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Original paper

Meta-analysis of the relationship between *Toxoplasma gondii* and schizophrenia

Tulay ONCU-ONER[1], Sengul CAN[2]

[1]Bioengineering Department, Faculty of Engineering, Manisa Celal Bayar University, Manisa, Turkey
[2]Research Entrepreneurship and Innovation Center, Manisa Celal Bayar University, Manisa, Turkey

Corresponding Author: Tulay Oncu-Oner; e-mail: tulay.oncu@cbu.edu.tr

ABSTRACT. *Toxoplasma gondii* (*T. gondii*), which is an obligate intracellular protozoan parasite, could infect a wide range of hosts including humans. It infects approximately one-third of the entire human population. Infection with *T. gondii* can lead similar psychotic symptoms of schizophrenia. Starting from this information, numerous studies have revealed that maternal, acute and chronic *T. gondii* infections predispose to schizophrenia. The aim of this work was to evaluate the relationship between *T. gondii* and schizophrenia with a meta-analysis study using current data. 112 studies were reached using PubMed, Google Scholar and Council of Higher Education (YÖK) Thesis Center databases. 15 studies which included a proportion of seropositive schizophrenia patients and controls were further examined in a meta-analysis. Among these studies, 13 of them showed a positive association between higher anti-*T. gondii* IgG level and patients with schizophrenia in the experimental groups whereas the remaining 2 studies showed a negative correlation. According to the random effects model, it was seen lower limit of 0.180 and upper limit of 0.490 with a standard error of 0.279 and a 95% confidence interval. The average effect size value was calculated as 0.335. This result having positive average effect size indicated that there was a positive association between *T. gondii* infection with a higher IgG level and the presence of schizophrenia.

Keywords: *Toxoplasma gondii*, schizophrenia, meta-analysis, CMA

Introduction

Toxoplasma gondii (*T. gondii*) is an intracellular protozoan parasite which has a wide range of intermediate hosts including humans and other warm-blooded animals, while its final hosts are felids [1,2]. This parasite causes a disease called toxoplasmosis that is a major public health problem [1]. It has been estimated that *T. gondii* infects approximately one-third of the world's human population [3]. Besides the prevalance varies according to geographic region, cultural factors and socioeconomic conditions [4].

Toxoplasmosis can be diagnosed using biological samples such as blood, bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF), aqueous humor, amniotic fluid or placenta [5]. Direct detection of *T. gondii* is confirmative but also very difficult. Therefore, serological tests, which are include IgG and IgM antibodies detection in the patient's serum, are generally preferred for the diagnosis. IgM antibodies could be detected within a few days to one week of infection. On the other hand, IgG antibodies could be detected within one up two weeks after infection and peaks 3 months [1,6]. Also, PCR-based molecular methods has recently gained popularity because of sensitivity and cost-effective [7].

Humans acquire a *T. gondii* infection by exposure from infected cat faeces, eating undercooked meat or congenital trans-placental transmission during pregnancy [2]. If primary infection occurs during pregnancy, severe damage to the foetus may occur including microcephaly, hydrocephaly, mental retardation, seizure, cerebral calcifications, convulsions and blindness [8,9]. On the other hand, acquired infections are mostly asymptomatic, but in some cases ocular disease and cervical lymphadenopathy could be detected [8]. In latent *Toxoplasma* infection, behavior could be affected

