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An Investigation into the Association Between *Toxoplasma gondii* Infection and Bipolar Disorder

Toxoplasma gondii Enfeksiyonu ile Bipolar Bozukluk Arasındaki İlişkiye Yönelik Bir Araştırma

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ABSTRACT

Objective: Studies have implicated *Toxoplasma gondii* in the etiology of mental disorders because of its neurotropic nature and its ability to modulate neurotransmitter pathways. This study aims to investigate *T. gondii* seroprevalence in patients with bipolar disorder and in healthy controls living in the Isparta Region of Turkey and to assess the probable relationship between *T. gondii* and bipolar disorder.

Methods: Fourty-eight patients with bipolar disorder and 50 healthy controls were included in the study. Sociodemographic data, possible risk factors for *T. gondii* infection and clinical characteristics were analyzed. Serum anti-*T. gondii* IgM and IgG antibody levels were measured by using chemiluminescence immunoassay method (Roche Cobas e601 analyzer, Roche Diagnostics, Mannheim, Germany).

Results: Anti-*T. gondii* IgG seropositivity rates were determined as 18.8% and 20% in the patient group and the control group, respectively. No statistically significant relationship was observed between *T. gondii* IgG seropositivity and bipolar disorder (p=0.876). In the study population, advanced age, low education level, living in a rural region and consumption of unwashed raw vegetable or fruit were found to be the significant risk factors for *T. gondii* infection (p<0.05).

Conclusion: Our preliminary findings do not support the hypothesis that *T. gondii* infection is related to bipolar disorder. However, further studies would require larger sample sizes to confirm our results.

Keywords: *Toxoplasma gondii*, bipolar disorder, seroprevalence

ÖZ

Amaç: *Toxoplasma gondii*'nin nörotropik yapısı ve nörotransmitter yolaklarını modüle etme yeteneği nedeniyle ruhsal bozuklukların etiyolojisinde rol oynadığı öne sürülmüştür. Bu çalışmanın amacı, Türkiye'de Isparta Bölgesi'nde yaşayan bipolar bozukluğu olan hastalarda ve sağlıklı kontrollerde *T. gondii* seroprevalansını araştırmak ve *T. gondii* ile bipolar bozukluk arasındaki olası ilişkiyi değerlendirmektir.

Yöntemler: Çalışmaya bipolar bozukluğu olan 48 hasta ve 50 sağlıklı kontrol dahil edildi. Sosyo-demografik veriler, *T. gondii* enfeksiyonu için olası risk faktörleri ve klinik özellikler analiz edildi. Serum anti-*T.gondii* IgM ve IgG antikor seviyeleri kemilüminesans immunoassay yöntemi (Roche Cobas e601, Roche Diagnostics, Mannheim, Almanya) kullanılarak ölçüldü.

Bulgular: Anti-*T.gondii* IgG seropozitiflik oranları hasta grubunda ve kontrol grubunda sırasıyla %18,8 ve %20 olarak belirlendi. *T. gondii* IgG seropozitifliği ile bipolar bozukluk arasında istatistiksel olarak anlamlı bir ilişki gözlenmedi (p=0,876). Çalışma popülasyonunda, ileri yaş, düşük eğitim düzeyi, kırsal bölgede yaşama ve yıkanmamış çiğ sebze veya meyve tüketimi *T. gondii* enfeksiyonu için anlamlı risk faktörleri olarak bulundu (p<0,05).

Sonuç: Bulgularımız, *T. gondii* enfeksiyonunun bipolar bozuklukla ilişkili olduğu hipotezini desteklememektedir. Sonuçlarımızın doğrulanması için daha büyük örneklemlere sahip çalışmalara ihtiyaç bulunmaktadır.

