The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Is chronic toxoplasmosis a risk factor for diabetes mellitus? A systematic review and meta-analysis of case–control studies

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ARTICLE INFO

Article history:
Received 30 July 2016
Received in revised form
28 August 2016
Available online 18 October 2016

Keywords:
Toxoplasma gondii
Diabetes mellitus
Systematic review
Meta-analysis

ABSTRACT

Introduction: The global protozoan parasite, *Toxoplasma gondii*, infects many warm-blooded animals and humans by employing different transmission routes. There have been some recent studies on the probable relevance of infectious agents and diabetes. Therefore, we conducted a systematic review and meta-analysis to identify the possible association between chronic toxoplasmosis and diabetes mellitus.

Methods: This study was conducted following the general methodology recommended for systematic reviews and meta-analysis. Nine English literature databases (Google scholar, PubMed, Scopus, Web of science, Science Direct, Ovid, ProQuest, IngentaConnect, and Wiley Online Library) were searched, up to January 2016. Random effects model was used to determine odds ratios and their 95% confidence intervals.

Results: Our review resulted in a total of seven publications meeting the inclusion criteria. Because of significant heterogeneity, we estimated a common OR by a random effects model at 1.10 (95% CI = 0.13–9.57) with $p = 0.929$ and 2.39 (95% CI = 1.20–4.75) with $p = 0.013$ for type 1 and type 2 diabetes mellitus, respectively.

Conclusion: Despite the limitations such as low number of studies, this meta-analysis suggests chronic toxoplasmosis as a possible risk factor for type 2 DM. However, based on random effects model no statistically significant association was observed between *T. gondii* and type 1 DM. It is highly recommended for researchers to carry out more accurate studies aiming to better understand this association.

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http://dx.doi.org/10.1016/j.bjid.2016.09.002

Introduction

The ubiquitous parasitic protozoan, *Toxoplasma gondii*, is one of the most successful microorganism on the planet owing to quite a lot of compatibility to many host species, especially mammals, various transmission pathways (*e.g.* food, water, congenital, blood transfusion, organs transplant, etc.) and approximately involving one-third of the human population.[1–4] Being the category B priority pathogen with zoonotic significance, *Toxoplasma* has frequently been associated with congenital complications (such as hydrocephalus, stillbirth and abortion) as well as neuropathic anomalies, predominantly in high risk populations, *i.e.* pregnant women and immunocompromised hosts.[2,5–7] While unusual, there are some evidence that *T. gondii* parasites may possibly have an undiscovered role in the putative pathogenesis of autoimmune diseases.[8]

A group of chronic metabolic disorders, specified as "Diabetes", are of medical importance with widespread distribution, especially in persons with high-calorie diets. They are distinguished by hyperglycemia elicited by the deficiencies in the insulin hormone release (type 1 diabetes) and/or failure to respond properly to insulin in target cells (type 2 diabetes), and this condition is probably overwhelmed by genetic elements, autoimmune processes, and environmental factors. According to scientific evaluations, it is anticipated that the number of diabetic patients will reach 522 million individuals by 2030.[9] Recently, some reports have spotlighted the probable relevance of diabetes mellitus (DM) and infectious agents like *Helicobacter pylori*[10] and Coxsakie B4 virus.[11] In this case, the Apicomplexan parasite, *T. gondii*, has been proposed as a likely cause of diabetes, and existing information nearly predicate on this issue.[12–16] Hence, this review was intended to shed light on the possible association between toxoplasmosis and diabetes.

Methods

Ethical aspects

As this review did not involve any human or animal subjects, therefore ethical approval was not required.

Search strategy

A systematic review was premised on screening the literature published online in English language up to January 2016, in order to address the association between toxoplasmosis and diabetes. The search was conducted on Google scholar, PubMed, Scopus, Web of science, Science Direct, Ovid, ProQuest, IngentaConnect, and Wiley Online Library (Supplementary Fig. 1). Toward that end, the medical subject headings (MeSH) terms in PubMed and Scopus databases using the search keywords "Toxoplasmosis", "*T. gondii*", "*Toxoplasma gondii*", "Diabetes mellitus" and "Diabetic patients" combined together using OR and/or AND. Also reference lists of the primary relevance records found were explored manually. Corresponding authors of papers were contacted for more details, if deemed necessary.

Study selection and data extraction

Only case–control studies on seroepidemiology of toxoplasmosis in diabetic individuals around the world were included. Other inclusion criteria were as follows: diabetes as a disease and *T. gondii* as an exposure, presence of healthy individuals as control group, and serologic diagnostic test. Records were evaluated by two independent reviewers. The selected articles were scrutinized and contradictions among studies were obviated by discussion and consensus. The data were extracted carefully from databases on the basis of title, year of publication, first author, diagnostic method, type of investigation, type of disease, aim of study, main findings, exact number of participants both in case and control groups, and details of *T. gondii* positive individuals as well. The PRISMA (preferred reporting items for systematic reviews and meta-analysis) guideline[17] was followed in the reporting of current systematic review.

Meta-analysis

For each included study, the common odds ratio (OR) and respective 95% confidence interval (CI) on the association among toxoplasmosis and diabetes were calculated. The outcome of pool estimates of studies in addition to their 95% CI of independent records were depicted in a forest plot. Cochran's Q and I^2 statistics were applied to assess heterogeneity and inconsistency, respectively. Furthermore, small study effects and their publication bias were discerned by a funnel plot on the cornerstone of Egger's regression test. To comply with the results of heterogeneity test, either Der Simonian and Laird's random-effects method or Mantel-Haenszel's fixed-effects were employed to pool the approximations.

Results

Based on inclusion criteria, a total number of 7 out of 1377 studies were qualified to be ultimately included in this systematic review and meta-analysis,[12,14,18–22] as demonstrated in Supplementary Fig. 1. The specifications of each study comprising the number of cases and controls as well as the number of IgG positive individuals, the utilized method and obtained *p*-value have been summarized in Table 1. Out of 2248 persons tested for toxoplasmosis infection, 717 were positive for *T. gondii* infection, 202 had type 1, and 1158 had type 2 DM; out of 888 healthy individuals 280 positive for *T. gondii* infection. The heterogeneity was statistically significant, for both type 1, $I^2 = 94.7\%$ and $Q = 38.09$ ($p < 0.001$), and type 2 DM, $I^2 = 88.1\%$ and $Q = 25.26$ ($p < 0.001$) (Table 2 and Supplementary Fig. 2). Accordingly, we calculated a common OR by random effects model at 1.10 (95% CI = 0.13–9.57) with $p = 0.929$ and 2.39 (95% CI = 1.20–4.75) with $p = 0.013$ for type 1 and type 2 DM, respectively (Table 2 and Supplementary Fig. 2). Also the calculated common OR (random effects model) for both type 1 and 2 diabetes was 1.86 (95% CI = 0.93–3.74) with $p = 0.0796$. The test of publication bias was clearly not significant in this case,