Narrative review

Seroprevalence of *Toxoplasma gondii* and its Relationship with Mental Disorders in the Adult Population

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Abstract
Toxoplasma gondii is a parasite that is found in approximately 30 % of the human population. In recent years, it has been shown that latent infection can be a risk factor for the development of mental disorders; particularly schizophrenia, anxiety, bipolar disorders, and conduct disorders. The association with neuropsychiatric disorders can be explained by the influence of the parasite on the expression of multiple neurotransmitters; among them, dopamine has received the most attention. A narrative bibliographic review article was done with the search of original and review articles in international scientific journals, in English and Spanish listing the relationship between the seroprevalence of *T. gondii* and the development of mental disorders in the adult population. The relationship between mental disorders in the adult population with *Toxoplasma gondii* infection is present and increases the possibility of developing schizophrenia and depression in individuals with no previous history, including the ability to worsen previous psychiatric conditions, making it difficult for standard management. Not all statistical data establish a direct relationship, some studies show an association and certain data are discordant, which opens a door for future research.

Keywords
Toxoplasmosis, Mental Disorders, Cognitive Disorders, Schizophrenia.

Resumen
El *Toxoplasma gondii* es un parásito que se encuentra, aproximadamente, en el 30 % de la población humana. Durante los últimos años se ha evidenciado que la infección latente puede ser un factor de riesgo para el desarrollo de trastornos mentales; particularmente para la esquizofrenia, ansiedad, trastornos bipolares y trastornos de conducta. La asociación con los trastornos neuropsiquiátricos pueden explicarse por la influencia que tiene el parásito sobre la expresión de múltiples neurotransmisores; entre ellos la dopamina. Se realizó una búsqueda en las bases de datos PubMed y SciELO de 2015 a 2023, se seleccionaron artículos originales y de revisión de revistas científicas internacionales, en idiomas inglés y español con el objetivo de describir la relación entre la seroprevalencia de *T. gondii* y el desarrollo de trastornos mentales en población adulta. Existe relación entre los trastornos mentales en la población adulta con la infección por *Toxoplasma gondii* y este aumenta la posibilidad de desarrollar esquizofrenia y depresión en individuos sin historial previo, y que podría exacerbar cuadros psiquiátricos previos con dificultad en el tratamiento. Sin embargo, no todos los datos estadísticos establecen una relación directa, algunos estudios demuestran una asociación, ciertos datos son discordantes, lo que abre una puerta para futuras investigaciones.

Palabras clave
Toxoplasmosis, Trastornos mentales, Trastornos cognitivos, Esquizofrenia, *Toxoplasma gondii*.

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Introduction

Toxoplasma gondii is a protozoan parasite found in approximately 30 % of the human population and has historically been a problem as congenital toxoplasmosis and disease in immunocompromised patients.[1]

Some studies have shown that this parasite produces biological alterations in the human brain.[2] Likewise, a direct association between patients' seropositivity is a causal factor in the development of mental illnesses.[3]

Latent toxoplasmosis has been associated as a risk factor for the development of mental disorders, particularly schizophrenia, anxiety, bipolar disorders, and conduct disorders.[4,5] Schizophrenia affects one in 300 people worldwide and has a significant impact on their life expectancy.[6]

The high incidence rate of latent toxoplasmosis contributes to the difficulty of clinical diagnosis and specific pharmacological treatment and makes it a community problem.[7] Seropositivity rates have been increasing in recent years, reaching 90 % depending on the country or region.[8,9] Due to the growing number of associations between *T. gondii* and mental disorders, the impact of this parasite in different investigations has been largely underestimated, and more studies are needed to strengthen this association.[6]

A narrative literature review article was prepared by searching for original and review articles in scientific journals, in English and Spanish, in databases such as PubMed, SciELO, and sites of international organizations related to the topic of interest. The search terms used were "Latent toxoplasmosis", "Mental disorders", "Seroprevalence of toxoplasmosis", "Cognitive disorders", "Schizophrenia" and "*Toxoplasma gondii*"; with the incorporation of Boolean operators (AND, OR & NOT). Original articles, meta-analyses and review articles published between 2015 and 2023 were cited. This investigation seeks to explore the connection between the prevalence of *T. gondii* and the emergence of mental health issues in the adult population.

