

Possible Link Between *Toxoplasma gondii* Infection and Mood Disorders in Lorestan Province, Western Iran

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Abstract

Background: A large number of epidemiological evidence in humans and experimental studies in rodents have hypothesized that *Toxoplasma gondii* is a potentially relevant etiological factor in some mood disorders.

Objectives: The aim of this study was to investigate whether latent toxoplasmosis has any role in mood disorders such as schizophrenia and bipolar disease in Western Iran.

Patients and Methods: A total of 170 patients including 85 schizophrenia and 85 bipolar patients referred to the only psychiatric hospital in Lorestan province in Khorramabd city, Western Iran, and 170 healthy volunteers were screened for IgG and IgM anti-*T. gondii* antibodies by the Enzyme Linked Immunosorbent Assay (ELISA). Structured questionnaires were used to obtain information on risk factors for *T. gondii* infection.

Results: Out of the 170 psychiatric patients, 103 (63.5%) patients were seropositive for IgG antibody and 14 (8.2%) were seropositive for IgM antibody. Of the 85 bipolar patients, 54 (63.5%) and 6 (7%) were found positive for anti-*T. gondii* IgG and IgM antibodies, respectively; whereas among 85 schizophrenia patients, 49 (57.6%) and 8 (9.4%) samples were found positive for anti-*T. gondii* IgG and IgM antibodies, respectively. From 170 healthy volunteers, 73 (42.9%) tested seropositive for anti-*T. gondii* antibodies; 65 (38.2%) tested seropositive for IgG antibody and 8 (4.7%) tested seropositive for IgM antibody. There was a significant difference in *T. gondii* IgG positivity between the psychiatric patients and control groups ($P = 0.009$). Several risk factors, which were significantly related to *T. gondii* seropositivity in psychiatric patients are being in contact with cats ($P = 0.004$), eating unwashed raw vegetables ($P < 0.001$), raw-milk/egg consumption ($P = 0.001$), and drinking clean water ($P = 0.035$).

Conclusions: We concluded that psychiatric patients in general and schizophrenia and bipolar cases in particular had a significantly higher relative frequency of *T. gondii* infection than healthy individuals of Lorestan Province, Western Iran.

Keywords: Schizophrenia, Bipolar, IgG, IgM, ELISA

1. Background

Toxoplasma gondii, as an intracellular protozoan parasite, infects nearly one-third of the world's population. Reviews have reported that seroprevalence toxoplasmosis varies widely between different countries (10% - 80%), depending on social and cultural habits, geographic factors, climate and transmission routes (1). Humans can be normally infected by three main routes: [i] ingestion of tissue cysts in raw/undercooked infected meat, [ii] ingestion of sporulated oocysts with food or water, and [iii] vertical transmission from mother to fetus across the placenta (2). Approximately 80% - 90% of human *T. gondii* infections are

usually asymptomatic; however, toxoplasmosis causes severe diseases and complications including lymphadenitis, congenital infection of fetuses, and life-threatening toxoplasmic encephalitis in immunocompromised individuals (3, 4). After acute infection and during the chronic phase in the central nervous system (CNS), parasite cysts can affect neuronal cell biology and neurotransmitter synthesis, which might cause personality changes and psychotic disorders (5-8).

In order to detect this parasite, different techniques including molecular methods were used (9-13).

Previous studies regarding the prevalence of mood dis-

orders in Iran and other countries around the world have demonstrated the necessity of paying more attention to mental health. According to the world health organization (WHO), nearly 450 million individuals are affected by one type of psychological disorder(14). Nowadays, studying specific and nonspecific risk factors of these disorders has led to the primary identification of people at risk, while it plays a key role for further prevention and treatment strategies of psychological disorders (15).

Although, many epidemiological evidence in humans and experimental studies in animals have hypothesized that *T. gondii* is a potentially relevant etiological factor in some psychological disorders such as Alzheimer's disease, schizophrenia, bipolar and anxiety disorders (16-19); however some other investigations have disproved this association (20). The Lorestan province, due to having suitable climate and spread of livestock, is amongst regions with high frequency of different parasites. To date, several studies have been conducted on frequency of different parasites in this province, which have indicated considerable prevalence of certain species (21-28).

