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Relationship between *Toxoplasma gondii* seropositivity and depression in children and adolescents

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ABSTRACT

Identification of the structural causes of depression is important for the treatment process, and toxoplasmosis may be related to psychiatric disorders. The aim of this study was to evaluate the relationship between *Toxoplasma gondii* (*T. gondii*) seropositivity and depression in children and adolescents.

This case-control study included 37 children and adolescents aged 11–18 years diagnosed with depression who were followed by the Manisa Celal Bayar University Child and Adolescent Mental Health Service and 36 children and adolescents aged 11–18 years with no history of depressive episodes or psychiatric disorder treated by the Pediatric Outpatient Department. The *T. gondii* serology of these two groups was evaluated and compared.

There were no statistically significant age or sex differences between the 37 participants with depression and the 36 healthy controls. Eight patients and two controls were seropositive for *T. gondii*, a statistically significant difference ($p = 0.046$). Seropositivity was significantly higher in patients with suicidal ideation ($p = 0.005$) than in those without suicidal ideation. The seropositivity of seven of the nine participants who attempted suicide was significantly higher ($p < 0.001$) than that of participants who did not.

Thus, *T. gondii* infection may affect the predisposition for and severity of depression.

1. Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular parasite that can infect eukaryotic cells. Humans are infected through various transmission modes, such as exposure to oocytes in cat feces, eating uncooked meats, vertical transmission from an infected mother, blood transfusion, and organ transplants. The course of *T. gondii* infection is usually asymptomatic in immune-competent humans (Dubey and Jones, 2008), and reactivation of latent *T. gondii* after primary infection is rare. Reactivation is thought to occur only in immune-compromised individuals, such as patients with acquired immunodeficiency syndrome (AIDS) or organ transplants. The clinical manifestations of this condition include encephalitis, korioretinitis, lymphadenopathy, and systemic infection (Kim and Weiss 2008). Moreover, latent toxoplasmosis has been found to affect human behavior (Flegr, 2007; Fekadu et al., 2010). Indeed, numerous studies have evaluated the relationship between exposure to *T. gondii* and development of psychological disorders. Although some of these studies are controversial (Sugden et al., 2016; Gale et al., 2014; Çakın-Memik et al., 2015; Miman et al., 2019), others have reported that *T. gondii* seropositivity is related to schizophrenia, bipolar disorder (BD), generalized anxiety disorder, obsessive compulsive-disorder (OCD), suicide, aggression, and impulsivity (Sutterland et al., 2015; Markovitz et al., 2015; Akaltun et al., 2018a; Cook et al., 2015; Zhang et al., 2012). Neuropsychiatric disorders are related to both host factors and parasitic factors. Host factors consist of genetic susceptibility and immunological factors as well as age at, duration of, and brain region of infection. Parasitic factors include the transmission mode, developmental stage of the parasite, number of exposures to the parasite, and virulence of the strain (types I–III) (Fabiani et al., 2015). For this reason, neuropsychiatric symptoms can vary by geographic region and age. Thus, although it is important to understand such differences, limited research has addressed this issue in children and adolescents. Recent studies in children and adolescents have examined OCD, anxiety disorder, tic disorder, and attention deficit hyperactivity disorder (ADHD) (Akaltun et al., 2018a; Çakın-Memik et al., 2015; Miman et al., 2019; Afsharpaiman et al., 2017; Akaltun et al., 2018b; Khademvatan et al., 2018). To the best of our knowledge there has been no research on the association of toxoplasmosis and depression in children and adolescents.

The etiopathogenesis of the relationship between *T. gondii* and

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depression can follow several routes. First, chronic toxoplasma infection can directly cause brain cysts, as it does in other organs. Indeed, it can infect neurons, microglia, and astrocytes in the cerebral hemisphere, hippocampus, amygdala, basal ganglia, cerebellum, cortex, and brain stem. Brain lesions can lead to psychiatric symptoms and paracrine secretion, affecting brain functions in the surrounding area (Fabiani et al., 2015).