Anahtar Kelimeler: *Toxoplasma gondii*, bipolar bozukluk, seroprevalans

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INTRODUCTION

Bipolar disorder is a debilitating chronic psychiatric disease affecting approximately 1-2% of the general population (1). Its clinical course is usually characterized by recurrent episodes of depression and mania, interspersed with normal euthymic periods, and the illness imposes a significant burden on the affected individuals and their families with serious socio-economic consequences (2,3). There are two common types of bipolar disorder: Type I (at least one episode of full-blown mania or mixed episode) and type II (several protracted depressive episodes and at least one hypomanic episode, but no full-blown manic episodes) (2). The etiology and pathogenesis of this mood disorder is not yet fully understood. Besides genetic and multiple environmental factors, immunological abnormalities and neuroinflammation have been regarded as possible contributors to the pathophysiology of bipolar disorder (4,5).

In recent years, the implication of infectious agents, especially *Toxoplasma gondii*, in the development of psychiatric disorders has gained increasing attention (5-7). Various infectious agents, bacteria, viruses or parasites, can cause neuropsychiatric symptoms both directly, by affecting neurons, glial cells and brain structures, and indirectly, by the stimulation of a microbe-specific immune response and the subsequent release of proinflammatory cytokines and neurotoxic factors (5,8,9).

T. gondii, the causative agent of toxoplasmosis, is an obligate intracellular protozoan parasite and it is assumed that approximately 25-30% of the world population is infected with this pathogen (10). In the latent stage of the infection, parasite can persist within cysts forms in neurons, microglia and astrocytes and in muscle cells throughout the life of the host (10-12). Although latent toxoplasmosis, diagnosed by immunoglobulin (Ig) G antibodies against *T. gondii*, was generally assumed to be asymptomatic in immunocompetent hosts, it is now proposed that it can induce cognitive and behavioral alterations in infected rodents and humans (5,13). The exact mechanism by which latent toxoplasmosis modifies cognition and behaviour is unclear. However, studies in animal models suggest that personality and behavior changes in rodents may occur as a result of the local inflammatory response induced by *T. gondii* neural cysts (4,13). Dormant parasites may also influence neurotransmitter pathways, and initiate a cascade of events leading to neuroinflammation and neurodegeneration by the direct stimulation of inflammatory cytokines in the central nervous system. *T. gondii* has been shown to increase dopamine concentration in the brain, as well as to modulate serotonin, glutamate and gamma-aminobutyric acid signaling, all of which are involved in the pathogenesis of psychological disturbances (4,5,14).

Among psychiatric disorders, *T. gondii* has been studied most extensively in schizophrenia, and a substantial body of literature have reported significantly increased levels of *T. gondii* antibodies in the serum of individuals with schizophrenia (4,14-16). However, contrary to schizophrenia, the role of toxoplasmosis as a risk factor for bipolar disorder remains controversial. While some studies have demonstrated a positive correlation between *T. gondii* seropositivity and bipolar disorder, others have not supported the role of *T. gondii* infection as a putative risk factor for bipolar disorder (4,5,7,14,17-27).

In Turkey, there is limited information about the epidemiology of *T. gondii* infection in psychiatric patients, and only one study was conducted examining the possible relationship between *T. gondii* and bipolar disorder (21). The aim of the present study was to investigate *T. gondii* prevalence in individuals with bipolar disorder and in healthy controls living in Isparta region of Turkey by using serologic diagnostic methods, and to evaluate the correlation between *T. gondii* and this mood disorder.

METHODS

This cross-sectional study was performed at the Department of Psychiatry in collaboration with the Department of Medical Microbiology, Süleyman Demirel University Research and Practice Hospital, between January 2019 and December 2019. Ethical approval was obtained from the Ethics Committee of Süleyman Demirel University Faculty of Medicine. The research was conducted in accordance with the Helsinki Declaration, and written informed consent was taken from all the participants.