2. Objectives

The present study aimed to investigate whether latent toxoplasmosis has any role in schizophrenia and bipolar disorder in psychiatric patients of Lorestan province, western Iran, by analyzing *T. gondii* antibodies.

3. Patients and Methods

3.1. Ethics

This study was approved by the ethics committee of Lorestan University of Medical Sciences (permit No. 200.93.11707). In addition, a written informed consent was obtained from all the participants before blood sampling.

3.2. Questionnaire

Before collection of blood samples, a questionnaire was filled out by the participants, based on demographic data including age, gender, education and residence. Moreover, possible risk factors, such as animal contact (cats), raw/half-cooked meat consumption (lamb and beef), consumption of raw vegetables and raw egg/milk, gardening or agriculture activity, organ transplant etc., were also evaluated.

3.3. Study Area

This case-control study was done in the Lorestan province, which is located west of Iran between the valley of Zagros Mountains that cover an area of 28.392 km². The population of this province is about 1.6 million. Climatically, the province is divided to three parts. The mountainous regions have cold winters and moderate summers. In the central region, the spring season is from mid-February until mid-May. The southern area, because of proximity to Khuzestan province, has a hot summer and relatively moderate winter.

3.4. Study Design

This case-control study was performed with two populations: psychiatric patients (schizophrenia and bipolar disorder) and healthy individuals. In 2015, 170 patients including 85 schizophrenia and 85 bipolar patients referred to the only psychiatric clinic in Lorestan province in Khorramabd city, Western Iran, were invited to participate in this study. The patients had been diagnosed clinically by psychiatrists. All patients had no evidence of immunodeficiency or other immunologic abnormalities, no history of head trauma, previous meningitis/encephalitis, or brain surgery and absence of mental retardation or other disorders of the socio-demographic general nervous system. Regarding the exclusion criteria, patients with other psychological disorders and background diseases were excluded from the study. One hundred and seventy healthy volunteers were selected as the control group. They were screened for the absence of physical and psychiatric disorders and matched with patients based on their socioeconomic status such as dietary habits, age and gender (29, 30). It was found that the case and control groups did not differ significantly with respect to these factors ($P > 0.05$).

3.5. Sample Collection

Five milliliters of blood was obtained from each of the patients and healthy subjects by means of venipuncture, under sterile conditions. The samples were centrifuged at 500 g and the sera were stored at 20°C until serological examination. The laboratory technician who performed the assays was blind to the samples.

3.6. Enzyme-Linked Immunosorbent Assay (ELISA)

To determine the anti-*T.gondii* antibodies, serum samples were transported to the parasitology laboratory, department of parasitology and mycology, Lorestan University of Medical Sciences (Khorramabad, Iran) and stored at -20°C until use. All the serum samples were tested using the commercial kit, de EIA de Toxoplasma IgG Foresight® ACON, according to the manufacturer's instructions. The

reaction cut-off was calculated as the mean optical density (OD) for negative control sera plus three standard deviations. The positive and negative control sera were included in each plate and were obtained from the kit. The reading was performed using a microplate reader (Bio-Tek, USA) with absorbance of 450 nm. All samples were run in triplicates. The results were considered positive when OD450 index was equal or higher than the cut-off value in ELISA.

3.7. Statistical Analyses

Statistical analysis was carried out using the SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Logistic regression models were used to evaluate the association between *T. gondii* seropositivity and potential risk factors. P values of < 0.05 were considered statistically significant.

4. Results

4.1. Participants

A total of 340 samples were included in the present study; including 170 psychiatric patients (85 schizophrenia and 85 bipolar patients) and 170 healthy volunteers, as the control group. Table 1 shows the demographic characteristics of both patients and healthy controls. The mean age of the participants was 37.2 years old (ranging from 19 to 63 years old). Most participants were male (58.8%), aged 25 - 50 years old, living in urban areas, and had not college education (less than diploma) (Table 1).