Discussion

Pathophysiology and effects of *Toxoplasma gondii* at the brain level

T. gondii uses a complicated mechanism to gain access to the central nervous system (CNS); when it manages to invade it, it can affect different brain cells, such as astrocytes and neurons, where it forms cysts.[10] The mechanism of invasion into the CNS has not been extensively studied, and there is still no consensus on how this parasite crosses the blood-brain barrier.[1] Different mechanisms used by *T. gondii* to cross the blood-brain barrier have been explored; one of the best-known mechanisms is transendothelial migration through integrins. It is also possible that the parasite enters the CNS on its own through transcytosis or parasitosis.[11] Another mechanism that has been studied *in vitro* is the Trojan horse mechanism, which consists of parasite transport by a cell, for example, a leukocyte.[11]

The association between *T. gondii* and neuropsychiatric disorders can be largely explained by the parasite's influence on the expression of multiple neurotransmitters. The neurotransmitter dopamine has received the most attention due to the parasite's ability to synthesize tyrosine hydrolase, an enzyme involved in dopamine biosynthesis.[12] Increased levels of dopamine in and around parasite cysts generated by multiple pathways are responsible for the positive symptoms of schizophrenia.[13] *T. gondii* also alters the expression of other neurotransmitters, such as glutamate, gamma-aminobutyric acid, serotonin, and noradrenaline.[12] These effects on neurotransmitters can be explained by the encystation of bradyzoites in brain cells, especially microglia or neuronal cells, causing alterations in host neurochemistry and receptor expression.[1]

The presence of this parasite in the brain parenchyma is also related to the secretion of proinflammatory cytokines and mediators from neurons, astrocytes, and microglia. Persistent neuroinflammation has also been related to alterations in neurotransmitter release.[14]

Psychiatric disorders associated with latent infection with *T. gondii*

Nessim *et al.* mention that the percentage of the population associated with *T. gondii* seropositivity and schizophrenia is 20.4 %, bipolar disorder 27.3 %, and suicidal behavior 0.29 % ; however, these percentages are subject to variations by geographical area due to regionally prevalent risk factors. For example, the risk factors for toxoplasmosis associated with mental illness were water contamination in Africa, and cooking conditions of meats in the European region.[15]

According to Lindgren *et al.*, there is an association between *T. gondii* infection and psychotic symptoms ($p = 0.001$) to the head, predominantly auditory hallucinations; these events considerably increase the risk of suffering psychosis in the future, even if they are transitory. Even if a DSM-V-diagnosed psychosis does not develop, these isolated events are associated with a worse functional capacity and general health in the population.[16]

The relationship between toxoplasmosis and schizophrenia has been demonstrated by Stepanova *et al.* in a prevalence study conducted in Russia, where there is an incidence of schizophrenia of 0.82 %,[17] and which showed that patients with underlying neuropsychiatric diseases had twice the inci-

dence of being infected by *T. gondii* (40 %), compared to the control group (25 %) with statistical significance (p = 0.007). However, the direct role of the parasite in the etiology is still questionable. Few longitudinal studies have examined the causal relationship between *T. gondii* and schizophrenia.[18]

Contopoulos-Ioannidis *et al.* examined 66 studies published in the last two decades, involving 11 540 patients with schizophrenia and 69 491 controls, to study the relationship between *T. gondii* and schizophrenia. Although there was heterogeneity across studies in the types of toxoplasmosis exposure and schizophrenia outcomes, on average, 45 % of schizophrenia patients were seropositive for *Toxoplasma* IgG (or IgG/IgM) versus 30 % of the control group. *Toxoplasma* IgG (or IgG/IgM) seropositivity increased the odds of schizophrenia by 1.91-fold.[19]

Although schizophrenia is a multicausal disease, risk factors for developing schizophrenia have been identified, including seropositivity to *T. gondii* (IgG). In an umbrella study by Radua *et al.* in which multiple published systematic reviews and meta-analyses were compiled, suggestive class III evidence for *T. gondii* (IgG) seropositivity was found.[20]

