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The Association between Suicide Attempts and *Toxoplasma gondii* Infection

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Objective: Chronic 'latent' infection by *Toxoplasma gondii* is common and most of the hosts have minimal symptoms or they are even asymptomatic. However, there are possible mechanisms by which *T. gondii* may affect human behavior and it may also cause humans to attempt suicide. This article aimed to investigate the potential pathophysiological relationship between suicide attempts and *T. gondii* infection in Korea.
Methods: One hundred fifty-five psychiatric patients with a history of suicide attempt and 135 healthy control individuals were examined with enzyme-linked immunoassays and fluorescent antibody technique for *T. gondii* seropositivity and antibody titers. The group of suicide attempters was interviewed regarding the history of suicide attempt during lifetime and evaluated using 17-item Korean version of Hamilton Depression Scale (HAMD), Columbia Suicide Severity Rating Scale (C-SSRS), State-Trait Anxiety Inventory (STAI) and Korean-Barratt Impulsiveness Scale (BIS).
Results: Immunoglobulin G antibodies were found in 21 of the 155 suicide attempters and in 8 of the 135 controls (p=0.011). The Toxoplasma-seropositive suicide attempters had a higher HAMD score on the depressed mood and feeling of guilt subscales and a higher total score than the seronegative suicide attempters. *T. gondii* seropositive status was associated with higher C-SSRS in the severity and lethality subscales. *T. gondii* IgG seropositivity was significantly associated with higher STAI-X1 scores in the suicide attempters group.
Conclusion: Suicide attempters showed higher seroprevalence of *T. gondii* than healthy controls. Among the suicide attempters, the *T. gondii* seropositive and seronegative groups showed several differences in the aspects of suicide. These results suggested a significant association between *T. gondii* infection and psychiatric problems in suicidality.

KEY WORDS: Suicide; Toxoplasma; Infection; Depression; Anxiety; Impulsive bahavior.

INTRODUCTION

Suicide is a major public health problem. According to the World Health Organization, suicide accounted for 1.4% of all deaths worldwide, making it the 15th leading cause of death in 2012. According to the Statistics Korea, approximately 13,000 people died in the year 2015 due to suicide in South Korea and the mortality rate was 26.5 per 100,000. Suicide is the 6th leading cause of death in South Korea. Efforts were made by the public health service to reduce the suicide rates; however, it has remained relatively constant over the past decade.[1)] More than 90% of people who attempt suicide suffer from a diagnosable mental illness, especially depression.[2,3)] A history of suicidal behavior is one of the most significant risk factors for suicide.[4)]

Toxoplasma gondii is a highly successful neurotropic protozoan parasite, which infects any warm-blooded animal including approximately one-third of all humans.[5)] The common infection pathway in humans is oral ingestion of *T. gondii*'s oocytes or tissue cysts present in contaminated food. The prevalence of immunoglobulin (Ig) G antibodies to *T. gondii* in South Korea is estimated to range from 6.9% to 12.9% among the provinces.[6)] Symptoms of the infection depend on the immune response of the host. In immunocompromised individuals and fetuses, severe consequences such as encephalitis have been reported. However, chronic "latent" infection

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by *T. gondii* is common and most of the hosts have minimal symptoms or they are even asymptomatic.[5]

Although it is thought to be relatively harmless in immunocompetent adults, latent toxoplasmosis has been linked to several psychiatric problems including suicide.[7] For instance, the prevalence of *T. gondii* seropositivity was found to be higher in schizophrenia patients.[8] Arling *et al.*[9] reported an association of *T. gondii* antibody titers with suicide attempts, and Coccaro *et al.*[10] reported about the relationship between *T. gondii* infection and aggression. Also, several studies have reported about the relationship between *T. gondii* and psychiatric problems. However, there is little information about the association of *T. gondii* infection with suicide attempts and behavioral aspects such as anxiety, impulsiveness and suicidal behaviors of attempters in South Korea. Therefore, we performed a seroprevalence case-control study to assess the association of anti-*T. gondii* seropositive status with suicide attempts and behavioral traits.