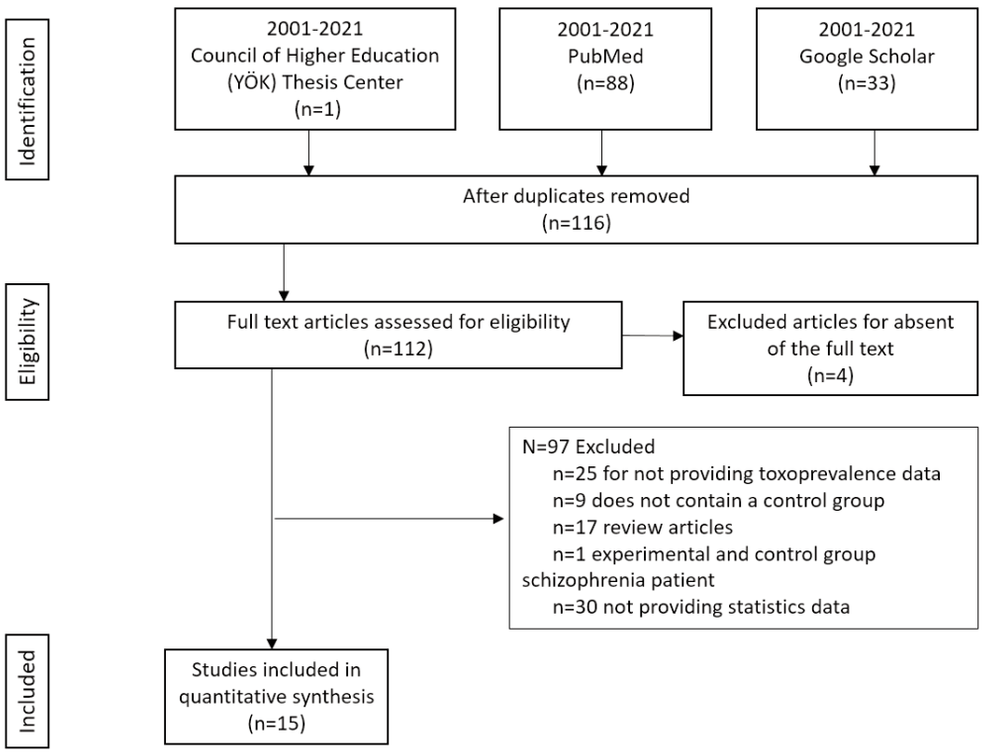

Figure 1. Flowchart of the study selection process

and increased risk could be observed for various psychiatric disorders including depression, suicidal behavior, anxiety, bipolar disorder and schizophrenia [1,10]. To date, several studies have been carried out to reveal the relationship between *T. gondii* infection and schizophrenia [11].

Schizophrenia is a chronic and severe neuropsychiatric disorder that affects about 20 million people worldwide [12]. This disorder is characterized by disturbances in effect, behavior, though, emotion and mood. Furthermore, it is associated with changes in personality, poor judgement and insight, deterioration in function and intelligence [13]. Neurodevelopmental disturbances, genetic predisposition and environmental factors including infectious agents are the risk factors for this mental disorder [11]. Cytomegalovirus (CMV), Herpes simplex viruses (HSV-1 and HSV-2), Epstein-Barr virus (EBV) and *T. gondii* are among the infectious agents [14]. The etiology and neurobiology of schizophrenia are not fully understood. It is thought that symptoms of schizophrenia are associated with an imbalance of dopaminergic system [15,16]. The genome of *T. gondii* was found to contain 2 genes encoding tyrosine hydroxylase which could affect dopamine biosynthesis [17]. On the other hand, there is evidence that other neurotransmitters such as serotonin, glutamate and γ-aminobutyric acid also play a role in schizophrenia [18]. Various animal studies have shown that infection with *T. gondii* could alter behavior and also change the levels of some neurotransmitters which are implicated in the pathogenesis of schizophrenia [19].

The aim of this work was to evaluate the relationship between *T. gondii* and schizophrenia with a meta-analysis study using current data.

Materials and Methods

Study selection

The present study was performed by PRISMA guideline (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20]. Accordingly, a systematic search investigating studies associated with seroprevalence of *T. gondii* infection in patients with schizophrenia compared to healthy controls was conducted in PubMed, Google Scholar and Council of Higher Education (YÖK) Thesis Center using the keywords of ”*Toxoplasma gondii*”, ”Schizophrenia”, ”*Toxoplasma gondii* + Schizophrenia”. The last search was performed on March 2021.