Patients and Controls

Subjects with any autoimmune disease, malignancy, severe chronic disease, recent infectious disease, comorbid psychiatric disease, cognitive impairment or dementia were excluded from the study. In the patient group (n=48), the diagnosis of bipolar disorder was established by an experienced psychiatrist according to the diagnostic and statistical manual of mental disorders, fourth edition, text revision criteria via independent clinical interview. The young mania rating scale (YMRS) and the Hamilton depression rating scale (HDRS) were used to evaluate the severity of manic and depressive symptoms, respectively. Euthymia was determined by YMRS score less than 7 and HDRS score less than 7 points. The control group (n=50) consisted of healthy volunteers with no personal or family history of psychiatric disorder attending outpatient clinics for routine health check-up. Data concerning probable risk factors for *T. gondii* infection (current or past living in a rural region, contact with cats; having a cat at home or playing closely with cats, consumption of raw or undercooked meat, consumption of unwashed raw vegetable or fruit, contact with soil; gardening or agricultural activities), socio-demographic data (age, gender, education level, socio-economic status) and clinical characteristics (bipolar disorder type, current mood status, duration of illness, number of lifetime episodes, YMRS, HDRS, family predisposition, suicide attempt history, lifetime total duration of medication) were recorded after clinical interviews.

Serological Analysis

Venous blood samples were taken from each subject, and then centrifuged prior to analysis. The serum anti-*T. gondii* IgM and IgG levels were measured by using an automated chemiluminescence immunoassay method (Roche Cobas e601 analyzer, Roche Diagnostics, Mannheim, Germany). Anti-*T. gondii* IgM test result of ≥1.0 COI and anti-*T. gondii* IgG test result of ≥3 IU/mL were considered as positive, according to the manufacturer's guidelines. All positive test results were retested in duplicate. The presence of anti-*T. gondii* IgM antibody suggested recent infection, while a positive test result for anti-*T. gondii* IgG antibody indicated past infection with *T. gondii*.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, IL, USA).

The Kolmogorov-Smirnov test was used to assess the normality of the data. Accordingly, Student's t-test or Mann-Whitney U test was used to compare the differences in continuous variables between groups. The chi-square test with Bonferroni correction was used for categorical variables. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Results were expressed as frequencies and percentages, or mean ± standard deviation. A p-value of <0.05 was considered statistically significant.

RESULTS

Fourty-eight patients with bipolar disorder (35 were type I and 13 were type II) and 50 healthy controls with similar age and sex distribution were included in the study. Comparison of socio-demographic data, possible risk factors for *T. gondii* infection, *T. gondii* seropositivity status and clinical characteristics in the patient and control groups is shown in Table 1.

None of the subjects was in an acute phase of *T. gondii* infection and revealed anti-*T. gondii* IgM seropositivity. Anti-*T. gondii* IgG positivity was found in 9 (18.8%; CI: 10.2-31.9) of the 48 patients with bipolar disorder and in 10 (20%; CI: 11.2-33) of the 50 control subjects (Table 1). No statistically significant association was observed between *T. gondii* IgG seropositivity and bipolar disorder (OR=0.923; CI: 0.339-2.516, p=0.876). In terms of IgG titers (serointensity), the difference was not significant (p=0.619) between the seropositive patients (293.84±180.23 IU/mL) and the seropositive controls (240.81±262.57 IU/mL) (data not shown).

The patient group and the control group did not differ significantly for age, age subgroups, gender, education level, socio-economic status, residence in rural region, contact with cats, raw or undercooked meat consumption, unwashed raw vegetable or fruit consumption and contact with soil (p>0.05) (Table 1).

In the patient group, six (66.7%) of the seropositive patients (n=9) were diagnosed as type II bipolar disorder and 3 (33.3%) of them as type I bipolar disorder (data not shown). The seropositive patients were found to be significantly (p=0.004) older than the seronegative patients (Table 2). Consumption of unwashed raw vegetable or fruit also differed significantly (p=0.001) between the seropositive patients and the seronegative patients (Table 2).

In the study population (n=98), there were significant differences in the age (p=0.001), education level (p=0.015), residence in rural region (p=0.039) and unwashed raw vegetable or fruit consumption (p=0.001) between the seropositive participants (n=19) and the seronegative participants (n=79) (Table 2). Advanced age, low education level, living in a rural region and consumption of unwashed raw vegetable or fruit were determined as the significant risk factors for *T. gondii* infection in our study population.