METHODS

Design and Setting

Through a case-control study design, we studied the patients who visited the Soonchunhyang University Cheonan Hospital for treatment of suicide attempts and the control subjects in Cheonan city, South Korea, from November 2015 to October 2016. The control subjects were healthy volunteers who did not have any psychiatric disorders. For these groups, written informed consents were obtained after the study procedure had been explained. The study protocols and the consent forms were approved by the Institutional Review Board of Soonchunhyang University (No. 2016-07-034).

Participants

The inclusion criteria for the subject group were a) inpatients and outpatients with a history of suicidal attempts in Soonchunhyang University Cheonan Hospital, b) 18 years or older, c) with depressive symptoms, d) no intellectual problems as a result of which they cannot understand this study, and e) agreed to participate in this study. Before enrolling the subjects, skilled psychiatrist had short interview to rule out the non-suicidal self-mutilation (e.g., self-mutilation for secondary gain). And through the interview, the patients who did not show any depressive symptoms or depressive equivalents also excluded.

The inclusion criteria for the controls were a) no history of psychiatric disorders, b) 18 years or older), c) no intellectual problems as a result of which they cannot understand this study, and d) agreed to participate in this study. Psychiatrist also had short interview to find out any psychiatric history.

Clinical Measures

The patients were interviewed by a skilled psychiatrist by using the 17-item Korean version of Hamilton Depression Scale (HAMD), Columbia Suicide Severity Rating Scale (C-SSRS), State-Trait Anxiety Inventory (STAI-State, STAI-Trait) and the Korean-Barratt Impulsiveness Scale (BIS).

Laboratory Tests

Serum blood samples were obtained from the participants via venipuncture. The samples were stored at 4°C and tested for antibodies at Samkwang Medical Laboratories (Seoul, Korea). Serum toxoplasmosis antibody titer was evaluated by using the chemiluminescent immunoassay (CLIA, access IgG or IgM; TOXO, Beckman, Switzerland). The tests were performed on a microtiter plate reader (Access Immunoassay System; Sanofi Diagnostics Pasteur, Marnes-la-coquette, France), which is an automated analyzer.

Statistical Analysis

To analyze demographic data, a two-tailed *t* test was used for continuous covariates. For discrete covariates, the chi-square test was used. For obtaining the odds ratio between cases and controls, logistic regression analysis was used. All statistical analyses were performed with IBM SPSS version 22.0 for Windows (IBM Co., Armonk, NY, USA). We used a 95% confidence level, and statistical significance was set at a p value of <0.05.

RESULTS

Demographic and Clinical Characteristics

One hundred fifty-five (75 men and 80 women) suicide attempters and 135 (66 men, 69 women) controls were enrolled in this study. Suicide attempters were aged from 18 to 80 years (mean±standard deviation, 43.75±16.75

Table 1. Demographic and *Toxoplasma gondii* IgG antibody seroprevalence among suicide attempters and normal controls

Variable	Suicide attempter	Normal control
Total (n)	155	135
Sex (M:F)	75:80	66:69
Age (yr)	43.74±16.31	41.59±11.54
IgG+	21 (13.5)	8 (5.9)
IgG−	134 (86.5)	127 (94.1)

Values are presented as number only, mean±standard deviation, or number (%).
IgG, immunoglobulin G; M, male; F, female.
Odds ratio=2.49, p=0.011 (<0.05), 95% confidence interval=1.265-4.927.

years) and the controls were aged from 22 to 59 years (41.59±11.54 years) (Table 1). There were no significant differences in age and gender.

T. gondii Antibody Seroprevalence Rates and Titers

T. gondii IgG antibodies were found in 21 (13.5%) of the 155 subjects who attempted suicide, and in 8 (5.9%) of the 135 controls (p=0.011). Only one control case had *T. gondii* IgM antibody in this study. *T. gondii* IgG seropositivity was associated with suicide attempt in the total group. In total participants, the odds ratio for suicide attempt according to seropositivity of *T. gondii* was 2.49 (95% confidence interval, 1.26 to 4.93) (Table 1).