T. gondii-infected individuals with schizophrenia often exhibit significant impairment in multiple cognitive domains; Guimarães *et al.* note that patients with positive IgG for *T. gondii* may experience deficits in verbal learning, social cognition, and even visual memory, in contrast to digital cognitive learning in those who showed improved adherence.[21]

In a study conducted by Veleva *et al.* on 89 patients who had been diagnosed with schizophrenia, they discovered that seropositive patients had worse visual memory and executive functions. At the same time, seroprevalence was linked to a higher score on the Positive and Negative Syndrome Scale, which measures the prevalence of both positive and negative symptoms in schizophrenia.[22]

Delusions and alogia were the most common symptoms in a cohort study by Fong *et al.* that examined ten community centers and 250 clinically stable patients diagnosed with schizophrenia. The study also found that latent infection with *Toxoplasma gondii* is associated with a higher score on the Positive and Negative Syndrome Scale. Latent *T. gondii* infection did not significantly correlate with age, gender, or the age at which schizophrenia first manifested itself in this study.[23]

Liu *et al.* present the results of their research, where they identified that schizophrenia, bipolar disorder, depression and recurrent depressive disorder were associated with *T. gondii* serological positivity, except for dissociative depressive disorder. Likewise, a potential association was found between depression or recurrent depressive disorder and *T. gondii* infection, and there was evidence that infection affects the susceptibility and severity of depression in children, adolescents, and pregnant women.[23]

The etiology of major depressive disorder is multifactorial, consisting of genetic and environmental factors.[25] According to the manuscript by Sapmaz *et al.*, a significant association was found between *T. gondii* seropositivity and the presence of clinical depression (p = 0.046). In addition, the data indicated that patients who reported suicide attempts and suicidal ideation had higher levels of antibodies that could be associated.[26]

A study by Nasirpour *et al.* found a higher prevalence of antibodies against *T. gondii* in patients with depression, which shows the possible impact of this parasite on the cause of depression and the intensity of its symptoms. On the other hand, it was found that the frequency of antibodies against *T. gondii* IgG was 59.8 % in patients with depression and 56.3 % in the control groups, and it was determined that the risk of depression in people with positive serology tests was 1.5 times more than with a negative response.[27]

Currently, the relationship between *T. gondii* seropositivity and depression is related to the geographical site of the study and the conditions of the study. Lin *et al.* found that both clinical depression and anxiety have a greater risk of developing in infected patients. However, he mentions that there are some differences between the results because infection may favor depression in different degrees of severity for each individual.[28]

A cross-sectional case-control study including 384 patients over 18 years of age with a diagnosis of depression and 400 healthy subjects found that patients with current depression have higher anti-G antibody positivity for *T. gondii* compared to healthy individuals. It was also shown that seropositive individuals with depression have a higher severity index with a higher risk of suffering a suicide attempt.30 Furthermore, it has been shown that the seroprevalence of *T. gondii* is related to higher suicide attempts compared to healthy individuals.[29]

Bahceci *et al.* recruited 100 patients diagnosed as depressed with suicidal ideation, 100 patients with depression without suicidal ideation, and 100 healthy patients in whom they assessed depression and

suicide risk with assessment instruments such as the Hamilton depression scale and suicide scales. It was found that seropositivity for *T. gondii* in depressed patients with and without suicidal ideation is higher than in healthy patients.[30] Likewise, a case-control study by Bak *et al.* of 155 patients with suicidal attempts and 135 healthy individuals found IgG antibodies to *T. gondii* in 13.5 % in the case group compared to 5.9 % in the controls.[32] Also, higher severity values were found in seropositive cases compared to controls. The results of this study suggest a relationship between seropositivity and suicidal behavior.[31]

There is evidence that treatment against *T. gondii* in seropositive patients with underlying psychiatric disease has significantly improved their symptoms and has demonstrated a decrease in antibodies against *toxoplasma* in diseases such as depression, obsessive-compulsive disorder, and schizophrenia. It has been shown that several drugs, including antipsychotics and sodium valproate, have an *in vitro* effect on preventing parasites from replicating in cell cultures.[32]

