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Evaluation of the relationship between cryptogenic epilepsy and *Toxoplasma gondii* infection: A meta-analysis

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Abstract

This study was conducted to evaluate the relationship between toxoplasmosis and cryptogenic epilepsy (CE) by performing a meta-analysis of the results of the studies that previously discussed the relationship between *Toxoplasma gondii* and CE.

A systematic search was first conducted using the Web of Science, PubMed, and Google Scholar databases for meta-analysis. Jamovi (Ver. 2.4.1.0) statistical analysis program was used for meta-analysis. The amount of heterogeneity was estimated using the restricted maximum-likelihood estimator. In addition to the estimation of tau², the Q-test for heterogeneity and the I² statistic are reported. The analysis was carried out using the log odds ratio as the outcome measure. A random-effects model was fitted to the data. Meta-analysis findings were presented as forest plots, and the correlation between *T. gondii* infection and epilepsy was demonstrated by the OR and 95% CI. Effect sizes of correlation coefficients were interpreted according to Cohen.

It was seen that four studies included in the analysis were conducted in Egypt, three studies in Türkiye, and two studies in Iran (k:9). The results of the meta-analysis that included nine studies showed a pooled OR of 0.89 (95% CI 0.39 to 1.39). This OR value suggests a strong association between *T. gondii* infection and increased risk of CE according to the Cohen classification.

There was a relationship between toxoplasmosis and increased CE. However, seroprevalence studies should be performed in larger populations to better understand the relationship between CE and *T. gondii*. In addition, molecular studies of how *T. gondii* infection affects the neurological system should be performed to interpret the relationship between toxoplasmosis and CE.

Keywords: Cryptogenic epilepsy, Meta-analysis, Toxoplasmosis

Introduction

Epilepsy is a chronic neurological disease characterized by recurrent seizures caused by abnormal electrical activity in the brain [1-3]. Epilepsy is a common health problem affecting millions of people worldwide and can develop from a variety of causes. One of the most complex types of epilepsy is cryptogenic epilepsy (CE). CE is defined as a type of epilepsy whose underlying cause cannot be fully determined but is not as dependent on genetic factors as idiopathic epilepsy [4]. It is thought that infectious diseases related to the central nervous system (CNS) may lead to CE [5].

Toxoplasma gondii (*T. gondii*) is an obligate intracellular parasite found worldwide and causes toxoplasmosis in humans [6]. *T. gondii* can cause serious neurological and psychiatric disorders, especially in immunocompromised individuals [5]. Recent studies suggest that *T. gondii* infection may be associated with various neurological diseases [7].

This study was conducted to evaluate the relationship between toxoplasmosis and CE by performing a meta-analysis of the results of the studies that previously discussed the relationship between *T. gondii* and CE. This evaluation may contribute to a better understanding of CE and the development of new approaches to treating and preventing this disease.

Material and Methods

Literature search and selection of studies

A systematic search was conducted on Web of Science, PubMed, and Google Scholar on 01.07.2024 to identify published studies on the relationship between *T. gondii* and CE. Using the keywords *Toxoplasma*, *T. gondii*, Toxoplasmosis, and cryptogenic epilepsy, a Web of Science search was conducted as ["cryptogenic epilepsy" (Topic) and "*Toxoplasma*" or "*Toxoplasma gondii*" or "*T. gondii*" or "toxoplasmosis" (Topic)], a PubMed search as [("cryptogenic epilepsy") and ("*Toxoplasma*" or "*Toxoplasma gondii*" or "*T. gondii*" or "toxoplasmosis")] and a Google Scholar search as [toxoplasma "cryptogenic epilepsy"]. Language, region, and date restrictions were not applied in searches.

The PRISMA Flow Diagram was used to identify studies to be included in the meta-analysis [8]. As a result of the search, the titles of the publications were checked, and duplicate publications were eliminated. Following the first screening, the abstracts of the publications were read, and the experimental studies or other studies that were not original articles (reviews, systematic reviews, case reports) were eliminated. The full texts of the remaining articles were read, and articles without CE patients in the patient group, without the control group, or serological data were eliminated. The remaining articles were included in the analysis (Figure 1).

Meta-analysis

As a result of the literature review, a meta-analysis was performed with nine studies included in the study (k:9). Jamovi (Ver. 2.4.1.0) statistical analysis program was used for meta-analysis. The amount of heterogeneity was estimated using the restricted maximum-likelihood estimator. In addition to the estimation of tau^2, the Q-test for heterogeneity and the I^2 statistic are reported. The analysis was carried out using the log odds ratio as the outcome measure. A random-effects model was fitted to the data. Meta-analysis findings were presented as forest plots, and the correlation between *T. gondii* infection and epilepsy was demonstrated by the OR and 95% CI. Effect sizes of correlation coefficients were interpreted according to Cohen [9].