The comparison of the seroprevalence rates of *T. gondii* infection after adjustment for age did not show statistically significant differences in the cases and the controls: 3.0% vs. 0% in the age group of 30 years or younger (p=0.49), 26.4% vs. 10.6% in the age group of 30 to 50 years (p=0.09), and 10.0% vs. 6.3% in the age group of 51 years or older (p=0.71). Anti-*T. gondii* IgG antibody levels in seven seropositive suicide attempters (33.3%) were higher than 150 IU/ml, and 14 subjects had anti-*T. gondii* IgG levels between 12 and 150 IU/ml. Of the 8 seropositive controls, 2 controls (25.0%) had IgG levels higher than 150 IU/ml and 6 controls had anti-*T. gondii* IgG levels between 12 and 150 IU/ml. There was no significant differences in the *T. gondii* Ab titers (Table 2).

In 155 subjects, there were 31 individuals who attempt suicide more than once. Five (16.1%) of the recurrent suicide attempters had *T. gondii* IgG and 16 (12.9%) of first attempters (n=124) had *T. gondii* IgG. There was no significant differences between two groups. In 21 seropositive subjects, the IgG titers between two groups had no significant differences (140.8 vs. 118.4, p=0.651) (Table 3).

Table 2. *Toxoplasma gondii* IgG Ab seroprevalence rates in different age groups and antibody titers

Variable	IgG+ suicide attempter (%)	IgG+ normal control (%)	p value
Age group (yr)			
<30	3.0	0	0.49*
30-50	26.4	10.6	0.09*
>51	10.0	6.3	0.71
IgG Ab level >150 IU/ml	33.3	25.0	0.517

IgG, immunoglobulin G; Ab, antibody.
*p<0.05.

Table 3. *Toxoplasma gondii* IgG Ab seroprevalence rates and titers in the first time suicide attempters and recurrent suicide attempters

Variable	Recurrent suicide attempter (n=31)	First time suicide attempter (n=124)	p value
IgG+	5 (16.1)	16 (12.9)	0.769
IgG Ab level in seropositive group (IU/ml)	140.8±82.69	118.4±131.66	0.651

Values are presented as number (%) or mean±standard deviation.
IgG, immunoglobulin G; Ab, antibody.

T. gondii Seropositive Status among Suicide Attempters and Depression

T. gondii IgG antibodies were found in 21 (13.5%) of the 155 subjects who attempted suicide. We examined the relationship between seropositivity and the HAMD score (Table 4). There was a significant difference in the total HAMD score (IgG+, 33.0±5.59 vs. IgG−, 29.43±5.62; p=0.048). In terms of the subscale, there were differences in the 'depressed mood' (IgG+, 3.33±0.49 vs. IgG−, 2.68±0.50; p=0.001) and 'guilty' (IgG+, 2.50±0.52 vs. IgG−, 1.85±0.80; p=0.009) subscales.

T. gondii Seropositive Status among Suicide Attempters and State-Trait Anxiety

We measured STAI-State and STAI-Trait in suicide attempters. There was a significant difference in the STAI-State scale between the anti-*T. gondii* IgG positive group and the negative group (IgG+, 45.4±5.72 vs. IgG−, 41.78±5.67; p=0.009). There was no significant difference in the STAI-Trait scale between the two groups (IgG+, 53.25±4.54 vs. IgG−, 51.31±4.56; p=0.077) (Table 5).

