

Toxoplasma gondii infection and chronic schizophrenia: is there any association?

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ABSTRACT

Background: *Toxoplasma gondii* (*T. gondii*) infection has been identified as a risk factor for schizophrenia. **Objectives:** Herein, we sought to evaluate the association between *T. gondii* infection and clinical symptoms and quality of life in patients with schizophrenia. **Methods:** We conducted a cross-sectional study with 48 patients with chronic schizophrenia and 40 controls. Peripheral blood was drawn, and IgM and IgG anti-*T. gondii* antibodies were evaluated by Enzyme-Linked Immunosorbent Assay (ELISA). Depressive, positive and negative symptoms were assessed, respectively, by the Calgary Depression Scale (CDS) and the Positive and Negative Syndrome Scale (PANSS). Cognitive performance was assessed in patients by the Brazilian version of the Schizophrenia Cognition Rating Scale (SCoRS-BR). Quality of life was assessed by the Brazilian version of the Quality of Life in Schizophrenia scale (QLS-BR). **Results:** The prevalence and titers of *T. gondii* IgM and IgG antibodies did not differ between patients and controls. The positive serology for *T. gondii* IgG antibodies was not associated with illness symptoms, cognitive performance, depressive symptoms or quality of life. **Discussion:** Our findings suggest that toxoplasmosis infection is not associated with severity of symptoms, quality of life, cognitive or depressive symptoms in schizophrenia patients.

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Keywords: *Toxoplasma gondii*, schizophrenia, cognition, depression, quality of life.

Introduction

Schizophrenia is a pervasive psychiatry disease whose etiopathogenesis results from complex gene-environmental interactions. Accumulating evidence suggests that infection is an important environmental factor implicated in schizophrenia pathogenesis¹. Epidemiological and meta-analytic studies have shown an association between infections and increased risk of schizophrenia².

Toxoplasma gondii is a protozoan with a worldwide distribution³. It has been estimated that up to one third of the world population has been exposed to the parasite⁴. The exposure rate and the prevalence of *T. gondii* infection varies according to geographic region, population habits as well as socioeconomic conditions⁵. For instance, in Brazil the rate of *T. gondii* infection in humans is high: up to 50% of elementary school children and 50-80% of women of child-bearing age have antibodies to *T. gondii*⁶.

In healthy adults, infection with *T. gondii* generally results in a latent infection that persists for life. This chronic infection was largely regarded as asymptomatic, but this assumption has changed lately. Latent toxoplasmosis has been linked to changes in cognitive function in both children⁷ and elderly individuals⁸. *T. gondii* infection has also been regarded as a risk factor for schizophrenia. A recent meta-analysis showed that *T. gondii* infection is associated with several psychiatric disorders including schizophrenia, bipolar disorder (BD) and obsessive-compulsive disorder⁹. Noteworthy, the reactivation of latent *T. gondii* infection may occur in patients with schizophrenia⁹. Moreover, *T. gondii* infection was associated with an increased risk for mortality in patients with schizophrenia¹⁰.

Although the association between *T. gondii* infection and schizophrenia has already been investigated, the results are still controversial and only few studies have focused on whether the infection is associated with clinical outcomes. Therefore, this study was carried out to investigate differences in *T. gondii* seroprevalence

in patients with schizophrenia and controls, as well as to evaluate whether seroprevalence and anti-*T. gondii* antibody titers are associated with clinical parameters.

Methods

Subjects

This is a cross-sectional study in which 48 patients with chronic schizophrenia and 40 controls were evaluated. Schizophrenia diagnosis was confirmed by the structured psychiatric interview MINI-Plus¹¹ using the DSM-IV-TR criteria¹².

Inclusion criteria for patients were: (a) age between 18-60 years; (b) diagnosis of schizophrenia; (c) patients who were clinically stable as assessed by scores on the PANSS (see below). Controls were recruited from the local community using the following inclusion criteria (a) age between 18-60 years; (b) no current or past history of psychiatric disorder; (c) no family history of major psychiatry disorder. Exclusion criteria for both groups were: (a) history of epilepsy, dementia, brain trauma, tumor or other primary neurological diseases; (b) current dependence/use of drugs (alcohol, cannabis, cocaine, opioid); (c) current or recent (past four weeks) infections; (d) autoimmune or severe clinical diseases; (e) current or recent (past four weeks) use of corticosteroid or anti-inflammatory drugs. The study conformed to the declaration of Helsinki, with its protocol approved by the local Ethics Research Committee. Both patients and controls provided written informed consent.