Serotonin, norepinephrine, and dopamine dysfunction are thought to be the primary underpinnings of major depression (Elhwuegi, 2004). According to the monoamine deficiency hypothesis, depressive symptoms result from a monoamine neurotransmitter deficiency (Delgado, 2000). T lymphocytes and natural killer (NK) cells release inflammatory cytokines, such as TNF-alpha and IFN-gamma, when the immune response is activated by infections such as *T. gondii*; these cytokines, in turn, induce indolamine 2,3 (IDO) enzyme secretion, which activates tryptophan in the kynurenin pathway. As a result, tryptophan levels and serotonin production diminish. Studies have shown that both major depression and suicidal behavior are related to serotonin levels (Mann, 2003). Inflammatory responses to infections such as *T. gondii* are regarded as important underlying mechanisms of increased depression and suicidal behaviors (Haroon et al., 2012; Sperner-Unterweger et al., 2014). The parasite genome consists of two aromatic amino acid hydroxylases that affect dopamine and serotonin biosynthesis, leading to depression and dopamine and serotonin biosynthesis defects (Gaskell et al., 2009).

This study evaluated the relationship between *T. gondii* and depression in children and adolescents.

2. Methods

This study was performed at the Manisa Celal Bayar University (MCBU) Medical Faculty Child and Adolescent Mental Health Outpatient Clinics. Ethical approval was granted by the MCBU Medical Sciences Ethics Committee, and the study was supported by the MCBU Coordinator of Scientific Research Projects (2017–173). Written informed consent was obtained after a detailed briefing was provided to all participants and their parents.

The sample size was calculated using the power analysis method; an effect size of 0.60 and a power of 0.70 (alpha 0.05) required a sample of 35/35 people for a case/control study.

Thirty-seven patients aged 11–18 years treated by the MCBU Medical Faculty Child and Adolescent Mental Health Outpatient Clinics between June 1, 2017, and February 19, 2018, and diagnosed with depression according to the Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-5) criteria were included. The inclusion criteria were aged 11–18 years, written informed consent, and normal mental capacity. Patients with mental retardation, developmental disabilities, neurological or medical disorders, psychotic disorders, or autistic spectrum disorder were excluded.

The control group consisted of 36 children and adolescents aged 11–18 years with the same sociodemographic characteristics as the depression group who had been treated by the Pediatric Outpatient Clinics of the MCBU Medical Faculty between June 1, 2017, and February 19, 2018. We excluded subjects with mental retardation, developmental disabilities, neurological disorders, comorbid conditions, or an active psychiatric disease according to the Schedule for Affective Disorders and Schizophrenia for School-age Children-Current and Lifelong-Turkish Version (KSADS-PL-CL-T) and those with a history of psychiatric illness.

In addition to the KSADS-PL-CL-T, we conducted psychological interviews with all participants to identify psychiatric diagnoses. Participants also completed the DSM-5 Level 2-Depression-Child Age 11–17 (PROMIS Emotional Distress-Depression-Pediatric Item Bank) and the DSM-5 Level 2-Irritability-Child Age 11–17 (Affective Reactivity Index [ARI]). Mental capacity was evaluated with clinical interviews, and those with normal mental capacity and no problems in basic adaptative skills (school achievment, reading, writing, comprehension, reasoning, problem solving, etc.) were included.

We took a 2-cm^3 venous blood sample for serological tests; these were stored at −20 °C. All blood samples were analyzed for anti-toxoplasma IgG and IgM antibodies using enzyme-linked immunosorbent assay (ELISA) (Abbott, USA). A different ELISA (Radim, Italy) was used for the avidity test. Results at 0.55 IU/mL were considered negative, those at 0.55–0.65 IU/mL borderline, and those at 0.65 IU/mL and above positive. The IgG at 4 IU/mL was considered negative, whereas it was considered borderline at 4–8 IU/mL and positive at 8 IU/mL and above.