DISCUSSION

Its neurotropic nature and the ability of affecting neurotransmitter pathways and immune system functions have made *T. gondii* an attractive candidate as a potential causative agent for psychiatric and neurodegenerative disorders (6,15). In contrast to numerous publications dealing with the relationship between *T. gondii* and schizophrenia (15,16), the link between this pathogen and bipolar disorder was relatively understudied. In addition, available data are still inconsistent (4). In this regard, we aimed to determine whether bipolar disorder is associated with *T. gondii* seropositivity in our study population in Isparta, Turkey.

It is well-known that the prevalence of *T. gondii* infection varies widely by age, ethnic group, nutritional habits, socio-economic status, and geographic region (10,11). For instance, according to the seroprevalence studies in different countries, the IgG seropositivity rate was reported as 4% in South Korea, 9% in England, 11% in China, 23% in Italy, 35% in New Zealand, 42% in Egypt, 50% in Brazil, 54% in France, 60% in Argentina, and 76% in Costa Rica (28). In our country, the seroprevalence of toxoplasmosis varies among different regions and populations, ranging from 17.5% to 69.5% (29,30). In the present study, we found anti-*T. gondii* IgG positivity rates as 18.8% and 20% in the patient group and control group, respectively. The seropositivity rates in both groups were similar to the findings reported in *T. gondii* seroprevalence studies in our country. However, the difference between the groups was not statistically significant (p>0.05) in terms of association between *T. gondii* infection and bipolar disorder.

In contrast to our findings, some researchers have found significantly elevated *T. gondii* seroprevalence in patients with bipolar disorder (7,14,18-20). An Ethiopian case-control study (18) revealed a significantly higher seropositivity rate for *T. gondii* infection (OR:3) in bipolar patients (95.3%) compared to unaffected controls (87.3%). In another case-control seroprevalence study from France, the prevalence of *T. gondii* infection was compared in a sample of 110 patients with bipolar disorder and 106 healthy controls (7). The results of this study showed that the seropositive group for IgG antibodies had a 3.6 fold increased odds of having the disease as compared to the seronegative group. In a population-based cross-sectional survey conducted in the United States, Pearce et al. (14) reported that *T. gondii* seroprevalence was not elevated in unipolar mood disorders (p>0.05), but a significant association was found between *T. gondii* seroprevalence and bipolar disorder type I (OR=2.4, p<0.05).

Due to the neurotropic properties of *T. gondii* as noted above, the hypothesis that *T. gondii* may be a possible cause of bipolar disorder seems quite reasonable. However, there are some difficulties with this proposition as also indicated in previous publications (6,15), and debate still exists on this causal relationship. The main issue is the obvious epidemiological inconsistency. Countries with a high seroprevalence of toxoplasmosis do not have a corresponding increased bipolar disorder prevalence and unlike toxoplasmosis, bipolar disease does not exhibit such marked geographic variation in prevalence (1,6). Hence, if *T. gondii* causes bipolar disorder as suggested, it can only lead to bipolar disorder in a fraction of individuals it infects. Secondly, in previous studies, it has not been feasible to demonstrate a relation between toxoplasmosis and the timing of onset of this psychiatric disease. Bipolar disorder is a complex condition that results from multiple interacting factors and it can be very difficult to show solely this relation. Lastly, if the relation between toxoplasmosis and bipolar disorder is confirmed, specific anti-protozoal therapy may prevent the development of bipolar disorder. However, there is not yet strong evidence from treatment trials that precisely evaluated the efficacy of anti-protozoal therapy against toxoplasmosis in patients suffering from bipolar disorder (6,7).