4.2. Seroprevalence of Anti-*T. gondii* Antibodies

In total, 190 (55.9%) samples from both groups were found to be seropositive for anti-*T. gondii* antibodies; 168 (49.4%) were seropositive for IgG antibody and 22 (6.5%) were seropositive for IgM antibody.

Out of the 170 psychiatric patients, 103 (63.5%) patients were seropositive for IgG antibody and 14 (8.2%) were seropositive for IgM antibody. Of the 85 bipolar patients 54 (63.5%) and 6 (7%) were positive for anti-*T. gondii* IgG and IgM antibodies, respectively; whereas among 85 schizophrenia patients, 49 (57.6%) and 8 (9.4%) samples were positive for anti-*T. gondii* IgG and IgM antibodies, respectively. From the 170 healthy volunteers, 73 (42.9%) were seropositive for anti-*T. gondii* antibodies; 65 (38.2%) were seropositive for IgG antibody and 8 (4.7%) were seropositive for IgM antibody (Table 2). There was a significant difference in *T. gondii* IgG positivity between the psychiatric patients and control groups ($P = 0.009$).

Out of 200 (58.8%) male participants, 102 (51%) and 13 (6.5%) tested seropositive for anti-*T. gondii* IgG and IgM antibodies, respectively; whereas from 140 (41.2%) female participants, 66 (47.1%) and 9 (6.4%) were seropositive for anti-*T. gondii* IgG and IgM antibodies, respectively. There was

no significant difference in the relative frequency of anti-*T. gondii* IgG and IgM antibodies among the female and male patients ($P = 0.811$). As shown in Table 1, there was no significant difference in the relative frequency of anti-*T. gondii* IgG and IgM antibodies among the patients living in urban and those living in rural areas ($P = 0.146$). Regarding relative frequency adjusted by age, the differences between patients and healthy participants were not significant in any of the age subgroups ($P = 0.673$).

4.3. Risk Factors of Being Anti-*T. gondii* Antibodies

According to the analysis, several risk factors, which were significantly related to *T. gondii* seropositivity in psychiatric patients were being in contact with cats ($P = 0.004$), eating unwashed raw vegetables ($P < 0.001$), raw-milk/egg consumption ($P = 0.001$), and drinking clean water ($P = 0.035$). However, other demographic and risk factors of the psychiatric patients did not show any association with *T. gondii* seropositivity (Table 3).

5. Discussion

T. gondii is a neurotropic parasite that is considered one of the world's most successful pathogens. This parasite has remarkable transmissibility, and has permanently infected a wide range of warm-blooded animals and approximately one-third of the world's human population. Despite evidence that has demonstrated *T. gondii* infection as a possible cause of some neurological disorders such as Alzheimer disease, personality disorders, obsessive compulsive disorder, and Parkinson's disease (19), no study has reported the possible relationship between *T. gondii* infection and schizophrenia and bipolar disorders in psychiatric patients of Lorestan province, western Iran. Studies in Iran have reported that the prevalence of toxoplasmosis, depending on geographic factors and climate is widely variable; so that its prevalence in humid mild northern, cold and mountainous northwestern and western, dry and mild mountainous western, warm and dry central, and warm and humid southern regions was about 70%, 18-38%, 33-68%, 39%, and 20-35%, respectively (31, 32).

In the present study and according to the obtained results in serological (ELISA) test, we found that in bipolar patients, 54 (63.5%) and 6 (7%) samples were found positive for anti-*T. gondii* IgG and IgM antibodies, respectively; whereas among schizophrenia patients, 49 (57.6%) and 8 (9.4%) samples were found positive for anti-*T. gondii* IgG and IgM antibodies, respectively. These findings revealed a significant difference in *T. gondii* IgG seropositivity between psychiatric patients and control individuals. In line with our results, Cetinkaya et al. (2007) re-