We took a 2-cm^3 venous blood sample for serological tests; these were stored at −20 °C. All blood samples were analyzed for anti-toxoplasma IgG and IgM antibodies using ELISA (Abbott, USA), as a current infection can be distinguished from a past infection based on the type of antibodies present (IgG or IgM). During acute infection, IgM antibodies are detected in serum. The IgM values were considered slightly negative at 0.55 IU/mL, suspicious at 0.55–0.65 IU/mL, and positive at 0.65 IU/mL and higher. The IgG values were considered negative < 4 IU/mL, suspicious at 4–8 IU/mL, and positive at 8 IU/mL. The IgG avidity test was developed to help discriminate between past and recently acquired infections. Following antigenic challenge, the IgG antibodies initially produced bind weakly to the antigen (low avidity). As the immune response develops, the IgG antibody response matures, and the avidity progressively increases over weeks or months (high avidity). The IgG avidity levels in patients with Toxoplasma IgG positivity were determined by ELISA. Toxoplasma IgG Avidity EIA Well-RADIM® (Italy) kits were used according to the manufacturer's instructions. According to the avidity percentage values in the user manual, low avidity is <20%, high avidity is >30%, and values of 20–30% (gray zone) are considered suspicious.

3. Assessment tools

1 A sociodemographic data form was used to collect data on the sociodemographic characteristics of the study population. Socioeconomic level was based on the educational level and employment status of the parents.
2 Schedule for Affective Disorders and Schizophrenia for School-age Children-Current and Lifelong Turkish Version (KSADS-PL-CL-T): This is a semi-structured interview form developed by Kaufmann et al. (1997) to identify current or prior psychopathology. Gökler et al. (2004) performed validity and reliability studies on a Turkish sample. This test was administered to all patients and controls.
3 The DSM-5 Level 2-Depression-Child Age 11–17 (PROMIS Emotional Distress- Depression-Pediatric Item Bank): This scale, which addresses the criteria for depressive disorder, consists of 14 items regarding symptoms during the last 7 days and response to treatment using a five-point Likert-type scale (1 = never; 2 = almost never; 3 = sometimes, 4 = often; 5 = almost always). Total scores range from 14 to 70, with higher scores indicating greater severity (Online Assessment Measures, 2013). The Turkish version was developed by Yalın Sapmaz et al. (2017a).
4 DSM-5 Level 2-Irritability-Child Age 11–17 (Affective Reactivity Index [ARI]): This self-report measure assesses irritability in children and adolescents (11–17 years old) in terms of seven items, each rated on a three-point Likert-type scale (0 = not true; 1 = somewhat true; 2 = definitely true). Scores on the first six items range between 0 and 12, and higher scores indicate more severe irritability (online assessment measures, 2013). The Turkish version was developed by Yalın Sapmaz et al. (2017b).

4. Statistical analysis

All analyses were performed using the Statistical Package for Social

Sciences (SPSS 15.0). Data on categorical variables are presented as mean ± standard deviation; data on categorical sociodemographic and clinical variables and on scale scores are presented as percentages and numbers. The means of two normally distributed variables were compared using the Student's *t*-test, and the Mann–Whitney *U* test was used were used to compare non-normally distributed data. Categorical data were also analyzed using chi-square tests and Fischer's exact test, and the strength and direction of correlations involving normally distributed data were determined by Pearson's test; those of non-normally distributed data were determined by Spearman's correlation coefficients. Statistical significance was set at $p < 0.05$.

5. Results

We evaluated 37 patients with depression and 36 healthy controls. The mean age of the depression group was 15.6 ± 1.59 years, and that of the control group was 14.55 ± 1.90 years. There were 31 (83.8%) girls and 6 (16.2%) boys in the depression group; the control group included 24 (66.7%) girls and 12 (33.3%) boys. The gender composition of the two groups did not differ significantly. Socioeconomic level was evaluated based on mothers' and fathers' education level and employment status; the two groups did not significantly differ in this regard (Table 1).

In the depression group, 26 (70.3%) respondents had a comorbid psychiatric disorder: anxiety disorder (14), conduct disorder (8), eating disorder (1), sexual identity disorder (1), OCD (1), and ADHD (1).