Clinical, cognitive and quality of life assessments

Positive and negative symptoms were assessed by the Positive and Negative Syndrome Scale, PANSS¹³. Clinical stability was defined as

a PANSS positive score of 19 or less, and less than 4 in any individual item of the positive scale for at least four weeks. The clinical stability criterion was based on positive symptoms due to their high impact on cognitive functioning assessment. The validity and applicability of SCoRS has been demonstrated in patients with clinical stable schizophrenia, but not in patients with a recent exacerbation of the illness and/or with significant positive symptomatology¹⁴. The Calgary Depression Scale (CDS) was used to assess depressive symptoms¹⁵.

Cognitive performance was assessed by the Brazilian version of the Schizophrenia Cognition Rating Scale (SCoRS-BR)¹⁶. This is an interview-based scale that includes information provided by both the patient and an informant. It generates three different ratings: from the patient, from the informant and from the interviewer. The interview is composed of 18 items covering several cognitive domains, including memory, attention, reasoning and problem solving, working memory, motor skills and language. The total score is the sum of scores on the 18 SCoRS items with a higher the score indicating greater degree of cognitive impairment. A global rating is also generated¹⁷.

Quality of life was assessed by the Quality of Life in Schizophrenia Scale (QLS) validated for use in Brazil (QLS-BR)¹⁸. This scale has a total of 21 items distributed among three factors: i) instrumental domain, ii) intrapsychic foundations and iii) interpersonal relations domain. Items include information on patient functioning during the three weeks preceding the interview. The sum of the values obtained in the 21 items of the scale is used to assess the overall quality of life. Higher scores denote better quality of life.

Serological evaluation

Peripheral blood was drawn from each subject by venipuncture into a vacuum tube without anticoagulant. Blood was immediately

centrifuged at 3,000 rpm for 10 minutes, serum was collected and kept frozen at -80°C until assayed. IgM and IgG anti-*T. gondii* antibodies were determined by Enzyme-Linked Immunosorbent Assay (ELISA), using kits SERION - ELISA classic test by VIRION (Würzburg, Germany), following the manufacturer's guidelines. The test sensitivity were 10 IU/mL and 5 IU/mL to IgM and IgG, respectively.

Statistical analysis

All variables were tested for Gaussian distribution by the Kolmogorov-Smirnov normality test. Association between dichotomous variables was assessed with the Fisher's exact test. Two groups were compared by Mann-Whitney or Student's *t* tests when non-normally or normally distributed, respectively. Spearman's correlation analyses were performed for correlation analyses. All statistical tests were two-tailed and were performed using a significance level of $\alpha = 0.05$. Statistical analyses were performed using SPSS software version 22.0 (SPSS Inc., Chicago, IL, USA), as well as GraphPad Prism 5.0 (GraphPad Software, Inc., La Jolla, California, EUA).

Results

Demographic and clinical data

Demographic and clinical data are shown in Table 1. Patients and controls did not differ regarding age and gender. Patients with schizophrenia had less years of formal education than controls. The mean (\pm SD) length of illness was 15.20 (\pm 10.50) years. The mean (\pm SD) scores in the positive and negative subscales of the PANSS were, respectively, 10.28 (\pm 2.78) and 19.67 (\pm 7.73), indicating a chronic condition with predominance of negative symptoms.

Table 1. Demographic, clinical and serological features of controls and patients

	Controls (N = 40)	Patients SZ (N = 48)	p values
Male gender [frequency in % (N)]	42.50 (17)	56.25 (27)	0.284 ^a
Age in years (mean \pm SD)	40.62 \pm 10.29	40.21 \pm 9.59	0.845 ^b
Educational levels in years (mean \pm SD)	12.25 \pm 4.77	8.04 \pm 4.25	< 0.001 ^c
Age of onset in years (mean \pm SD)	—	24.58 \pm 9.91	—
Length of illness in years (mean \pm SD)	—	15.20 \pm 10.50	—
Medication in use [frequency in % (N)]			
Potent typical antipsychotics	—	60.86 (28)	—
Sedatives typical antipsychotics	—	39.13 (18)	—
Atypical antipsychotics	—	34.78 (16)	—
Clozapine	—	4.34 (2)	—
Mood stabilizers	—	8.69 (4)	—
Antidepressants	—	6.52 (3)	—
Chlorpromazine equivalent (mean \pm SD)	—	351.74 \pm 232.29	—
Previous electroconvulsive therapy [frequency in % (N)]	—	8.33 (4)	—
PANSS (mean \pm SD)			
Positive	—	10.28 \pm 2.78	—
Negative	—	19.67 \pm 7.73	—
General	—	26.22 \pm 7.27	—
Total	—	56.55 \pm 12.07	—
CDS (mean \pm SD)	—	1.95 \pm 2.54	—
SCoRS-BR (mean \pm SD)			
SCoRS-BR patient	—	37.48 \pm 11.12	—
SCoRS-BR informant	—	36.59 \pm 10.40	—
SCoRS-BR interviewer	—	40.49 \pm 11.38	—
SCoRS-BR global	—	5.64 \pm 1.58	—
QLS-BR total /126 (mean \pm SD)	—	54.41 \pm 24.76	—
Positive IgM antibodies anti- <i>T. gondii</i> (%) (N)	7.50 (3)	4.17 (2)	0.656 ^a
Positive IgG antibodies anti- <i>T. gondii</i> (%) (N)	56.41 (22) ^d	56.25 (27)	1.000 ^a
IgM IU/mL (mean \pm SD)	130.67 \pm 114.82	121.31 \pm 97.99	0.630 ^c
IgG IU/mL (mean \pm SD)	115.59 \pm 166.53	127.58 \pm 218.12	0.785 ^c

