

Original Article

An investigation into the association between latent toxoplasmosis and suicide attempts among adolescents

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Abstract

Introduction: There have been several studies investigating the association between *Toxoplasma gondii* seropositivity and psychiatric disorders although there is insufficient data on causality. Suicide, depression, and anxiety disorders have been especially investigated in this regard. In this study, we aimed to investigate whether there is any causal association between *Toxoplasma gondii* seropositivity and suicide attempts in adolescents.

Methodology: This is a case-control study conducted between January and December 2019. A total of 27 adolescents who had attempted suicide and were aged between 12 and 18 years were included in the study. 26 age and sex ratio matched healthy volunteers were taken as the control group. A possible association between suicide attempts and *Toxoplasma gondii* serology (IgM and IgG) was investigated.

Results: The suicide attempt group consisted of 17 females and 10 males. The mean age was 15.9 ± 1.4 (13.5-17.9) years. *Toxoplasma gondii* IgG seropositivity was 3.7% (1/27) in the suicide attempt group and 3.8% (1/26) in the control group. There was no significant association between the suicide attempt group and the control group in terms of the presence of *Toxoplasma gondii* IgG antibodies ($p > 0.05$).

Conclusion: Our study is one of the few studies examining the association between *Toxoplasma gondii* seropositivity and suicide attempts in adolescents yet we did not find any significant association. Further evidence is needed to clarify this controversial issue.

Key words: adolescent; suicide; toxoplasmosis; psychiatry; infection.

J Infect Dev Ctries 2020; 14(12):1437-1441. doi:10.3855/jidc.13632

(Received 06 August 2020 – Accepted 31 October 2020)

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Introduction

Suicide, which is the second leading cause of death for those aged from 10 to 24, is a public health problem, especially for adolescents, young people, and middle-aged adults. From the age of 10 to 14, suicide accounts for 2.1 per 100,000 death rates and 14.7% of all deaths. Self-injury behavior that does not result in death is called suicide attempt [1]. In Turkey, it is reported that the number of deaths caused by suicide was 3161 per year according to Turkish Statistics Institute data for 2018. Most of these deaths are between the ages of 15 and 19 years. Several methods are used to commit suicide including drug intake, hanging, firearms, jumping, and drowning [1]. Committing suicide is more common among girls and more serious suicide attempts are more common among boys [2]. The most common method of suicide attempt among adolescents is taking an overdose of drugs [3].

Toxoplasma gondii (*T. gondii*) is an obligate intracellular protozoan that is estimated to infect more than one-third of the world population [4]. *Toxoplasma gondii* infection occurs by the ingestion of water and food contaminated with *T. gondii*'s oocysts and tissue cysts [5]. Symptoms of the infection depend on the host's immune response. Latent toxoplasmosis is considered to be mostly harmless in immunocompetent hosts. Immunocompromised individuals such as those infected with human immunodeficiency virus (HIV), transplant, or cancer patients treated with immunosuppressive agents may have severe consequences [6].

Although presumed to be relatively harmless in immunocompetent patients, latent toxoplasmosis has been linked to several psychiatric problems [7], resulting in many changes in human behavior [8] and eventually leading to serious public health problems [9]. There are several psychiatric disorders associated

with latent toxoplasmosis such as major depressive disorder [10], generalized anxiety disorder, obsessive-compulsive disorder [11], autism spectrum disorder, Alzheimer's disease [12], alcoholism [13], and schizophrenia [14,15]. There are several biological mechanisms asserted to explain toxoplasma seropositivity and psychiatric disorders. First, *T. gondii* infection has been associated with dopamine modulation in brain neurons, while dopamine disturbances are generally recognized abnormalities described in the brain of patients with schizophrenia [16]. Second, the body defends itself against toxoplasmosis by a reduction in tryptophan supply because tryptophan is essential for *T. gondii* replication and *T. gondii* IgG titers correlate with tryptophan reduction [17]. Low tryptophan supplies limit serotonin production and low serotonin levels are linked to a risk of major depressive disorders and suicide attempts [18,19].

In addition to psychiatric disorders, there are studies reporting that behavior patterns such as impulsivity, aggression [20] and suicide attempts [21] could be associated with latent toxoplasmosis. There are relatively more studies investigating the relationship between suicide and latent toxoplasmosis in particular [6,22,23]. A recent meta-analysis about this association suggested that latent *T. gondii* infection may play an important role in the risk of suicide attempts. However, although there are studies supporting this relationship, causality in this relationship is not proven [24]. The largest study investigating the relationship between CMV and latent toxoplasmosis was published recently and reported no statistically significant association between *T. gondii* infection and suicide [25].