Table 1. Demographic Characteristics and *T. gondii* Relative Frequency Among Patients and Healthy Controls^a

| Variables | Groups | | | Anti-Toxoplasma Antibodies | | | P Value |
|---|------------|------------|------------|----------------------------|----------------------|-----------|--------------------|
| | Patients | Control | Total | IgG+ | P value | IgM+ | |
| Gender | | | | | 0.484 | | 0.979 |
| Male | 97 (57.1) | 103 (60.6) | 200 (58.2) | 102 (51) | | 13 (6.5) | |
| Female | 73 (42.9) | 67 (39.4) | 140 (41.8) | 66 (47.1) | | 9 (13.6) | |
| Age groups, y | | | | | 0.673 | | 0.02 ^b |
| < 25 | 24 (14.2) | 38 (22.3) | 62 (18.2) | 29 (43.9) | | 1 (1.6) | |
| 26 - 50 | 116 (68.2) | 98 (57.7) | 214 (63.0) | 104 (48.6) | | 19 (8.7) | |
| > 50 | 30 (17.6) | 34 (20.0) | 64 (18.8) | 35 (54.7) | | 2 (3.2) | |
| Residential area | | | | | 0.146 | | 0.773 |
| Urban | 118 (69.4) | 123 (72.4) | 241 (70.9) | 113 (46.9) | | 15 (6.2) | |
| Rural | 52 (30.6) | 47 (27.6) | 99 (29.1) | 55 (55.5) | | 7 (7.1) | |
| Education | | | | | 0.02 ^b | | 0.574 |
| Less than diploma | 20 (11.8) | 22 (12.9) | 42 (12.3) | 32 (76.2) | | 3 (7.1) | |
| Diploma and above | 150 (88.2) | 148 (87.1) | 298 (87.7) | 136 (45.6) | | 19 (6.3) | |
| Being in contact with cats | | | | | < 0.001 ^b | | 0.019 ^b |
| No | 144 (84.7) | 146 (85.9) | 290 (85.3) | 131 (45.2) | | 15 (5.2) | |
| Yes | 26 (15.3) | 24 (14.1) | 50 (14.7) | 37 (74) | | 7 (14) | |
| Raw/half-cooked meat consumption | | | | | 0.01 ^a | | 0.337 |
| No | 114 (67.1) | 160 (94.1) | 274 (80.6) | 126 (46) | | 16 (5.8) | |
| Yes | 56 (32.9) | 10 (5.9) | 66 (19.4) | 42 (63.6) | | 6 (9.1) | |
| Eating unwashed raw vegetables | | | | | < 0.001 ^b | | 0.01 ^b |
| No | 112 (65.9) | 161 (94.7) | 273 (80.3) | 116 (42.5) | | 13 (4.7) | |
| Yes | 58 (34.1) | 9 (5.3) | 67 (19.7) | 52 (77.6) | | 9 (13.4) | |
| Gardening or agriculture | | | | | 0.001 ^b | | 0.233 |
| No | 71 (41.8) | 154 (90.6) | 225 (2.7) | 96 (42.6) | | 12 (5.4) | |
| Yes | 99 (58.2) | 16 (9.4) | 115 (33.8) | 72 (62.6) | | 10 (8.7) | |
| Raw-milk/egg consumption | | | | | < 0.001 ^b | | 0.666 |
| No | 11 (6.5) | 40 (23.5) | 55 (16.2) | 35 (69.1) | | 4 (7.2) | |
| Yes | 159 (93.5) | 130 (76.5) | 285 (83.8) | 133 (46.6) | | 18 (6.3) | |
| Drinking clean water | | | | | < 0.001 ^b | | 0.225 |
| No | 11 (6.5) | 9 (5.3) | 20 (5.9) | 18 (90) | | 0 (0.0) | |
| Yes | 159 (93.5) | 161 (94.7) | 320 (94.1) | 150 (46.9) | | 22 (6.8) | |
| Access to sanitation facilities | | | | | 0.239 | | 0.573 |
| No | 3 (1.8) | 4 (2.4) | 7 (2.0) | 5 (71.4) | | 0 (0.0) | |
| Yes | 167 (98.2) | 166 (97.6) | 333 (98.0) | 163 (48.9) | | 22 (6.6) | |
| Organ transplant/blood transfusion | | | | | 0.145 | | 0.885 |
| No | 159 (93.5) | 168 (98.8) | 327 (96.2) | 159 (48.6) | | 21 (6.42) | |
| Yes | 11 (6.5) | 2 (1.2) | 13 (3.8) | 9 (69.2) | | 1 (7.7) | |
| Consumption of corticosteroids | | | | | 0.905 | | 0.446 |
| No | 141 (82.9) | 168 (98.8) | 309 (90.9) | 153 (49.5) | | 19 (6.1) | |
| Yes | 29 (17.1) | 2 (1.2) | 31 (9.1) | 15 (48.4) | | 3 (9.6) | |