^a Fisher's exact test; ^b Student's *t* test; ^c Mann-Whitney test; ^d One individual presented indeterminate results for IgG.

CDS: Calgary Depression Scale; PANSS: Positive and Negative Syndrome Scale; QLS-BR: Quality of Life in Schizophrenia scale validated for use in Brazil; SCoRS-BR: Brazilian version of the Schizophrenia Cognition Rating Scale; SD: standard deviation.

T. gondii seroprevalence and association with clinical parameters

Patients with schizophrenia and controls presented similar seroprevalence and titers for both IgG and IgM anti-*T. gondii* antibodies (Table 1).

Patients with schizophrenia were then categorized into two groups: anti-*T. gondii* IgG positive (*Toxoplasma*-seropositive, N = 27) and anti-*T. gondii* IgG negative (*Toxoplasma*-seronegative, N = 21). We did not find any difference between *Toxoplasma*-seronegative and *Toxoplasma*-seropositive patients regarding age, gender, educational level, age of onset, length of illness, chlorpromazine equivalent level and PANSS subsets (Table 2). *Toxoplasma*-seropositive and *Toxoplasma*-seronegative patients presented similar scores in the scales that evaluated depressive symptoms, cognitive performance and quality of life (Table 2).

We did not find any significant correlation between anti-*T. gondii* IgM and IgG levels and age, age at onset, duration of illness, chlorpromazine equivalent level, positive PANSS, negative PANSS, total PANSS, patient SCoRS, informant SCoRS, interviewer SCoRS, global SCoRS, CDS or QLS scores. No difference was found when comparing male and female participants.

Discussion

The current study was conducted in order to compare the prevalence of *T. gondii* infection between patients with schizophrenia and controls, as well as to evaluate the potential association between *T. gondii* infection and clinical symptoms in Brazilian patients with schizophrenia. We found similar rates of positive serological reaction to *T. gondii* in controls and patients with schizophrenia. In addition, we did not find any association between *T. gondii* seroprevalence and demographic data, positive, negative and depressive symptoms, cognitive performance and quality of life in patients with schizophrenia.

Previous studies found higher rates of *T. gondii* infection in patients with schizophrenia in comparison with controls¹⁹⁻²³. In contrast, some authors have questioned this association^{24,25}. A recent meta-analysis reported a significant association between *T. gondii* infection as estimated by IgG antibodies and schizophrenia (odds ratio 1.81, $P < 0.0001$). A very high heterogeneity was observed

among studies, and the amplitude of the odds ratio was influenced by region and general seroprevalence⁹. Accordingly, the possibility of finding association between toxoplasmosis and schizophrenia is lower in regions with high seroprevalence rates when compared with regions with low rates. Brazil has a high prevalence of *T. gondii* infection which could be an explanation for the current findings. Moreover, our sample was composed by chronic patients under high dose of antipsychotics that may affect anti-*T. gondii* IgG titers²⁶.

T. gondii infection has been associated with symptom severity in schizophrenia^{23,27,28}. In addition, latent toxoplasmosis may have a negative impact on the disease course and treatment response in patients with schizophrenia²⁹. Corroborating these clinical data, patients with schizophrenia *T. gondii*-seropositive presented more significant morphological changes in the caudate, cingulate, thalamus and occipital cortex in comparison with seronegative patients³⁰. In the current study, we did not find significant differences between seropositive and seronegative patients regarding the clinical symptoms of schizophrenia as assessed by PANSS. The fact that the enrolled patients were clinically stable comprising a relatively homogenous sample may partially explain this result.

