Association of Toxoplasmosis with suicide: A systematic review and meta-analysis

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Eissa Soleymani  
Hamadan University of Medical Sciences Medical School

Fariba Faizi  
Hamadan University of Medical Sciences Medical School

Rashid Heidarimoghadam  
Hamadan University of Medical Sciences School of Public Health
  Corresponding Author

Lotfollah Davoodi  
Mazandaran University of Medical Sciences

Younes Mohammadi  
Hamadan University of Medical Sciences School of Public Health

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Abstract

Background findings on association of Toxoplasmosis and suicide is contradictory. This paper aimed to resolve this uncertainty with help of Meta-analysis.

Methods using keywords include “Toxoplasmosis” and “suicide” and the relayed synonyms in international databases such as ISI, Medline and Scopus, we found the relevant studies. The eligible studies included into Meta-analysis phase. Random effect approach was used to combine the results.

Results out of 150 initial studies, 16 were included into meta-analysis. Odds of suicide in person with toxoplasmosis was 47% (OR: 1.47, 95%CI; 1.20 to 1.79) higher than of that without toxoplasmosis. Test for publication bias was not statistically significant, which indicate absence of likely publication bias.

Conclusion This study confirm which toxoplasmosis is a potential risk factor for suicide. To reduce cases of suicide attributable to Toxoplasmosis, it deserving the measures to prevent and control of transmission of toxoplasmosis should be taken.

Background

Suicide is the most critical sequel of mental disease which lead to more than 800000 deaths globally, that is, in every second one person die from suicide. Therefore, suicide account for 1.5 % of all deaths (1, 2).

Many risk factors have been identified which increase the risk of suicide. The mental disorders, misuse of drugs, mental states, cultural factors and family, social and genetic conditions may reinforce the risk of suicide. (3).

The studies found that latent toxoplasmosis may cause the reduced Intelligence Quotient (IQ) (4), personality changes(5) and psychomotor performance (6). Hidden toxoplasmosis impresses the behavior of humans. Recently clinical data demonstrate that infectious
disease such as Toxoplasma gondii may play role in the pathophysiology of suicide. 

*Toxoplasma gondii* is agent of toxoplasmosis, that infected about one third of the humans worldwide (7). Consumption of Toxoplasma-contaminated food, vegetable and water is the most common route of disease transmission (8). Complications of the disease are so crucial. Developing Toxoplasmosis in pregnancy is associated with mental disorders and deafness, abortion and vision disturbances after birth (9, 10). Moreover, meningoencephalitis and psychiatric complications can occur in *T.gondii* infected immunocompetent human (11, 12). Notably, tachyzoite form of the disease is responsible for the acute stage of the infection. (13).

However, results of the studies on association of toxoplasmosis and suicide are not consistent. While some studies claim that there is no association between suicide and toxoplasmosis (14, 15), some suggest that these two factors are correlated (16). One of the resolutions to overcome this conflict is to perform meta-analysis. Meta-analysis is a statistical method to extract one single effect size from several multiple studies. In this regard, the present study aimed to provide summary estimates for the available data on association of toxoplasmosis with suicide and to evaluate whether *T. gondii* may associate with the risk of suicides or not.

**Methods**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to write this study.

**Protocol and registration**

The protocol has been registered in Hamadan university of Medical Sciences (No. 9710256386).

**Eligibility criteria**

All analytical studies reported association of toxoplasmosis with suicide regardless of age,
sex, and race and time and language limitation were included.

**Information sources**

Medline, ISI and Scopus databases were searched to retrieve the related studies up to 25 March 2019. Moreover, we searched reference list of the screened studies to find the missed studies.

**Searching literature**

Two keywords include suicide and Toxoplasmosis were used to construct search strategy for each database.

**Study selection**

The studies which assess association of toxoplasmosis with suicide were included. Cross-sectional, case-control and cohort studies were eligible to be included. Two independent reviewers searched the databases, and then screened the title and subtract and full text of the studies to choose the relevant studies. Disagreement between two reviewers was resulted by third person.

**Data collection process**

An excel form was designed to extract the required data of the selected studies. This from included name of first author, year of publication, country of the study, age, sex, sample size and effect size of association.

**Risk of bias in individual studies**

Newcastle and Ottawa statement (NOS) checklist was used to assess the quality of the studies.

**Summary measures**

Odds Ratio (OR) with 95% Confidence Interval (95%CI) was determined as effect size for this study.

**Synthesis of results**
The final selected studies included into Meta-analysis. Random-effect approach was used to combine the studies and produce one single estimate. I² and chi-square test were used to assess existence of heterogeneity among the studies.