Antipsychotic drugs such as haloperidol, chlorpromazine, and valproic acid have been shown to inhibit the *in vitro* growth of *T. gondii* as well. Nevertheless, Kezai *et al.* describe that *T. gondii* could interfere with the effectiveness of antipsychotic treatment; individuals with therapy-resistant forms of schizophrenia had a higher prevalence of anti-*toxoplasma* antibodies, in contrast to the control group with non-drug-resistant forms of schizophrenia ($p = < 0.0001$).[33,34]

In patients with a diagnosis of schizophrenia and seroprevalence for toxoplasmosis, antiparasitic drugs have not demonstrated clinical improvement in the severity of schizophrenia symptoms.[35,36]

T. gondii seroprevalence and cognitive changes

It has been demonstrated that the seroprevalence of *T. gondii* is associated with alterations in cognitive functions, mainly in working memory tests. This result was identified through a questionnaire called "National Health and Nutrition Examination Survey 2013-2014" and the analysis of cognitive tests performed on a group of adults over 60 years of age with positive IgG to *T. gondii*.[37]

Similarly, *T. gondii* seropositivity was linked to worse reasoning and pattern completion, including with arithmetic tasks, in a community study involving individuals aged 40 to 70 years. Although few tests for memory assessment were conducted in this cohort, the executive component of cognitive function, such as decision-making, was primarily affected.[38]

Haan *et al.* conducted a meta-analysis that included 13 studies with 12 289 healthy individuals, in which an association was observed between seropositivity to *Toxoplasma gondii* and impairment in cognitive tests affecting processing speed, working memory, and executive functioning.[39]

The role of *T. gondii* in the development of neurological diseases that affect memory remains unclear; Mendy *et al.* analyzed the database of the United States Center for Disease Control in which 4485 people over 60 years of age participated, in whom a significant difference in seroprevalence of *T. gondii* was observed with short-term memory impairment, but not long-term.[40] In contrast, Wyman *et al.* analyzed 117 older adults without a diagnosis of dementia without finding evidence of a significant association between *T. gondii* seropositivity and memory impairment.[41]

Another study in laboratory mice showed that *T. gondii* infection significantly alters behavior, decreases fear of predators, decreases anxiety, and consequently produces immune and inflammatory reactions in the brain. In humans, other types of behavioral changes have been found, such as increased suicidal behavior, aggressiveness, and increased risk of traffic accidents.[42]

On the other hand, Zouei *et al.*, in their study, showed that the population infected by *T. gondii* had hormonal alterations, regardless of sex, with a significant increase in testosterone levels ($p = 0.02$ and $p = 0.04$ for men and women, respectively) in contrast to the control group, which did not show this increase. The increase in testosterone has been associated with behavioral changes, such as antisocial behavior, aggressiveness, and dominant behaviors, as well as immunosuppressive reactions.[43]

According to Postolache *et al.*, there is an increased incidence of suicide attempts in the *T. gondii*-infected population, ranging from 39 % to 57 % in seropositive individuals, regardless of any underlying mental disorder. Similarly, impulsive conduct throughout life has been linked to *T. gondii* infection and is a risk factor for suicide attempts.[44]

Similarly, Johnson *et al.* found that *T. gondii* infection is associated with a lower fear of failure and a stronger inclination to take chances. Under this concept, infection can be biased toward specific activities, demonstrating that modifying some behaviors can have a holistic impact on the human being.[45] Although not all statistical data

prove a direct relationship, certain studies show an association, which is a significant health problem for future investigation.

Conclusion

In the adult population, there is a relationship between mental disorders and *Toxoplasma gondii* infection, which increases the possibility of developing schizophrenia and depression in individuals with no previous history, with a risk of exacerbation of previous psychiatric conditions that are difficult to treat. The pathophysiological mechanisms that support such claims are mostly based on the parasite's ability to produce biochemical reactions at the CNS level. These mechanisms also include increases in neurotransmitters such as dopamine, glutamate, gamma-aminobutyric acid, serotonin, and noradrenaline. These biochemical changes are responsible for predisposing to predominantly impulsive and aggressive behaviors, suicidal tendencies, and cognitive changes such as altered memory, cognitive speed, and executive functioning.

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