To determine the effect of sample size on correlation, meta-regression analysis was performed by Comprehensive Meta-Analysis (CMA Ver.4).

Studies with a Cook's distance larger than the median plus six times the interquartile range of the Cook's distances are considered influential. The rank correlation test and the regression test, using the standard error of the observed outcomes as predictors, are used to check for funnel plot asymmetry.

Table 1. *Characteristics of the studies included in the analysis*

Authors	CE patient group		Control group	
	N	n (%)	N	n (%)
El-Tantawy et al. [16]	132	80 (60.1)	60	26 (43.3)
El Aal et al. [17]	72	25 (34.7)	60	7 (11.7)
Eraky et al. [18]	40	8 (20.0)	20	2 (10.0)
Khatab et al. [19]	30	12 (40.0)	20	2 (10.0)
Zibaei et al. [20]	85	12 (14.1)	85	4 (4.7)
Babaie et al. [21]	262	94 (38.9)	63	24 (38.1)
Yazar et al. [22]	50	27 (54.0)	50	9 (18.0)
Akyol et al. [23]	100	31 (31.0)	50	10 (20.0)
Aydemir et al. [5]	200	31 (15.5)	164	47 (28.7)

N: total number of individuals

n: number of T. gondii seropositive individuals

Results

The results of the search are presented in Fig. 1. It was seen that four studies included in the analysis were conducted in Egypt, three studies in Türkiye, and two studies in Iran. While *T. gondii* seroprevalence was high in the control group in one