Furthermore, it should be noted that there have been some studies which have failed to find a statistically significant association between exposure to *T. gondii* and risk of bipolar disorder (21-

Table 1. Comparison of socio-demographic data, possible risk factors for *T. gondii* infection, *T. gondii* seropositivity status and clinical characteristics in the patient and control groups

	Patient group (n=48)	**Control group (n=50)**	**p**
Age (years)	37.13±12.19	36.08±14.44	0.700
Age subgroups			0.060
18-29 years	13 (27.1)	25 (50)	
30-49 years	27 (56.3)	18 (36)	
>50 years	8 (16.6)	7 (14)	
Gender (male/female)	21 (43.8)/27 (56.2)	23 (46)/27 (54)	0.823
Education level			0.076
Primary school	15 (31.3)	7 (14)	-
High school	16 (33.3)	16 (32)	
Higher education	17 (35.4)	27 (54)	
Socio-economic status			0.078
Low	6 (12.5)	12 (24)	
Middle	38 (79.2)	29 (58)	
High	4 (8.3)	9 (18)	
Residence in rural region	16 (33.3)	16 (32)	0.888
Contact with cats	17 (35.4)	15 (30)	0.568
Raw or undercooked meat consumption	8 (16.7)	4 (8)	0.191
Unwashed raw vegetable/fruit consumption	15 (31.3)	11 (22)	0.300
Contact with soil	17 (35.4)	24 (48)	0.207
Anti-*T. gondii* IgG positivity	9 (18.8)	10 (20)	0.876
Anti-*T. gondii* IgM positivity	0 (0)	0 (0)	
Bipolar disorder type (type 1/type 2)	35 (72.9)/13 (27.1)	-	
Current mood status		-	
Depression	4 (8.3)	-	
Mania	21 (43.8)	-	
Remission	23 (47.9)	-	
Duration of illness (years)	10.5±8.67	-	
Number of lifetime episodes	4.94±4.16	-	
Young mania rating scale score	10.46±9.64	-	
Hamilton depression rating scale score	7.83±6.37	-	
Family predisposition	12 (25)	-	
Suicide attempt history	9 (18.8)	-	
Lifetime total duration of medication (years)	9.32±8.42	-	

Values are expressed as n (%) or mean ± standard deviation

27). To our knowledge, only one study in our country investigated the possible relationship between *T. gondii* infection and bipolar disorder, and no significant relationship was detected in this study (21). In an Iranian sample including 117 patients with bipolar disorder type I and 200 control subjects, the authors found no significant difference between *T. gondii* seropositivity and bipolar disorder (22). Similarly, in other studies with smaller sample sizes conducted in Germany (23,24) and Mexico (25), no significant relationship between *T. gondii* seroprevalence and bipolar disorder was reported. In a recent meta-analysis included 11 different studies investigating the association between *T. gondii* and bipolar disorder, Snijders et al. (31) revealed that the overall OR was not significant for *T. gondii* (OR=1.4, p>0.05). However, the authors indicated that *T. gondii* exposure may be a risk factor for bipolar disorder in certain age groups and subpopulations (31).

Prenatal exposure to neurotropic infectious agents is known to be a possible risk factor for later development of mental disorders. Several studies demonstrated that maternal infection with *T. gondii* was associated with a higher risk of schizophrenia in adult offspring (15,16). However, in two different case-control studies performed by Mortensen et al. (32), and Freedman et al. (33), no statistically significant association was observed between prenatal exposure to *T. gondii* and the risk of bipolar disorder in adult offspring. The authors suggested that congenital *T. gondii*

Table 2. Comparison of socio-demographic data and possible risk factors for *T. gondii* infection in seropositive/seronegative patients and in all seropositive/seronegative participants