Table 1. Summary of included studies

Reported by	Country	Method	Number of patients with schizophrenia	Seropositivity rate among patients with schizophrenia
Al-Hussainy et al. (2015) [21]	Saudi Arabia	ELISA	63	20 (31.75%)
Alipour et al. (2011) [2]	Iran	ELISA	62	42 (67.7%)
Ansari-Lari et al. (2017) [22]	Iran	ELISA	99	42 (42%)
Campos-Carli et al. (2017) [4]	Brazil	ELISA	48	27 (56.25%)
Cevizci et al. (2015) [23]	Turkey	ELISA	30	10 (33.3%)
Dickerson et al. (2014) [24]	USA	Solid-phase immunoassays	408	263 (64.4%)
Dogruman-Al et al. (2009) [25]	Turkey	ELISA	88	42(47.7%)
El-Gebaly et al. (2019) [26]	Egypt	ELISA	120	54 (45%)
El-Sayed et al. (2012) [27]	Egypt	ELISA	60	34 (56.7%)
Esshili et al. (2016) [28]	Tunisia	ELISA	246	184 (74.8%)
Hamdani et al. (2018) [29]	France	Solid-phase enzyme immunoassay	75	51 (68%)
Nascimento et al. (2012) [30]	Brazil	ELFA, ELISA	41	18 (43.9%)
Park et al. (2012) [31]	Korea	CLIA	96	21 (21.9%)
Shirbazou et al. (2015) [32]	Iran	ELISA	513	8 (74.5%)
Wang et al. (2006) [33]	China	ELISA	600	99 (16.5%)

Abbreviations: CLIA: Chemiluminescent immunoassay, ELFA: Enzyme-linked fluorescence assay, ELISA: Enzyme-linked immunosorbent assay

Inclusion criteria were as follows: (a) research article; (b) published in English or Turkish; (c) investigation of the seroprevalence of *T. gondii* infection (toxoplasmosis); (d) patients with schizophrenia and healthy individuals; (e) utilization of ELISA.

The number of obtained study was 88, 33 and 1 in PubMed, Google Scholar and Council of Higher Education (YÖK) Thesis Center, respectively. After same studies (n:6), and studies (n:4) that we did not obtained full text, were discarded, total of 112 studies were detected to be eligible. Among these 112 studies, 15 of them could be analyzed by meta-analysis because the remaining 97 studies did not present toxoprevalence data, does not contain a control group (Tab. 1) [2,4,21–33]. Detail information about excluded articles is given in figure 1.

Meta-analysis

Meta-analysis was performed by CMA (Comprehensive Meta-Analysis). During CMA, publication bias was checked by Begg-Mazundar and Egger test and then the heterogeneity analysis was applied to decide a model between fixed and random effect size according to Q and *P*-value as well as degrees of freedom [34].

Results

Total of 15 studies examined by meta-analysis contained 2087 patients with schizophrenia and 1786 healthy individuals. When the potential publication bias in the studies was controlled by the funnel plot and Egger statistical values, the tests were bilaterally found to be statistically significant at the level of α=0.05. The results of Egger's test did not show evidence for potential publication bias. Also, for degree of freedom=14 and *P*=0.05, the Q value in the table was 23.685. Since the Q-value (=66.547) obtained as a result of the analysis was greater than the table value (=23.685), it was