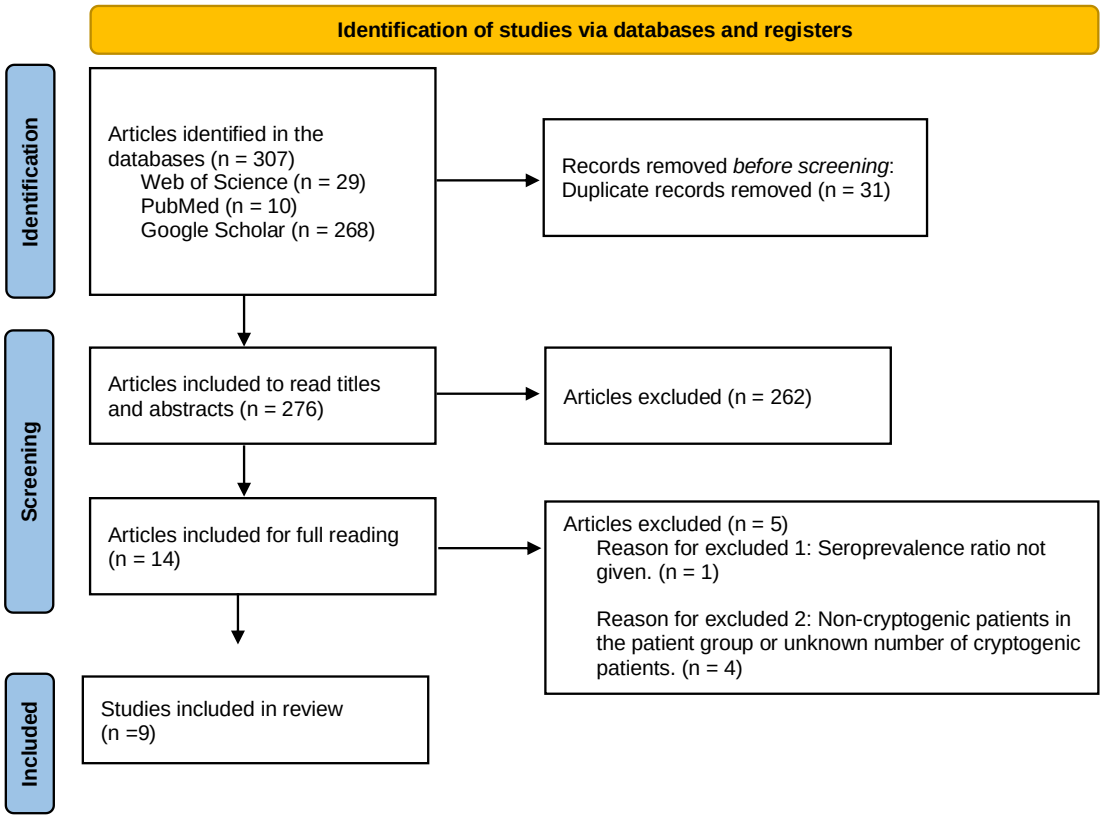

Figure 1. *Flow chart of studies included in the analysis.*

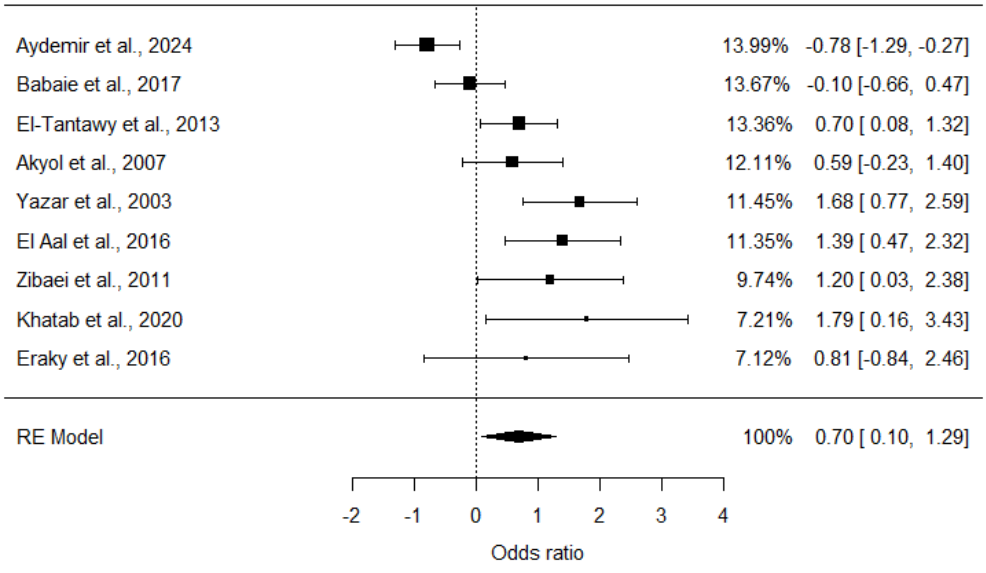

Figure 2. *Forest plot of odds ratios for epidemiological correlation between T. gondii and CE.*

study, it was high in the CE patient group in eight studies (Table 1).

The results of the meta-analysis that included nine studies showed a pooled OR of 0.7 (95% CI 0.1 to 1.3) (Figure 2). This OR value suggests a strong association between *T. gondii* infection and increased risk of CE according to the Cohen classification. However, according to meta-regression, the relationship between *T. gondii* and CE decreases as the "sample size of the study" increases (p=0.001).

According to the Q-test, the true outcomes appear heterogeneous (Q = 41.1, p<0.001, tau² = 0.6, I²=78.1%). A 95% prediction interval for the true outcomes is given by -0.9 to 2.3. Hence, although the average outcome is estimated to be positive, in some studies, the true outcome may be negative. According to Cook's distances, none of the studies could be considered overly influential. The regression test indicated funnel plot asymmetry (p = 0.02) but not the rank correlation test (p = 0.26).

Discussion

We systematically reviewed the literature to estimate the association between toxoplasmosis and CE. Our literature search was comprehensive, as we searched different databases and specific journals without restrictions on publication language and year. However, only nine articles were included.

It is discussed that some behavioral and neurological disorders may occur due to latent toxoplasmosis, especially in congenitally infected children and those with weak or suppressed immune systems [10]. Studies are reporting that it may be associated with some neurological disorders such as Parkinson's, Alzheimer's, schizophrenia, epilepsy [11-13]. Still, there is consistency only in the results of studies on schizophrenia [14]. In addition to studies reporting that the seropositivity rate for *T. gondii* in patients with epilepsy is the same as in healthy controls, there are also studies reporting that the seropositivity rate in patients with epilepsy is high [5]. It has been reported that neurological diseases may occur depending on the localization of tissue cysts in the central nervous system, and only some *T. gondii* strains may cause epilepsy [5].

Toxoplasmosis was found to be a risk factor for CE, but the degree of risk reported in a previous meta-analysis [15] (OR 4.8, 95% CI 2.6-7.8) was higher than that estimated by us (OR 0.7, 95% CI 0.1-1.3). However, the previous meta-analysis was based on only three studies, whereas our study included eight studies.

According to the meta-analysis results, there was a strong association between toxoplasmosis and an increased risk of CE. However, the association was found to change with increasing sample size. Of the eight studies included in the meta-analysis, two studies with the largest sample size found a negative association between *T. gondii* and CE. This suggests that studies with larger sample sizes should be conducted to determine the relationship between *T. gondii* and CE.

In conclusion, we believe that *T. gondii* can cause CE. However, comprehensive control group studies should be conducted to confirm the association, and molecular studies of how *T. gondii* infection affects the neurological system should be performed to interpret the relationship between toxoplasmosis and CE.

Ethics committee approval

The study is not subject to ethics committee approval.

Conflict of interest

The authors declared no conflict of interest.

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