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Is there any association between *Toxoplasma gondii* infection and bipolar disorder? A systematic review and meta-analysis

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ABSTRACT

Background: The relationship between *Toxoplasma gondii* infection and the development of bipolar disorder (BD) has long been investigated, yet to date it is still poorly understood and documented. The aim of this review is to derive a summary estimate of the strength of the association between infection with *T. gondii* and BD from the available published studies.

Methods: A systematic review was performed using PubMed, LILACS, PsycINFO, and Embase databases. Studies which included a proportion of seropositive BD patients and controls were further examined in a meta-analysis.

Results: One hundred eighteen citations were initially retrieved. Thirteen studies were included in our systematic review. Eight out of these thirteen studies were included in our meta-analysis. Statistical analyses showed that *T. gondii* infection is associated with with BD (OR=1.26).

Limitations: Small sample size was the major limitation among the studies that carried out serological analyses. In addition, the available studies did not have enough information on disease status/severity or type of bipolar disorder. Also, it was not possible to analyze pregnancy status or perinatal infection. Future studies addressing the aforementioned topics are clearly needed.

Conclusions: Despite heterogeneous results, patients with BD are more likely to be infected by *T. gondii* than controls. Early *T. gondii* infection might predispose the development of BD. *T.gondii* infection is becoming clinically relevant in psychiatric disorders and future mechanistic studies are required to elucidate the underlying pathophysiological mechanisms.

1. Introduction

Toxoplasma gondii (T. gondii) is an obligate intracellular protozoan parasite. Human infection occurs either after the ingestion of oocysts shed by infected cats or the consumption of undercooked meat derived from infected animals, particularly pork (Montoya and Liesenfeld, 2004). *T. gondii* infection is usually asymptomatic in healthy adults, and might reach the human central nervous system (CNS) where cysts persists lifelong (Opsteegh et al., 2011). However, immunocompromised patients might develop severe clinical complications, such as toxoplasmic encephalitis, chorioretinitis, and pneumonitis (Abedalthagafi et al., 2009). Moreover, infection during gestation could lead to congenital syndromes, seizures and intellectual impairment (Kaye, 2011). Infection with *T. gondii* has also shown to lead to psychotic symptoms (Hamidinejat et al., 2010) and changes in personality (Novotna et al., 2005; Khademvatan et al., 2013b). These symptoms are widely observed in several psychiatric conditions, including bipolar disorder.

Bipolar disorder (BD) is a severe mood disorder that affects approximately 2.4% of the world's population (Merikangas et al.,

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2011). BD is characterized by depressive and manic cycles, with depressive episodes tending to predominate over the course of the illness. The neurobiology of BD is highly complex and not fully understood (Shih et al., 2004; Escamilla and Zavala, 2008). Immunological abnormalities have been regarded as possible contributors to the pathophysiology of BD (Barbosa et al., 2014, Hamdani et al., 2012; Söderlund et al., 2011; Jakobsson et al.2013, Leboyer et al., 2012; Drexhage et al., 2011; Rege and Hodgkinson, 2013). One recent systematic review has shown that several studies suggested that infectious agents might be associated with the pathogenesis of BD, such as *T. gondii, Herpes simplex virus* (HSV)−1, HSV-2, human herpes virus 6 (HHV-6) cytomegalovirus, Epstein-Barr Virus (EBV), and Varicella zoster virus (Barichello et al., 2016). The specific nature of the association between *T. gondii* and BD is yet to be elucidated.

Given the aforementioned points, the main purpose of the present study was to evaluate whether *T. gondii* status is associated to BD and possibly predisposes this psychiatric condition, through a systematic review in addition to a confined meta-analysis of the previously published studies in the literature.

2. Methods

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines were used for conducting the systematic review (Moher et al., 2009). We performed a systematic search to find original studies that investigated the association between *T. gondii* and BD in MEDLINE, LILACS, PsycINFO and Embase databases using the keywords Bipolar Disorder AND toxoplasmosis OR *Toxoplasma gondii*.

Our inclusion criteria were as follows: (i) original articles; (ii) published in English, Spanish, or Portuguese; (iii) clearly evaluated possible association between BD and *T. gondii* through serological analyses (iv) published within January 1980 until June 2015. Studies that addressed possible immunological abnormalities in seropositive patients were grouped in a special category that is further discussed.

Two independent reviewers (JLVMB and AK) screened the titles and abstracts of all potentially eligible articles. When a title and/or an abstract appeared suggestive for inclusion, the full text reprint was obtained and examined to assess its relevance according to our inclusion criteria. Both authors applied the inclusion criteria, and a list of full text articles was developed independently from each other. The two reviewers then considered the full texts of these articles and a final list of relevant articles was reached through consensus. A third investigator (ALT) did additional independent assessment when discrepancies occurred.