	Seropositive patients (n=9)	Seronegative patients (n=39)	p	All seropositive participants (n=19)	All seronegative participants (n=79)	p
Age (years)	49.55±14.64	34.25±9.68	**0.004**	53.84±15.87	32.44±8.54	**0.001**
18-29 years	1 (11.1)	12 (30.8)		2 (10.5)	36 (45.6)	
30-49 years	2 (22.2)	25 (64.1)		4 (21.1)	41 (51.9)	
>50 years	6 (66.7)	2 (5.1)		13 (68.4)	2 (2.5)	
Gender (female)	5 (55.6)	22 (56.4)	0.963	10 (52.6)	44 (55.7)	0.809
Education level			0.594			**0.015**
Primary school	4 (44.4)	11 (28.2)		9 (47.4)	13 (16.5)	
High school	2 (22.2)	14 (35.9)		4 (21.1)	28 (35.4)	
Higher education	3 (33.4)	14 (35.9)		6 (31.5)	38 (48.1)	
Socio-economic status			0.585			0.068
Low	1 (11.1)	5 (12.8)		6 (31.5)	12 (15.2)	
Middle	8 (88.9)	30 (76.9)		13 (68.5)	54 (68.3)	
High	0 (0)	4 (10.3)		0 (0)	13 (16.5)	
Residence in rural region	3 (33.3)	13 (33.3)	1.000	10 (52.6)	22 (27.8)	**0.039**
Contact with cats	4 (44.4)	13 (33.3)	0.530	9 (47.4)	23 (29.1)	0.128
Raw or undercooked meat consumption	2 (22.2)	6 (15.4)	0.620	4 (21.1)	8 (10.1)	0.192
Unwashed raw vegetable/fruit consumption	7 (77.8)	8 (20.5)	**0.001**	11 (57.9)	15 (19)	**0.001**
Contact with soil	3 (33.3)	14 (35.9)	0.885	9 (47.4)	32 (40.5)	0.586

Values are expressed as n (%) or mean ± standard deviation

infection could be a risk factor only for the development of schizophrenia and related psychosis, but not for bipolar disorder. Reasons for this contradictory results across the studies mentioned above are not known with certainty, but may include methodological differences in the serological diagnosis, differences in the prevalence of *T. gondii* infection, the timing of infection, or differences in the genetic background of the participants. On the other hand, our study has the similar limitations that were pointed out in previous seroprevalence studies. Failure to estimate the initiation of exposure is one of the most important difficulties in these studies, and in our research, we were not able to determine the duration of exposure to *T. gondii* infection in patients with bipolar disorder. Control subjects did not undergo a structured clinical interview like DSM-IV, the absence of personal or family history of psychiatric disorder in the control group was obtained from their statements (via non-structured clinical interview) and their medical records. Another limitation was that medications (mood stabilizers, antipsychotics, etc.) or other unpredictable confounding factors might affect the antibody levels in patient group. Furthermore, our results should be interpreted with caution because of relatively small sample size. Beside these limitations, the present study has a number of strengths. First, we minimized unwanted heterogeneity by studying participants with similar chronological age. Because of the fact that the prevalence of *T. gondii* infection increases with age, it is important to reduce the chance of fraudulent relationships obtaining from age-related exposure differences. Second, we used an automated and standardized laboratory method to determine the serum antibody levels.

CONCLUSION

In conclusion, our preliminary findings do not support the hypothesis that latent *T. gondii* infection is related to bipolar disorder. However, in the presence of conflicting reports, the potential role of toxoplasmosis in bipolar disorder cannot be completely ruled out. It is necessary to perform further studies with larger sample sizes to clarify the effect of latent toxoplasmosis on the development of bipolar disorder.

* Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Süleyman Demirel University Faculty of Medicine (decision no: 242, date: 13/12/2018).

Informed Consent: Written informed consent was taken from all the participants.

Peer-review: Internally peer-reviewed.

* Authorship Contributions

Surgical and Medical Practices: F.K., A.D., Concept: M.C.Ş., F.K., B.A., E.S.Ç., Design: M.C.Ş., F.K., B.A., E.S.Ç., Data Collection or Processing: M.C.Ş., F.K., A.D., B.A., E.S.Ç., Analysis or Interpretation: M.C.Ş., F.K., A.D., B.A., E.S.Ç., Literature Search: M.C.Ş., A.D., B.A., E.S.Ç., Writing: M.C.Ş., F.K.

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