There is considerably limited data about the association between exposure to *T. gondii* and suicide attempts in adolescents, so we aimed to investigate any possible association between suicide attempts and *T. gondii* seropositivity in adolescents in this study to add knowledge to literature.

Methodology

The study was conducted between January and December 2019 at Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital. A total of 27 adolescents aged between 12 and 18 years who were admitted to Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital because of suicide attempts were included in the study. Adolescents diagnosed with neurodevelopmental disorders such as autism, schizophrenia, bipolar disorder, and intellectual

disability were excluded. The control group (n = 26) consisted of age and sex equalized adolescents without any psychiatric disorder and who had not previously attempted suicide, who had applied to pediatric and adolescent health outpatient departments. All participants were evaluated by a child and adolescent psychiatrist (BA). A semi-structured psychiatric interview was applied to all participants. This interview was used to determine their psychiatric diagnosis. Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version (K-SADS-PL) was used for this interview. The psychiatric interview and diagnostic evaluation were made according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition, DSM-5 [26].

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the parents. Venous blood samples (2 mL) were taken from the patient group and control group for serological tests. Ig M and IgG antibody levels against *T. gondii* were studied by enzyme-linked immunosorbent assay (Siemens, Pennsylvania, USA). According to the manufacturer's instructions, IgM values were considered negative at < 0.9 IU/ mL, suspicious at 0.9 – 0.99 IU/mL, and positive at ≥ 1.0. The IgG results at < 6.4 IU/mL were considered negative, whereas it was considered borderline at 6.4–9.9 IU/mL and positive at ≥ 10 IU/mL.

The data was analyzed statistically using SPSS 15.0 version software (SPSS Inc., Chicago, Illinois, USA). Categorical data was presented as numbers and percentages. Chi-square test was used to test significance. T-test was used to compare the means. The values of $p < 0.05$ were considered statistically significant.

Results

There were 17 female and 10 male participants in the suicide attempt group. The mean age of the suicide attempt group was 15.9 ± 1.4 (13.5-17.9) years. There were 17 female and 9 male participants in the healthy control group. The mean age of the control group was 16 ± 1.3 (13.4-18.0) years. There was no difference between these two groups in terms of gender and age ($p > 0.05$). After diagnostic evaluation, in the suicide attempt group, 14 patients (51.8%) were diagnosed with major depressive disorder, 2 patients (7.4%) were diagnosed as having generalized anxiety disorder, 2 patients (7.4%) were diagnosed with attention deficit hyperactivity disorder and comorbid conduct disorder and 9 patients (33.4%) were evaluated as having

Table 1. *Toxoplasma gondii* seropositivity among suicide and control groups.

Group	Suicide group n (%)	Control group n (%)	χ^2/T	P- value
Toxoplasma Ig G seropositivity	1 (3.7%)	1 (3.8%)	0.001	0.978
Toxoplasma IgG titers	0.85 ± 3.67	0.44 ± 1.53	0.529	0.599

impulsive suicidal behavior and no psychiatric diagnosis was conducted at the first interview. There was no psychiatric diagnosis in the control group.

The frequency of *T. gondii* IgG seropositivity was 3.7% (1/27) in the suicide attempt group and 3.8% (1/26) in the control group. There was no statistically significant difference between the suicide group and the control group in terms of the presence of *T. gondii* IgG antibodies ($p > 0.05$) (Table 1). *T. gondii* IgM seropositivity was not detected in any of the adolescents in either the suicide attempt group or the control group.

Discussion

In our study, we investigated the relationship between *T. gondii* seropositivity and suicide attempts. We did not find a significant difference between the groups regarding *T. gondii* IgG seropositivity. *T. gondii* IgM seropositivity was not detected in any of the adolescents in the suicide attempt group or the control group.

In a recent meta-analysis, it was indicated that developing *T. gondii* infection may increase the risk of suicide by 43% and individuals with *T. gondii* infection had a higher probability of suicide than without *T. gondii* infection. The following explanations were noted in this meta-analysis about the possible mechanisms of association between *T. gondii* and suicidal behavior. It was mentioned that *T. gondii* could induce the synthesis of pro-inflammatory cytokines (i.e. IFN- γ , IL-6, and IL-12) by activating lymphocytes and macrophages. These cytokines lead to an increase in the activity of the enzymes kynurenine monooxygenase (KMO) and indoleamine 2, 3-dioxygenase (IDO). This rise increases the metabolism of tryptophan that could result in decreasing neurotransmitter serotonin synthesis in the brain. Decreased synthesis of serotonin may raise the susceptibility to trigger suicide risk factors such as depression, impulsivity, and aggression. Besides that, changes in glutamate and dopamine neurotransmission have shown a key role in suicide and suicidal behavior. As a result, it was mentioned in this meta-analysis that changes in neurotransmitters can play a role in behavioral development that increases the risk of suicide [27]. In contrast to these results, we could not find any association between *T. gondii* seropositivity and suicidal behavior. The reason for the