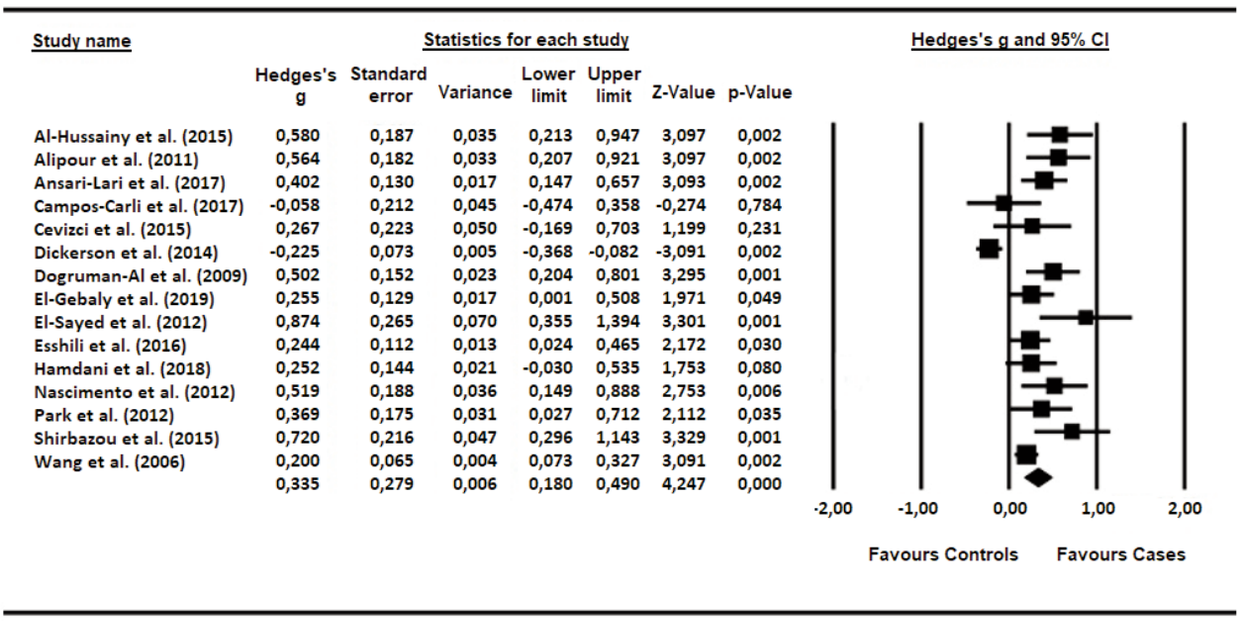

Figure 2. Forest Plot for meta-analysis

determined that the studies were heterogeneous. The effect sizes of the individual studies included are shown in figure 2. When the effect sizes of each study were analyzed, it was detected that the highest effect size was 0.874 whereas the lowest was -0.225. Among these studies, 13 of them showed a positive association between higher anti-*T. gondii* IgG level and patients with schizophrenia in the experimental groups whereas the remaining 2 studies showed a negative correlation. According to the random effects model, the average effect size value was calculated as 0.335 with a standard error of 0.279 and a 95% confidence interval and with lower limit of 0.180 and upper limit of 0.490. This result having positive average effect size indicated that there was a positive association between *T. gondii* infection with a higher IgG level and the presence of schizophrenia.

Discussion

T. gondii, which has a complex life cycle, is one of the most common zoonotic parasites worldwide [35]. Detection of antibodies against *T. gondii* can be achieved by various serological tests such as indirect fluorescent antibody test (IFAT), latex agglutination test (LAT), indirect hemagglutination test (IHAT), Sabin-Feldman dye test (SFDT) and enzyme linked immuno-sorbant assay (ELISA) [36]. Elevation of IgG antibodies *to T. gondii* shows lifetime exposure to toxoplasmosis while elevation of IgM antibodies to *T. gondii* indicates recent infection [37].

It was observed that seroprevalence values of *T. gondii* infection changed depending on culture, socioeconomic status, environmental condition, populations sampled, contact with cats and hygiene, types of the laboratory method used [1]. Moreover, the prevalence of *T. gondii* infection could vary, even within a country. For example, the prevalence of *T. gondii* infection in China is 8.4% (85/1014) in Anhui Province [38], 10.3% (46/448) in Shanghai Province [39], and 15.13% (227/1500) in Shandong and Jilin Provinces [40].

A number of studies have revealed that *T. gondii* infection may alter human behavior and causes psychiatric disorders such as schizophrenia. Thus, numerous studies have been conducted to understand the relationship between *T. gondii* infection and schizophrenia [1]. While some studies showed an association between schizophrenia and *T. gondii* infection [2,41], some studies failed to demonstrate the same results [42]. Though, a higher prevalence of *T. gondii* infestation in humans with schizophrenia was detected in numerous epidemiological case-control studies [11].