Eight participants (21.6%) in the depression group and two (5.6%) participants in the control group were positive for anti-toxoplasma IgG, a significant difference between the two groups ($p = 0.046$) (Table 2). All participants were Toxoplasma IgM negative.

Toxoplasma avidity values, which indicate time of infection, were positively correlated with DSM-5 Level 2-Depression-Child Age 11–17 and DSM-5 LEVEL 2-Irritability-Child Age 11–17 scores (Table 3).

Eight (38.1%) of the 21 participants in the depression group with suicidal ideation had positive toxoplasma IgG results, and the toxoplasma IgG results were negative in the remaining 16 participants. The IgG results were positive in 7 (77.8%) of the 9 patients with a history of suicide attempts. The IgG results were positive in 1 (3.6%) of the 28 patients with no suicide history. The IgG-positivity rate of patients with both suicidal ideation and a suicide attempt were higher than that in patients without suicidal ideation and those without a suicide attempt ($p = 0.005$ and $p < 0.001$, respectively) (Table 4 and 5).

We evaluated the relationship between toxoplasma IgG positivity and co-morbidity in the depression group. The toxoplasma IgG values were positive in 7 (26.9%) of the 26 patients with a co-morbid condition and in 1 (9.1%) of the 11 patients without one ($p = 0.391$).

Table 1
Sociodemographic characteristics of study population.

	Depression group $n = 37$	Control group $n = 36$	p
Age	15.16 ± 1.59	14.55 ± 1.90	0.144
Sex F/M	31/6	24/12	0.077
Working/Non-working mother	13/24	7/29	0.133
Working/Non-working father	32/5	35/1	0.199
Maternal educational level			0.287
Primary school	28	21	
Middle school	5	8	
High school/University	4	7	
Paternal educational level			0.564
Primary school	19	14	
Middle school	5	6	
High school/University	13	16	
DSM 5 Level 2 Depression: Aged 11–17	52.70 ± 9.51	23.77 ± 7.95	0.000
DSM-5 Level 2-Irritability: Aged 11–17	9.75 ± 3.74	3.30 ± 3.19	0.000

Table 2
The comparison of toxoplasma IgG positivity in two groups.

	Depression group ($n = 37$)	Control group ($n = 36$)	p
Toxoplasma IgG +	8 (21.6%)	2 (5.6%)	0.046
Toxoplasma IgG -	29 (78.4%)	34 (94.4%)	

Table 3
The correlation of toxoplasma avidity values and scale scores.

	R	p
DSM 5 LEVEL 2 Depression, Child Age 11–17	0.307	0.008
DSM 5 LEVEL 2 Irritability, Child Age 11–17	0.323	0.005

Table 4
The comparison of toxoplasma IgG positivity in patients with suicidal ideation and patients without suicidal ideation among depression group.

	With suicidal ideation ($n = 21$)	Without suicidal ideation ($n = 16$)	p
Toxoplasma IgG +	8 (38.1%)	0 (0%)	0.005
Toxoplasma IgG -	13 (61.9%)	16 (100%)	

Table 5
The comparison of toxoplasma IgG positivity in patients with suicide attempt and patients without suicide attempt among depression group.

	With suicide attempt ($n = 9$)	Without suicide attempt ($n = 28$)	p
Toxoplasma IgG +	7 (77.8%)	1 (3.6%)	0.005
Toxoplasma IgG -	2 (22.2%)	27 (96.4%)	

6. Discussion

The *T. gondii* IgG seropositivity rate of the depression group was higher than that of the healthy controls. Research performed in Mexico by Alvarado-Esquivel et al. (2016) found *T. gondii* IgG antibody positivity in 11 (12.4%) of 89 patients with depression and in 22 (6.2%) of 356 controls without depression; the current study also reported a relationship between *T. gondii* and depression. Additionally, Duffy et al. (2015) found a relationship between *T. gondii* infection and depression and dysphoric mood. A population-level study in Finland suggested that *T. gondii* seropositivity and serointensity were related to depressive symptoms (Suvisaari et al., 2017). A study using a mouse model reported that chronic *T. gondii* infection was reactivated by an immunosuppressive regimen and induced behaviors related to depression (Mahmoud et al., 2016). Fond et al. (2015) found that BD patients with positive serum antibodies against *T. gondii* exhibited more lifetime depressive episodes when treated by drugs with no anti-toxo activity compared to patients treated by drugs with anti-toxo activity. Our results are compatible with these studies.