Table 4. HAMD scores of *Toxoplasma gondii* antibody positive group and negative group

Variable	IgG+	IgG−	t	*p* value
HAMD total	33.00±5.59	29.43±5.62	2.009	0.048*
1 Depressed mood	3.33±0.49	2.68±0.50	4.093	0.001*
2 Guilty	2.50±0.52	1.85±0.80	2.697	0.009*
3 Suicidality	3.75±0.45	3.72±0.45	0.232	0.817
4 Early insomnia	1.50±0.67	1.52±0.70	−0.076	0.94
5 Mid insomnia	1.67±0.49	1.27±0.69	1.919	0.059
6 Late insomnia	1.50±0.52	1.18±0.73	1.437	0.155
7 Work activity	2.42±0.52	2.50±0.70	−0.39	0.698
8 Retardation	2.17±0.72	1.97±0.66	0.941	0.35
9 Agitation	1.83±0.94	1.62±0.96	0.717	0.476
10 Anxiety-psychic	2.42±0.67	2.43±0.65	−0.081	0.936
11 Anxiety-somatic	1.92±0.99	1.42±1.28	1.276	0.206
12 GI symptom	1.00±0.60	0.90±0.78	0.498	0.624
13 General symptom	1.50±0.67	1.35±0.63	0.741	0.461
14 Genital	1.75±0.45	1.67±0.51	0.526	0.601
15 Hypochondriasis	1.08±0.67	0.75±1.00	1.435	0.165
16 Weight loss	1.33±0.65	0.92±0.70	1.912	0.06
17 Insight	1.42±0.52	1.58±0.53	−0.999	0.321

Values are presented as mean±standard deviation.
HAMD, 17-item Korean version of Hamilton Depression Scale; IgG, immunoglobulin G; GI, gastrointestinal.
*$p<0.05$.

Table 5. STAI, BIS and C-SSRS scores of *Toxoplasma gondii* antibody positive group and negative group

	IgG+	IgG−	t	*p* value
STAI				
State	55.40±5.716	51.78±5.666	2.665	0.009*
Trait	53.25±4.541	51.31±4.557	1.78	0.077
BIS	72.95±12.37	69.44±14.03	1.082	0.281
C-SSRS				
Severity	3.85±0.813	3.22±0.870	3.222	0.003*
Intensity	15.05±3.62	13.96±3.614	1.253	0.222
lethality	2.75±1.02	2.23±0.822	2.548	0.012*

Values are presented as mean±standard deviation.
STAI, State-Trait Anxiety Inventory; BIS, Korean-Barratt Impulsiveness Scale; C-SSRS, Columbia Suicide Severity Rating Scale; IgG, immunoglobulin G.
*$p<0.05$.

T. gondii Seropositive Status among Suicide Attempters and Impulsiveness

For evaluating impulsiveness, we measured the BIS in suicide attempters and compared between the seropositive and seronegative groups. The IgG+ group had a higher BIS score (72.95±12.37) than the IgG− group (69.44±14.03), but there was no significant difference.

T. gondii Seropositive Status among Suicide Attempters and Severity of Suicidal Behaviors

We examined the relationship between *T. gondii* seropositivity and severity of suicidal behaviors. The seropositive group showed higher values in the 'severity' (IgG+, 3.85±0.81 vs. IgG−, 3.22±0.87; $p=0.003$) and 'lethality' (IgG+, 2.75±1.02 vs. IgG−, 2.23±0.82; $p=0.012$) subscales.

DISCUSSION

Our study aimed to determine whether *T. gondii* seroprevalence is associated with suicidal behavior and other psychiatric symptoms. The results of our study show that suicide attempters had a significantly higher seropositivity and antibody titers of *T. gondii* infection than the normal control group. In our study, there were several differences among the suicide subjects whether *T. gondii* seropositive or seronegative. *T. gondii* IgG seropositive subjects showed higher depressive symptoms and state anxiety. The seropositive group also showed severe suicide behaviors.

In this study, we investigated the seroprevalence of *T. gondii* in 155 suicide attempters and 135 normal controls. After that, we divided the suicide attempters into the seropositive and seronegative groups based on seropositivity

of Ig and compared the features of the two groups to identify the specific trait of *T. gondii* infected suicide attempters.