^a Values are expressed as No. (%).^b Statistically significant.

ported that seropositivity rate for anti-Toxoplasma IgG antibodies among schizophrenia patients (66%) was significantly higher than patients with depressive disorder or healthy volunteers ($P < 0.01$) (33). Thus, Toxoplasma infection might have a causal relationship between toxo-

plasmosis and the etiology of schizophrenia. Omar et al. (2015) revealed that the sero-frequency of *T. gondii* IgG antibodies (51.5%, 52/101) and DNA (32.67%, 33/101) among patients with schizophrenia was significantly higher than IgG (18.2%, 10/55) and DNA (3.64%, 2/55) of the controls (34).

Table 2. Seropositivity of *Toxoplasma gondii* IgG and IgM Antibodies in Psychiatric Patients and Healthy Controls^a

| Antibody | Patient Group | Healthy Individuals | P Value | OR | CI 95 |
|----------|---------------|---------------------|--------------------|------|--------------|
| IgG | Positive | 103 (60.5) | 0.009 ^b | 1.94 | 1.6 - 2.99 |
| | Negative | 67 (39.5) | | | |
| IgM | Positive | 14 (6.5) | 0.124 | 2.28 | 0.776 - 6.72 |
| | Negative | 156 (93.5) | | | |

^aValues are expressed as No. (%).^bStatistically significant.**Table 3.** Binary Logistic Regression Analysis of Potential Factors Associated With *T. gondii* IgG Sero-Prevalence Among Patients and Healthy Individuals in Lorestan Province, Iran

| Variables | IgG Positive | | | |
|----------------------------------|-------------------|----------------------|-------|----------------|
| | P Value | OR | CI 95 | |
| Education | Less than diploma | 0.014 ^a | 0.758 | 0.608 - 0.944 |
| | Diploma and above | | | |
| Being in contact with cats | No | 0.004 ^a | 0.330 | 0.154 - 0.706 |
| | Yes | | | |
| Raw/half-cooked meat consumption | No | 0.774 | 1.1 | 0.549 - 2.232 |
| | Yes | | | |
| Eating unwashed raw vegetables | No | < 0.001 ^a | 0.203 | 0.102 - 0.407 |
| | Yes | | | |
| Gardening or agriculture | No | 0.755 | 1.106 | 0.587 - 2.062 |
| | Yes | | | |
| Raw-milk/egg consumption | No | < 0.001 ^a | 0.053 | 0.017 - 0.169 |
| | Yes | | | |
| Drinking clean water | No | 0.035 ^a | 5.765 | 1.128 - 29.465 |
| | Yes | | | |

^aStatistically significant.

Alipour et al. (2011) also showed that the seropositivity rate among patients with schizophrenia (67.7%) in Tehran, Iran, was significantly higher than the control group (37.1) ($P < 0.01$) (29).