**Risk of bias across studies**

We used egger and beg test to investigate publication bias in reporting of the results.

**Results**

Figure 1 demonstrates process of the study. Initial search in the databases yielded 150 studies. After discarding duplicates and the irrelevant studies, 16 studies were qualified to be included into final phase. In term of setting of study, the selected studies were conducted in the United States, Turkey, Germany, Mexico, Poland, Denmark, France, Russia, South Korea, and Iran. Out of 16 studies, seven studies reported the significant association of Toxoplasmosis with suicide. In contrary, nine studies did not find any significant relationships between Toxoplasmosis and suicide.

The strongest and the weakest association reported by Dickerson (2.41) Okusaga (1.14) respectively.

Result of Meta-analysis indicate that odds ratio of Toxoplasmosis and suicide was 1.47, that is, it is statistically significant. Therefore, the person who infected by Toxoplasmosis have more 47% risk of attempting suicide relative to person who not infected by Toxoplasmosis.

To assess existence of publication bias, Begg test was not statistically significant (P-value = 0.28), which indicate absence of publication bias in the study.

Examining degree of heterogeneity among studies using I² test demonstrated a moderate heterogeneity (I² = 0.73). Therefore, we used random effect model to perform meta-analysis.
One study assessed the association of Toxoplasmosis with suicide through ecological study. This study showed that after adjusting potential confounders, a significant association is present between sero-prevalence of Toxoplasmosis and suicide rate among European countries (17).

Discussion

In this paper, we presented result of meta-analysis for association of Toxoplasmosis and suicide. Our analysis confirmed that developing Toxoplasmosis may increase risk of suicide by 47%. Mechanisms presented by literature endorse our results. The studies show that people who attempt suicide had significantly the higher IgG antibody to *T. gondii* as compared with people without suicide attempt (18). Moreover, report of an association of *toxoplasma* antibodies and suicidal behavior in patients with schizophrenia is in consistent with reports on associations between *T. gondii* and suicidal behavior in patients with mood disorders (19), overall psychiatric patients (16) and the completed suicide (17).

The experimental studies on animals demonstrate existence of effect of toxoplasmosis on their behaviors. In rodents, it has been reported which *T. gondii* enforce self- Malicious performances and reduce rodent learning and memory (20, 21). These changes result in reduction in harm avoidance, fear of death and attempting suicide.

*T. gondii* make pro-inflammatory cytokines (22) Pro-inflammatory cytokines, such as Interleukin-6 (IL-6) in the pleural fluid (23) and IL-6 and TNF> in the plasma (24) have lately been related with suicidal behavior. It is likely that promotions of kynurenine (KYNA) and its metabolites, and the stimulation of indoleamine 2,3<dioxygenase (IDO) by immune mediators targeting *T. gondii*, could result in changes in dopaminergic and glutaminergic neurotransmission and eventually lead to the affective and behavioral alterations to commit suicide (25).

Seropositivity to toxoplasmosis has a role in the higher the later occurrence of suicide in
lifespan (17). Studies indicate that individuals with depression and without a history of suicide attempt had smaller KYNA levels than depressed patients with a history of suicide attempts (26). Consistently, KYNA condensation in pleural fluid have been found to be related with severe suicide attempts and IL-6 levels (27). In fact, interferon gamma, by triggering lymphocytes and macrophages blocks the development of *T. gondii* (28). Also *T. gondii*, is a Collaborative agent increase the risk of suicide in the early- sickness phase patients (29). Low pleural fluid 5-hydroxyindoleacetic acid (5-HIAA), the metabolite of serotonin, has been related with suicide (30). Changes in glutamate and dopamine neurotransmission have been displayed to play a role in suicide and suicidal behavior (31, 32).

One major limitations present is this paper. We just included English language studies and not included non-English studies. Therefore, we can't assess the effect of non-English studies on our final result.

Despite the mentioned limitation of the study, but this study yield important clues which policy-maker would get serious role of toxoplasmosis in attempting suicide. Therefore, considering squeals and complications of Toxoplasmosis such as suicide, control, prevention and treatment of Toxoplasmosis is very important.

**Conclusion**

Our study is the first meta-analysis and systematic review to assess association of toxoplasmosis and suicide. *T. gondii* significantly increases risk of suicide. Therefore, to reduce suicide attributable to Toxoplasmosis, it deserving the measures to prevent and control of transmission of toxoplasmosis should take.

**Abbreviations**

Intelligence Quotient (IQ)
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Odds Ratio (OR)

Confidence Interval (CI)

Newcastle and Ottawa statement (NOS)

Declarations

Ethical consideration

The protocol of study has been endorsed by Ethics Committee of Hamadan University of Medical Sciences (No. IR.UMSHA.REC.1397.73).

