also, it results in prominent changes in the level of nitric oxide in microglia and other neural cells (29). In an autopsy of some schizophrenic patients with positive culture *T. gondii*, a reduction in the number of asterocytes was evident (30). Neurological outcomes in congenitally transmitted toxoplasmosis is linked to MHC class II (31).

The current study showed lower age of onset in schizophrenic cases, which were infected by *T. gondii*. Previous studies have also suggested that *T. gondii* infection as a maternal parasitic infection is capable of leading to the development of schizophrenia in the offspring (22). The strong point of the present study was having family members as the controls, which was done to match the two groups (patient and control) in terms of genetic and environmental etiological factors, including socioeconomic status, housing conditions, dietary habits and other possible factors involved in acquiring the infection. As this study was a case-control study, results cannot be generalized and further epidemiological and cohort studies are recommended. It would have been beneficial if we were able to check antibody levels in all family members of each patient; as all family members did not cooperate and consent to enter the study, we remained within this limit. We suggest future cohort studies on family members of schizophrenic patients who have socioeconomic parameters of schizophrenia, and follow up in *T. gondii* infected and non-infected family members, can better define the relationship between *T. gondii* infection, prevalence and onset of the symptoms of schizophrenia.

Our results support the longstanding hypothesis of the correlation between *T. gondii* infection and schizophrenia. We also consider this parasite as a possible etiological factor in the development of selected cases of schizophrenia. Thus, long term follow up of schizophrenia-free individuals with positive serum antibody in future studies will result in the determination of the possibility of schizophrenia occurrence.

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Authors' Contribution

Mehrnoosh Ebadi, Haniyeh Akhlaghi, Mohammad Mahdi Zamani, Hani Beheshti, Hassan Abolhassani, Ahmad Ayadi, Jaleh Dezdar, Seyedeh Hamideh Mortazzavi, Gholam Reza Karami, Morteza Izadi, have cooperated in this study, by about 15%, 10%, 10%, 10%, 10%, 10%, 10%, 10%, 5% and 10% respectively.

Financial Disclosure

There are no relevant financial interests.

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References

1. Sadock BJ, Kaplan HI, Sadock VA. *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry.*: Wolter Kluwer/ Lippincott Williams & Wilkins; 2007.
2. Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol.* 2011;**93**(1):23–58.
3. Hanson DR, Gottesman II. Theories of schizophrenia: a genetic-inflammatory-vascular synthesis. *BMC Med Genet.* 2005;**6**:7.
4. Brown AS. Further evidence of infectious insults in the pathogenesis and pathophysiology of schizophrenia. *Am J Psychiatry.* 2011;**168**(8):764–6.
5. Yudofsky SC. Contracting schizophrenia: lessons from the influenza epidemic of 1918-1919. *JAMA.* 2009;**301**(3):324–6.
6. Berdoy M, Webster JP, Macdonald DW. Fatal attraction in rats infected with Toxoplasma gondii. *Proc Biol Sci.* 2000;**267**(1452):1591–4.
7. Jones JL, Kruszon-Moran D, Wilson M, McQuillan G, Navin T, McAuley JB. Toxoplasma gondii infection in the United States: seroprevalence and risk factors. *Am J Epidemiol.* 2001;**154**(4):357–65.
8. Webster JP, McConkey GA. Toxoplasma gondii-altered host behaviour: clues as to mechanism of action. *Folia Parasitol (Praha).* 2010;**57**(2):95–104.
9. Tenter AM, Heckeroth AR, Weiss LM. Toxoplasma gondii: from animals to humans. *Int J Parasitol.* 2000;**30**(12-13):1217–58.
10. Alvarado-Esquivel C, Urbina-Alvarez JD, Estrada-Martinez S, Torres-Castorena A, Molotla-de-Leon G, Liesenfeld O, et al. Toxoplasma gondii infection and schizophrenia: a case control study in a low Toxoplasma seroprevalence Mexican population. *Parasitol Int.* 2011;**60**(2):151–5.
11. 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.
12. Yolken RH, Bachmann S, Ruslanova I, Lillehoj E, Ford G, Torrey EF, et al. Antibodies to Toxoplasma gondii in individuals with first-episode schizophrenia. *Clin Infect Dis.* 2001;**32**(5):842–4.
13. Ahmad D, Mehdi S, Sayed HH, Sayed AK, Shirzad G. Serological survey of Toxoplasma gondii in schizophrenia patients referred to Psychiatric Hospital, Sari City, Iran. *Trop Biomed.* 2010;**27**(3):476–82.
14. Garcia GD. [Toxoplasmosis y enfermedades mentales]. *Rev Cub Med Trop.* 1979;**31**:127–31.
15. Torrey EF, Bartko JJ, Lun ZR, Yolken RH. Antibodies to Toxoplasma gondii in patients with schizophrenia: a meta-analysis. *Schizophr Bull.* 2007;**33**(3):729–36.
16. Torrey EF, Yolken RH. Toxoplasma gondii and schizophrenia. *Emerg Infect Dis.* 2003;**9**(11):1375–80.
17. Torrey EF, Yolken RH. Schizophrenia and toxoplasmosis. *Schizophr Bull.* 2007;**33**(3):727–8.
18. 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.
19. Wang HL, Wang GH, Li QY, Shu C, Jiang MS, Guo Y. Prevalence of Toxoplasma infection in first-episode schizophrenia and comparison between Toxoplasma-seropositive and Toxoplasma-seronegative schizophrenia. *Acta Psychiatr Scand.* 2006;**114**(1):40–8.
20. Laursen TM, Munk-Olsen T, Mortensen PB, Abel KM, Appleby L, Webb RT. Filicide in offspring of parents with severe psychiatric disorders: a population-based cohort study of child homicide. *J Clin Psychiatry.* 2011;**72**(5):698–703.
21. 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.
22. Hinze-Selch D, Daubener W, Erdag S, Wilms S. The diagnosis of a personality disorder increases the likelihood for seropositivity to Toxoplasma gondii in psychiatric patients. *Folia Parasitol (Praha).* 2010;**57**(2):129–35.
23. 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.
24. Flegr J. Influence of latent toxoplasmosis on the phenotype of intermediate hosts. *Folia Parasitol (Praha).* 2010;**57**(2):81–7.
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, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. *Schizophr Bull.* 2012;**38**(3):642–7.
27. Stibbs HH. Changes in brain concentrations of catecholamines and indoleamines in Toxoplasma gondii infected mice. *Ann Trop Med Parasitol.* 1985;**79**(2):153–7.
28. Rozenfeld C, Martinez R, Figueiredo RT, Bozza MT, Lima FR, Pires AL, et al. Soluble factors released by Toxoplasma gondii-infected astrocytes down-modulate nitric oxide production by gamma interferon-activated microglia and prevent neuronal degeneration. *Infect Immun.* 2003;**71**(4):2047–57.
29. Halonen SK, Lyman WD, Chiu FC. Growth and development of Toxoplasma gondii in human neurons and astrocytes. *J Neuropathol Exp Neurol.* 1996;**55**(11):1150–6.
30. Doyle C, Deakin JFW. Fewer astrocytes in frontal cortex in schizophrenia, depression and bipolar disorder. *Schizophr Res.* 2002;**53**(3):106.
31. Suzuki Y. Host resistance in the brain against Toxoplasma gondii. *J Infect Dis.* 2002;**185 Suppl 1**:S58–65.