We found higher seropositivity of *T. gondii* antibodies in suicide attempters than in the healthy control group. This suggests that *T. gondii* infection increases the risk of suicide and its odds ratio was 2.49. In accordance with the present study, some of the previous studies reported that *T. gondii* infection represents a risk factor for suicidal behavior. Zhang *et al.*[11] reported about the association between toxoplasma infection and nonfatal suicidal self-directed violence, suggesting that the *T. gondii* infected group had a 7.12 times greater risk of nonfatal suicide attempts. Ling *et al.*[12] reported that *T. gondii* seropositivity significantly increases the risk of suicide in women older than 45 years. Pedersen *et al.*[13] reported that *T. gondii* infection increased the risk of self-directed violence. However, the results of other studies did not correspond with the results of the present study. Alvarado-Esquivel *et al.*[14] found no statistical differences with respect to *T. gondii* between suicide attempters and normal controls. But, they also reported that higher *T. gondii* antibody titers were related to the risk of suicidal behavior. Our study showed a similar result which supports the association between suicide attempts and seroprevalence.

We compared the characteristics between suicide attempters with detectable *T. gondii* IgG antibody and those without detectable *T. gondii* IgG antibody. There were several differences between these two groups in their traits. We measured the HAMD scale in these groups. The seropositive group had a significantly higher total score, and scores on the 'depressed mood' and 'guilty' subscales were also higher in the seropositive group. In other studies, Dalimi and Abdoli[15] and Fekadu *et al.*[16] suggested that latent *T. gondii* infection is associated with depression. Although Coccaro *et al.*[10] reported no significant difference in depressive symptoms between the seropositive and seronegative groups, a case-control study performed by Alvarado-Esquivel *et al.*[17] reported a higher seroprevalence in depressive patients. Our result also supports the relationship between depression and *T. gondii* infection.

Kwon *et al.*[18] has reported agitating tendencies of suicide attempters in Korea. To examine the anxious tendencies among the suicide attempters, we evaluated state-trait anxiety level in the subject group by STAI. There was a significant difference in the state anxiety score between the seropositive group and the seronegative group. Coccaro *et al.*[10] reported increased state and trait anxiety scores in *T. gondii* seropositive patients. Alvarado-Esquivel *et al.*[17] also reported about the association between *T. gondii* infection and mixed anxiety and depressive disorder. Markovitz *et al.*[19] reported that the *T. gondii* seropositive group has a greater risk of generalized anxiety disorder. Some other studies did not support the relationship between anxiety and *T. gondii* infection. Mitra *et al.*[20] and Afonso *et al.*[21] reported that *T. gondii* infection reduces anxiety-like behavior in rodents. However, our study in humans showed the relationship between anxiety and *T. gondii* infection.

To evaluate impulsiveness, we compared the BIS score between suicide attempters in the seropositive and seronegative groups of *T. gondii*. In a birth cohort study performed by Sugden *et al.*,[22] there was no significant association between *T. gondii* infection and impulsiveness. However, in the other study by Cook *et al.*,[23] there was a significant relationship between impulsiveness and *T. gondii* infection. In our study, there was no significant difference between the two groups in impulse control.

We also measured the C-SSRS score to evaluate the severity of suicidal behaviors in the seropositive and seronegative groups. There were significant differences in the "severity" and "lethality" subscales. We cautiously suggest that these differences may be the result of increased aggression. Cook *et al.*[23] reported about the association between aggression and *T. gondii* IgG positivity in women. Coccaro *et al.*[10] also reported that the seropositive group showed higher aggression scores than the seronegative group.

Several previous reports have presented the relationship between *T. gondii* infection and mental illness. Especially, depressive disorder is a complex mood disorder that is influenced by inflammatory processes. Immune system proinflammatory cytokine production and production of C-reactive protein by the liver commonly have a correlation with behavioral changes.[24] The immune system communicates with the neural circuit in a bidirectional fashion. The immune system responds to inflammatory stimuli and activates neuroendocrine pathways. This change induces behavioral changes such as sickness behavior (vigor, appetite, changed sleep cycles, and altered cognition). The brain regulates the immune response through the hypothalamic-pituitary-adrenal axis, and the

sympathetic nervous system acts as the immune function modulator in the depression model.[25] Infectious pathogens can trigger systemic whole immune responses. Cytokines are produced by various stimulated immune cells in response to various types of infectious pathogens. The innate immune response to infectious pathogens results in the production of proinflammatory cytokines that include interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). There are two types of adaptive immunity. Type-1 immunity promotes cellular cytotoxicity to secrete type-1 cytokines (interferon [IFN]-γ, IL-2). Type-2 immunity is considered to be anti-inflammatory and it includes both the T helper 2 (Th2) and secretion of type-2 cytokines (IL-4, IL-5, IL-13) from multiple sources.[26]