Extracted data items comprised articles' details such as first author's surname, year of publication, method of studies), sample size, and the prevalence of positive results of toxoplasmosis test.

The meta-analysis pooled the prevalence of toxoplasmosis seropositivity in BD and control groups, from the included different study designs to determine their pooled risk estimate. The meta-analysis was performed in a random effect model with the risk ratio (RR) and its 95% confidence interval (95% CI) estimated for each study. The free software Review Manager 5.2 (RevMan) used for Cochrane reviews was applied for meta-analysis in this study.

3. Results

We extracted an initial cohort of 118 citations in MEDLINE, LILACS, PsycINFO and Embase databases. Fifty were duplicates and after an abstract and title screening, 43 articles were excluded for clearly not fully meeting our inclusion criteria. From the 25 remaining articles, 12 were excluded for not meeting our inclusion criteria. Finally, a total of 13 studies were included in our systematic review. Eight out of these 13 studies met our inclusion/exclusion criteria and were further included in our meta-analysis (Fig. 1).

3.1. Serological analyses of T. gondii infection: systematic review

Demographic data regarding the studies included in the systematic review are shown in Table 1. Data about the serological analyses are given in Table 2.

The great majority of the studies used the ELISA technique and measured IgG antibodies (Table 2). Four case-control studies reported an association between *T. gondii* infection and BD (Garcia and Perdomo, 1980; Tedla et al., 2011; Hamdani et al., 2013; Hamdani et al., 2015). Conversely, other five studies failed to show the same association (Hinze-Selch et al., 2010; Mortensen et al., 2011; Khademvatan et al., 2013a; Avramopoulos et al., 2015). Some studies investigated the association between *T. gondii* antibodies' levels and mood episodes in BD. IgG levels were associated with BD type I with manic and depressive episodes (Pearce et al., 2012). IgM levels were associated with acute mania at hospital admission but decreased across three time-points of assessment (Dickerson et al., 2014a). In addition, seropositive BD patients presented more lifetime depressive episodes (Fond et al., 2015). On the other hand, one study reported that individuals with acute bipolar depression did not differ from controls regarding the levels of antibodies to *T. gondii*. Unfortunately, the study did not specifically report the results regarding mania group (Dickerson et al., 2015).

Immune-related mechanisms capable of explaining the link between *T. gondii* infection and BD were investigated. One study measured IL-6 transcript levels in both seropositive and seronegative BD patients through cDNA product amplification. BD patients had significantly higher levels of IL-6 than healthy controls, regardless the serological status of both groups. Therefore, no association was found between *T. gondii* status and altered IL-6 transcript levels in BD patients (Hamdani et al., 2013). Another study evaluated the association between levels of IL-6 in seropositive BD patients and cognitive performance. BD patients displayed higher cognitive deterioration index than controls. Among seropositive BD patients, IL-6 mRNA levels were positively correlated to the deterioration index. Seronegative patients and controls (seropositive and seronegative) displayed a negative correlation between IL-6 and deterioration index (Hamdani et al., 2015).

Eight studies that carried out serological analyses to investigate the rate of infection with *T. gondii* in patients with BD in comparison with controls were also included in our meta-analysis (studies # 1- 8, Tables 1, 2). One study was excluded from the meta-analysis because authors used the toxoplasmin intradermal test to diagnose toxoplasmosis instead of measuring anti-*T. gondii* antibodies (Garcia and Perdomo, 1980). Three studies did not estimate the prevalence of *T. gondii* seropositivity in BD or control groups (Avramopoulos et al., 2015; Dickerson et al., 2014a; Dickerson et al., 2015). Finally, one last study was not included as authors did not inform the prevalence of seropositivity in the control group (Fond et al., 2015).

3.2. Meta-analysis

Eight out of the 13 studies were eligible for meta-analysis (studies # 1- 8, Tables 1, 2). A total of 797 patients with BD and 8,090 controls were included in this meta-analysis. The prevalence of *T. gondii* seropositivity ranged from 15.6–95.3% in patients with BD and from 16.3–87.3% in controls. The overall meta-analysis indicated that the combined prevalence of toxoplasmosis was 53.7% in patients with BD and 18.4% in controls, indicating that patients were more frequently infected by *T. gondii* [odds ratio (OR) =1.26 (Fig. 2)].

Among the eight studies included in the meta-analysis, two focused on evaluating *T. gondii* infection in type 1 BD patients (Khademvatan et al., 2013a; Pearce et al., 2012). The remaining studies either included type 1 and type 2 BD patients in their samples and never conducted statistical analyses towards each type separately (Hamdani et al., 2013; Hamdani et al., 2015; Mortensen et al., 2011) or failed to

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