In contrast, Daryani et al. (2010) demonstrated that IgG antibodies, indicating the chronic form of toxoplasmosis, were found in 28 (35%) and 25 (25.3%) of schizophrenia patients and control groups, respectively ($P > 0.05$); however, IgM antibodies were also seen in 9 (11.2%) and 11 (11.1%) of the psychiatric patients and control group, respectively ($P > 0.05$) (30). Khademvatan et al. (2014) also showed that the seroprevalence of anti-*T. gondii* IgG antibodies in schizophrenia patients and healthy volunteers in Ahvaz, Iran, was 34% and 26.5%, respectively (35). Hamidinejat et al. (2012) also demonstrated that the positivity rate

of anti-*T. gondii* IgG antibodies among individuals with schizophrenia (57.1%) was significantly higher than healthy controls (29.2%) (36). A case-control study conducted by Cevizci et al. showed that in the schizophrenia group, the *Toxoplasma* seropositivity was 33.3%, while in the control group, the *Toxoplasma* positivity was 21.7% and there was no significant difference with regards to the seroprevalence between the two groups (37).

Consistent with our findings and regarding the relationship between *T. gondii* infection and bipolar disorder, Hamdani et al. (2013) from France, demonstrated that the sero-positive group for IgG antibodies to *T. gondii* had a 2.7-fold odds of having bipolar disorder as compared to the sero-negative group (OR=2.17 CI 95% = 1.09 - 4.36, $P = 0.028$) (38). In contrast, in the other study, there was no signif-

icantly elevated IgG seroprevalence among patients with bipolar I disorder compared to healthy individuals ($P = 0.3$) (39). These variations in the prevalence of *T. gondii* among the psychiatric patients might be related to sociocultural habits, geographical and environmental factors, sample size, and methodology in the studied population (2, 3, 40). Furthermore, there are evidences that different genotypes of *T. gondii* have diverse effects on the course of psychosis.

Here we found that there was no significant difference in *T. gondii* IgG positivity between male and female individuals in both groups. Similarly, in several studies there were no significant differences in *T. gondii* IgG positivity between males and females with psychiatric disorders including schizophrenia disorder. However, in another study, there were 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 (35).

We did not find any statistically significant difference in *T. gondii* IgG positivity when age groups were compared. Consistent with our results, various investigations did not find any significant association in *T. gondii* IgG positivity when age groups were compared. The obtained findings in the present study revealed there is no statistically significant difference in relative frequency of anti-*T. gondii* IgG between individuals living in urban and rural areas. According to these findings, residential area has no effect on the risk of toxoplasmosis. In line with our results, Khademvatan et al. (2014) and Xiao et al. (2010) found that individuals living in urban and rural areas in Iran did not have significantly different seroprevalence of *T. gondii* infection (35, 41). In contrast, Yuksel et al. and Kolbekova et al. reported a significant correlation between residences in a small town/village and toxoplasmosis (42, 43).

In this investigation, it was found that contact with cats, consumption of raw vegetables, raw-milk/egg consumption, and drinking clean water (as potential risk factors for acquiring toxoplasmosis) were associated with the seropositivity of *T. gondii* (2, 44). However, no difference was found between education, raw-milk/egg consumption, and blood transfusion on the one hand seroprevalence of anti-*T. gondii* antibodies on the other. However, other demographic and risk factors of psychiatric patients did not show any association with *T. gondii* seropositivity.

We conclude that psychiatric patients in general, and schizophrenia and bipolar cases in particular, had a significantly higher relative frequency of *T. gondii* infection than healthy individuals in Lorestan province, western Iran. The results suggest that contact with cats, consumption of raw vegetables, and contamination of drinking clean wa-

ter with oocysts, might be the most important routes of *T. gondii* transmission in our psychiatric patients. Additional studies will have to elucidate the causative relationship between infection with *T. gondii* and psychiatric disorders.

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Footnotes

Authors' Contribution: Study supervision: Farnaz Kheirandish; study concept and design: Farnaz Kheirandish, Behrouz Ezatpour and Hedayat Nazari; drafting of the manuscript: Farnaz Kheirandish, Behrouz Ezatpour and Hossein Mahmoudvand; critical revision of the manuscript for important intellectual content: Farnaz Kheirandish, Hossein Mahmoudvand and Shirzad Fallahi; statistical analysis: Mohammad Javad Tarahi; sample collection: Yaser Yaseri.

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