Consent for publication

Not applicable.

Availability of data and materials

Corresponding author is responsible of data. Access to all relevant raw data will be freely available to any scientist.

Competing interests

The authors have no conflict of interest.

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Authors’ contributions

Eissa Soleymani: search, Reviewing, data extraction, writing primary draft, final approval

Fariba Faizi: search, Reviewing, writing primary draft, final approval of manuscript

Rashid Heidarimoghadam: Design, Reviewing, final approval of manuscript

Lotfollah Davoodi: design, data extraction, reviewing, final approval of manuscript

Younes Mohammadi: design, statistical analysis, final approval of manuscript

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Not Applicable
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Tables

Table 1. Characteristics of the studies included into the study
| Author                | Country                   | Study Type                  | Outcome                                    | Number of Suicide        |
|-----------------------|---------------------------|-----------------------------|--------------------------------------------|--------------------------|
| Timothy A (2009)      | United state              | Case-control                | suicide attempt                            |                          |
| Yagmur F (2010)       | Turkey                    | Case-control                | suicide attempt                            |                          |
| Ling, V. J. (2011)    | 20 European countries     | Ecological                  | Seroprevalence of Toxo                     |                          |
| Okusaga (2014)        | Germany                   | Case-control                | suicide attempt                            |                          |
| Pedersen, M. G (2012) | Denmark                   | prospective cohort study    | suicide attempt                            |                          |
| Alvarado-Esquivel, C  | Mexico                    | Case-control                | suicide attempt                            |                          |
| Samojlowicz, D (2013) | Poland                    | Case-control                | death from suicide                         |                          |
| Coryell W (2016)      | United state              | prospective cohort study    | suicide attempt                            |                          |
| Gale, S. D (2016)     | United state              | Cross-Sectional             | suicidal ideation                          |                          |
| Okusaga, O (2016)     | United states OR Germany  | Case-control                | suicide attempt                            |                          |
| Sugden, K (2016)      | United state              | prospective cohort study    | suicide attempt                            |                          |
| Ansari-Lari, M (2017) | Iran                      | Case-control                | suicide attempt                            |                          |
| Dickerson, F (2017)   | United state              | Case-control                | suicide attempt                            |                          |
| Bak, J (2018)         | South Korea               | Case-control                | suicide attempt                            |                          |
| Dickerson, F (2018)   | United state              | prospective cohort study    | death from suicide                         |                          |
| Fond, G (2018)        | France                    | prospective cohort study    | suicide attempt                            |                          |

Figures
Figure 1

Process of performing systematic review
| Study name                  | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|----------------------------|------------|-------------|-------------|---------|---------|
| Timothy A (2009)           | 1.55       | 1.14        | 2.11        | 2.77    | 0.01    |
| Yagmur F (2010)             | 1.79       | 1.18        | 2.71        | 2.72    | 0.01    |
| Okusaga (2014)              | 1.18       | 0.90        | 1.54        | 1.18    | 0.24    |
| Pedersen, M. G (2012)       | 1.53       | 1.27        | 1.85        | 4.43    | 0.00    |
| Alvarado-Esquível, C (2013) | 0.55       | 0.20        | 1.49        | -1.18   | 0.24    |
| Samołłowicz, D (2013)       | 1.78       | 0.79        | 4.03        | 1.39    | 0.16    |
| Coryell W (2016)            | 5.93       | 0.78        | 45.40       | 1.71    | 0.09    |
| Gale, S. D (2016)           | 1.22       | 0.85        | 1.75        | 1.08    | 0.28    |
| Sugden, K (2016)            | 2.63       | 0.97        | 7.14        | 1.90    | 0.06    |
| Ansari-Lari, M (2017)       | 0.40       | 0.16        | 1.03        | -1.89   | 0.06    |
| Dickerson, F (2017)         | 2.41       | 1.02        | 5.70        | 2.00    | 0.05    |
| Bak, J (2018)               | 2.68       | 1.15        | 6.27        | 2.28    | 0.02    |
| Dickerson, F (2018)         | 6.45       | 2.15        | 19.33       | 3.33    | 0.00    |
| Fond, G (2018)              | 1.27       | 0.26        | 6.25        | 0.29    | 0.77    |
| Okusaga, O (2016)           | 1.14       | 0.86        | 1.50        | 0.91    | 0.36    |
|                            | 1.47       | 1.20        | 1.79        | 3.70    | 0.00    |

**Figure 2**

Odds ratio with 95% confidence Interval the studies and meta-analysis.