In animal studies, feline defensive rage behaviors were related to IL-1β and IL-2. These cytokines affect the hypothalamus, and serotonin 5-HT2 receptors and gamma aminobutyric acid receptors in the midbrain periaqueductal gray.[27] In human studies, chronic exposure to inflammatory cytokine (IFN-α or IL-2) treatment in patients with hepatitis C virus infection or cancer resulted in increased depression symptoms.[28,29]

After primary infection with *T. gondii*, the plasma antibody titers remain elevated for life.[30] *T. gondii* seropositivity is associated with mental and behavioral disorders. Arling *et al.*[9] first reported the relationship between *T. gondii* infection and suicidal behavior in a study including 218 participants. They found that depressed individuals who had a history of attempted suicide had higher *T. gondii* IgG titer levels than suicide non-attempters. A series of studies on *T. gondii* infection and suicide in China and European countries also found that countries with high *T. gondii* prevalence had higher suicide rates.[31] A further interesting case reported that depressive symptoms were successfully resolved after treatment of *T. gondii* infection, despite the fact that antidepressant treatment did not resolve the patient's depressive symptoms.[32]

The pathophysiological mechanism of *T. gondii* still remains unclear. Zhu[33] suggested that psychosis might be associated with *T. gondii* infection, and the potential mechanism of *T. gondii* infection in behavioral change may be through its direct effect on neuronal function and immune-mediated dopamine and serotonin synthesis. The host immune response in *T. gondii* infection produces proinflammatory cytokines such as IL-6 and TNF, and it activates Th cells, which secrete IFN-γ, blocking *T. gondii* growth by inducing the activation of an enzyme, indoleamine 2,3-dioxygenase (IDO), which causes tryptophan depletion and ultimately results in a decrease in serotonin production in the brain.[3,15,34,35] Resultant tryptophan depletion leads to a decrease in serotonin production in the brain, which may contribute to depression.

These mechanisms underlying the inflammatory pathways that affect the central nervous system may be related to the relationship between *T. gondii* antibodies and psychiatric symptoms. We suggest that the inflammation in response to *T. gondii* infection may contribute to depression and anxiety and as a result it leads to suicide.

There are several limitations in this study. First, the healthy control group showed a lower seroprevalence of *T. gondii* than the general population in the earlier study in South Korea. This occurred because the collection of subjects included in the control group was performed in an urban area. In general, the seropositivity of *T. gondii* is higher in rural areas than in cities. Second, we evaluated only psychiatric symptoms of suicide attempters and did not classify diagnoses. The purpose of this study was to investigate the general tendency of suicide attempters. Third, the people who died by suicide were excluded from this study, and hence this study may not reflect the tendency of all suicide attempters. Fourth, we could not examine the other cytokines which might affect the psychiatric symptoms. Fifth, the timely distances of previous suicide attempt were not collected. Sixth, the sample size was small. Lastly, our study was performed in one hospital.

The results of the present study suggest associations between *T. gondii* seropositivity and suicidal behaviors and their related symptoms. In suicide attempters, *T. gondii* IgG seroprevalence rates were higher than those in healthy controls. *T. gondii* IgG seropositive suicide attempters showed higher scores for depressive symptoms, anxiety, and the severity and lethality of suicide behaviors. It may present the aspect of suicide attempt. Several previous studies have examined the relationship between *T. gondii* seropositivity and suicide attempts. Also, there were several limitations in this study. Despite these limitations, our study is significant as it investigated the association in the South Korean population. Further studies should include larger number of subjects and they should be classified by the diagnosis.

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