lack of association in our study may be related to the small sample size, distribution of diagnosis of our sample, and the low rate of Toxoplasma IgG antibodies in the study population. 33.4% of our patient group had no psychiatric diagnosis and were evaluated as having impulsive suicide behavior. The relatively high proportion of patients who were not diagnosed with any psychiatric diagnosis after psychiatric evaluation and evaluated as impulsive suicide attempts may have prevented us from finding an association between *T. gondii* seropositivity and suicide attempts.

Bak *et al.* found higher *T. gondii* seropositivity among patients over 18 years of age with suicide attempts [6]. In a study by Ling *et al.* [23] data based on the reported seroprevalence levels of 20 European countries revealed a significant relationship between *T. gondii* and suicide rates in older women. In a study by Coryell *et al.* [28], 110 participants between 15 and 20 years of age who were within one month of starting selective serotonin reuptake inhibitor (SSRI) were included in the study and individuals who had recently begun a trial of SSRI and also a history of suicide attempts were found to have significantly higher toxoplasmosis IgG titers. The results of the study conducted by Zhang *et al.* [29], also revealed an association between *T. gondii* infection and non-fatal suicidal self-directed violence in an adult age group. In addition to these studies, Alvarado-Esquivel *et al.* [10] mentioned this association in adult patients with depression. They did not present any data about suicidal ideation. In a recent study conducted among depressed adolescents, it was found that *T. gondii* IgG seropositivity was higher in adolescents with depression than healthy controls. In this study, a significantly higher rate of IgG seropositivity was found in patients with suicidal ideation than without suicidal ideation [30]. In a large study consisting of 8,028 participants, *T. gondii* IgG seropositivity was found to be associated with depressive symptoms while there was no relation with major depressive disorders [31]. The data of another large study investigating 81,912 patients suggested that *T. gondii* infection was not associated with psychiatric disorders (i.e. mood disorders, neurotic, stress-related, and somatoform disorders or attempted or real suicide) except schizophrenia [25]. This study revealed that there was

no significant association between suicide attempts and latent toxoplasmosis when the contribution of a psychiatric disease was also evaluated. We think, the common feature of these studies discussed above is that they are either related to a specific psychiatric disorder (i.e. major depressive disorder) or conducted in the adult population which has increased the probability of a psychiatric disorder when compared to adolescents. It is known that > 90% of people who have attempted suicide have at least one psychiatric disorder but this frequency is lower in adolescents [32]. The psychopathology was at a frequency of 66.6% in the suicide attempt group in our study which was consistent with literature [32]. In our study we focused on suicide attempts rather than a specific psychopathology. It is possible that the comparably low mean age and sample size, and diagnostic heterogeneity of our study group may have contributed to the result of our study. It may also be difficult to show a relationship between toxoplasmosis and history of suicide attempt in this age group because *T. gondii* infection rate increases steadily with age and is relatively low among teenagers.

Alvarado-Esquivel *et al.* [33], suggested that the seroprevalence of *T. gondii* infection did not show statistically significant differences between patients with suicide attempts and the controls as in our study. Sari *et al.* [34], also did not find any association in their study investigating an association between suicide attempt and *T. gondii* serology. Their patient inclusion criteria were very similar to those of our study. Further comprehensive studies with appropriate sampling in this age group are required for a better understanding of the causal relationship.

Our study has certain limitations. Firstly, our sample size is relatively small. Secondly, our study design is cross-sectional which could interfere with determining causality between these two issues. Thirdly, we did not use a questionnaire to measure psychiatric symptoms. If we had applied a questionnaire to the groups, the results of comparisons could have been more reliable. Nevertheless, the finding of an insignificant association between exposure to *T. gondii* and suicide attempts in adolescents of this study should be of interest to clinicians and provide additional information to literature.

Conclusion

As a conclusion in our study, we did not find a significant difference between the groups regarding *T. gondii* IgG seropositivity. *T. gondii* IgM seropositivity was not detected in any of the adolescents in the suicide

attempt and control groups. We think that the association between latent toxoplasmosis and suicide attempts is not clear especially among adolescents. Our study is one of the few studies examining the association between *T. gondii* seropositivity and suicide attempts in adolescents. We did not find any significant association. Further evidence is needed to clarify this controversial issue.

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Conflict of interests: No conflict of interests is declared.