Data on whether *T. gondii* infection is associated with cognitive aspects in schizophrenia are still controversial. For instance, one study showed that people diagnosed with schizophrenia who were exposed *in utero* to *T. gondii* presented impaired performance in two executive function tests: the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT) part B³¹. These patients also exhibited deficits on figural fluency, letter-number sequencing and backward digit span³¹. Conversely, other studies failed to show any association between latent toxoplasmosis and cognitive function in schizophrenia^{32,33}. According to our results, *T. gondii* infection is not associated with self-reported cognitive performance as evaluated by the SCoRS. Discrepancies among studies can also be explained, at least in part, by strain related specific effects of *T. gondii* on human brain⁹. Indeed, regional differences in strain distribution have been reported, and *T. gondii* strain-specific effects in depression have already been demonstrated⁹.

It is worth mentioning that the use of antipsychotic and/or mood stabilizers presenting *in vitro* anti-toxoplasmic activity was associated with a better clinical outcome in a population of BD patients. Patients with BD seropositive for *T. gondii* presented more lifetime depressive episodes when treated by drugs having no anti-toxoplasmic activity

Table 2. Demographic, clinical, cognitive performance and quality of life in patients with schizophrenia, according to serology for IgG anti-*T. gondii*

	Seronegative (N = 21)	Seropositive (N = 27)	p value
Male gender [frequency in % (N)]	66.67 (14)	48.15 (13)	0.249 ^a
Age in years (mean ±SD)	39.71 ± 10.10	40.59 ± 9.35	0.757 ^b
Educational level in years (mean ±SD)	8.10 ± 4.81	8.00 ± 3.86	0.940 ^b
Age of onset in years (mean ±SD)	23.25 ± 9.81	25.61 ± 10.04	0.428 ^b
Length of illness in years (mean ±SD)	15.94 ± 11.19	14.69 ± 10.37	0.715 ^b
Chlorpromazine equivalent (mean ±SD)	375.78 ± 233.31	333.71 ± 234.49	0.637 ^c
PANSS (mean ±SD)			
Positive	10.67 ± 2.82	9.96 ± 2.76	0.306 ^c
Negative	21.24 ± 7.97	18.36 ± 7.41	0.212 ^b
General	28.05 ± 6.49	24.76 ± 7.66	0.133 ^b
Total	58.50 ± 11.75	54.77 ± 12.35	0.324 ^b
CDS (mean ±SD)	1.81 ± 2.31	2.04 ± 2.72	0.777 ^c
SCoRS-BR (mean ±SD)			
SCoRS-BR patient	35.70 ± 9.19	38.85 ± 12.40	0.431 ^c
SCoRS-BR informant	32.65 ± 6.57	39.64 ± 11.86	0.072 ^c
SCoRS-BR interviewer	36.71 ± 7.65	43.41 ± 13.01	0.124 ^c
SCoRS-BR global	5.27 ± 1.07	5.95 ± 1.88	0.591 ^b
QLS-BR total/126 (mean ±SD)	60.65 ± 25.76	49.10 ± 23.20	0.160 ^b

^aFisher's exact test; ^bStudent's t test; ^cMann-Whitney test.

CDS: Calgary Depression Scale; PANSS: Positive and Negative Syndrome Scale; QLS-BR: Quality of Life in Schizophrenia scale validated for use in Brazil; SCoRS-BR: Brazilian version of the Schizophrenia Cognition Rating Scale; SD: standard deviation.

(e.g. aripiprazole, carbamazepine, clozapine, lamotrigine, lithium, olanzapine, quetiapine) compared to patients who received drugs with anti-toxoplasmic activity (e.g. fluphenazine, haloperidol, levomepromazine, paliperidone, risperidone, thioridazine, valproate)³⁴. It remains to be determined whether the treatment with drugs with anti-toxoplasmic activity is also associated with better clinical outcomes of the patients with schizophrenia.

We are aware of the limitations of our study. First the sample size is small and consists of chronic patients using antipsychotics. It is uncertain whether our results can be applied to patients with prodromal or early schizophrenia. Cohort studies involving a larger sample of drug naïve patients are critical to confirm the specificity to clarify the pathogenic role of *T. gondii* in schizophrenia and its symptoms. Cognitive assessment of patients was based on self-reported measures. Although SCoRS is highly correlated to cognitive performance and functioning, a comprehensive neuropsychological evaluation in both patients and controls could add more specific information, including the domains potentially affected by toxoplasmosis.

In conclusion, our data showed that *T. gondii* infection is not associated with schizophrenia. In addition, *T. gondii* seroprevalence and levels of IgG antibodies were not associated with demographic data, disease severity, depressive and cognitive symptoms and quality of life. Our results might be influenced by strain-specific brain effects and high prevalence of *T. gondii* infection in our sample. Further studies are needed in order to elucidate the role of *T. gondii* in schizophrenia pathophysiology.

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