In contrast, other studies found no relationship between *T. gondii* infection and depression. For example, the third US National Health and Nutrition Examination Survey (NHANES) found no relationship between *T. gondii* seroprevalence and major depression (Pearce et al., 2012). A meta-analysis of 50 studies that evaluated the relationship between *T. gondii* infection and various psychiatric disorders (Sutterland et al., 2015) found that the strength of relationship between *T. gondii* and mental disorders in Africa, South America, Asia, and the Middle East was higher than that in Europe and North America. They suggested that these results may be attributable to differences in the strains studied (Sutterland et al., 2015). Indeed, genotype studies of *T. gondii* have identified three main serotypes: genotypes (Type I, II, and

III), recombinant, and atypical strains. Genotype II is the most common strain in Europe, whereas Types I and III are more common in South America. Chorioretinitis is more severe in Brazil than in Europe. It is possible that different genotypes have different levels of virulence and cause different disease patterns (Boothroyd and Grigg, 2002; Lehmann et al., 2006). In a mouse model, all animals infected by toxoplasma showed increased anxiety, but only those with genetic susceptibility exhibited depressive behaviors (Bay-Richter et al., 2019). Differences in the prevalence and virulence in different populations may be attributable to genetic variations in *T. gondii* and in the host. Additional studies that examine parasite typology and human factors (e.g., immune system characteristics and genetic background) are needed to clarify human susceptibility and toxoplasmosis resistance (Xiao and Yolken, 2015). Studies in the literature that could not find a relationship between depression and toxoplasmosis were conducted in adults. Another possible explanation of the inconsistent results may relate to the age of the participants in our study. An animal study suggested that age at *T. gondii* exposure was related to psychiatric symptoms, as it identified age-related differences in glutamatergic, GABAergic, and monoaminergic system markers and regional expression of NMDAR subunits. Additionally, it is possible that age at *T. gondii* exposure is an important contributor to the development of various behavioral and neurobiological abnormalities (Kannan et al., 2016). There is positive correlation between toxoplasma avidity and depression and irritability scales scores in our study. This result could be due to the impact of early infection and young age group. Our study is the first to evaluate the relationship of anti-toxoplasma gondii IgG antibodies to depression in children and adolescents, and the positive correlation in our study can be attributed to age.

We evaluated the *T. gondii* IgG antibody levels of the depression group according to history of suicide attempts and suicidal ideation and found that patients who reported suicide attempts and suicidal ideation had higher antibody levels. A series of studies from China and Europe reported higher suicide rates in countries with higher *T. gondii* prevalence (Hurley and Taber, 2012). The study performed by Arling et al. (2009), which included 218 patients with depression, found higher *T. gondii* titers in patients with suicide attempts compared with patients without a suicide history. Bak et al. (2018) reported that the rate of seropositive *T. gondii* antibodies in patients with a history of suicide attempts was higher than that in healthy controls, and *T. gondii* infection increased the risk of suicide. They also suggested that patients with *T. gondii* IgG seropositivity and suicide attempts had more severe depressive symptoms, anxiety, and suicidal behavior. Our results are compatible with this literature.

A relationship between psychiatric disorders and either toxoplasma or certain viral diseases has been identified (Sutterland et al., 2015). Furthermore, patients with treatment-refractory toxoplasmosis have exhibited depression (Kar and Misra, 2004). Detailed studies of the course of psychiatric disorders, treatment of infection during reactivation episodes, and infection screening during treatment for psychiatric disorders are required. It is important to evaluate *T. gondii* genotypes in cats and to identify common genotypes in humans in Turkey. In conclusion, although our study population was small, it demonstrated a relationship of toxoplasma seropositivity with depression and suicide attempts.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.031.

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