In recent years, a number of meta-analysis studies have been published exploring the seroprevalence of *T. gondii* in schizophrenia in different country. A meta-analysis by Torrey et al. [43], which consisted a

total of 3873 patients with schizophrenia and 7046 healthy control people in 23 studies, revealed that the prevalence of antibodies to *T. gondii* in patients with schizophrenia was significantly higher than the prevalence of antibodies in control groups, with an combined odds ratio (OR) of 2.73 (OR: 2.10–3.60, confidence interval CI: 95%). Second meta-analysis study reported by Torrey et al. [44] contained 15 additional *T. gondii* antibody studies with OR of 2.71 (OR: 1.93–3.80, CI: 95%), where again patients with schizophrenia have an increased prevalence of antibodies to *T. gondii*. They have also informed that the cumulative OR was 2.73 (OR: 2.21–3.38, CI: 95%) in a total of 38 studies in these two meta-analysis which comprise 6058 patients with schizophrenia and 8715 healthy controls. In another meta-analysis study reported by Sutterland et al. [35], which focused on *T. gondii* infection in bipolar disorder, schizophrenia and addiction, a significant OR of 1.81 (OR: 1.51–2.16, CI: 95%, $P < 0.00001$) was found with IgG antibodies in schizophrenia.

A meta-analysis of the prevalence of *T. gondii* in Ethiopia including 5718 humans and 5689 animals was published in 2015. Analysis of seroprevalence estimates was pooled using the DerSimonian and Laird random effects. The pooled IgG seroprevalence was estimated at 74.73% (61.85– 84.36%, CI: 95%, inverse variance index (I^2): 98.6%) in humans, while 93.88% (81.47–98.16%, CI: 95%, $P < 0.001$, I^2: 88.2%) in patients with behavioral disorders (bipolar disorder/ schizophrenia). These estimates highlight the overall magnitude of *T. gondii* infections in humans from Ethiopia [45].

A meta-analysis reported by Monroe et al. [37], which comprises studies of *T. gondii* IgM antibodies, includes 2353 patients with acute psychosis and 1707 controls. Data of 15 studies were pooled using DerSimonian and Laird random effects. According to the results, a significant association of acute psychosis and *T. gondii* IgM antibodies was observed. This association was especially stronger in patients with chronic schizophrenia (4.6–8.7%, OR: 2.54 (1.63–3.96), CI: 95%, $P < 0.001$).

Apart from these studies, Sutterland et al. [46] published a meta-analysis study which aim was to investigate the potential effect of *T. gondii* on clinical characteristics of patients with schizophrenia. They analyzed 2368 patients, 741 of them were seropositive to *T. gondii*, in 13 studies. They used random effects model, and suggested that *T. gondii* may affect severity of symptomatology – mainly positive symptoms – in the early stages of schizophrenia.

In our meta-analysis study, among 15 studies, 13 of them demonstrated a positive association between higher anti-*T. gondii* IgG level and patients with schizophrenia in the experimental groups whereas 2 studies showed a negative correlation. According to the random effects model, it was seen lower limit of 0.180 and upper limit of 0.490 with a standard error of 0.279 and a 95% confidence interval. The average effect size value was calculated as 0.335. According to our meta-analysis result, there is a higher frequency of *T. gondii* infection in patients with schizophrenia than in healthy controls, similar to previous meta-analysis studies.

Further research is needed to fully understand the relationship between *T. gondii* infection and schizophrenia. Studies should be conducted on more schizophrenia patients from different countries. In addition, patients' clinical characteristics should be examined in detail.

It should be noted that this study has some limitations. First of all, the most studies included in the meta-analysis did not have statistical values. Second, some studies did not offer seroprevalence values for toxoplasmosis. The last limitation was that some studies did not include healthy individual control groups.

In conclusion, infection with *T. gondii* can lead similar psychotic symptoms of schizophrenia. Starting from this information, numerous studies have revealed that maternal, acute and chronic *T. gondii* infections predispose to schizophrenia. We aimed to evaluate the relationship between *T. gondii* and schizophrenia with a meta-analysis study using current data. Our meta-analysis result having positive average effect size indicated that there was a positive association between *T. gondii* infection with a higher IgG level and the presence of schizophrenia.

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