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TOXOPLASMA GONDII INFECTION AND DEPRESSION: A CASE–CONTROL SEROPREVALENCE STUDY

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We assessed the association of *Toxoplasma gondii* infection and depression in a sample of psychiatric patients and control subjects without depression. We performed an age- and gender-matched case–control study of 89 patients suffering from depression attended in a public psychiatric hospital in Durango City, Mexico and 356 control subjects without depression from the general population of the same city. Participants were tested for the presence of anti-*Toxoplasma* IgG and IgM antibodies using enzyme-linked immunoassays. Anti-*T. gondii* IgG antibodies were found in 11 (12.4%) of the 89 cases and in 22 (6.2%) of the 356 controls (OR = 2.14; 95% CI: 1.00–4.59; $P = 0.04$). Anti-*T. gondii* IgM antibodies were found in four (19%) of 21 anti-*T. gondii* IgG seropositive controls but not in 11 anti-*T. gondii* IgG seropositive cases ($P = 0.27$). Patients aged 30 years old and younger had a significantly higher seroprevalence of *T. gondii* infection than controls of the same age group ($P = 0.001$). Results of the present study suggest a potential association between *T. gondii* infection and depression. Furthers studies to confirm our results and to determine the epidemiology of *T. gondii* in young depressed patients should be conducted.

Keywords: *Toxoplasma gondii,* seroprevalence, depression, psychiatric patients, case–control study

Introduction

The coccidian parasite *Toxoplasma gondii (T. gondii)* causes infections all around the world [1]. Main routes of *T. gondii* infection are eating raw or under cooked meat containing tissue cysts, and ingestion of water contaminated with oocysts shed by cats [2, 3]. Infection with *T. gondii* can also occur vertically [2, 4]. Most infections with *T. gondii* are asymptomatic. However, infection with *T. gondii* may lead to eye, lymph node, and central nervous system disease, i.e., in congenital toxoplasmosis and in immunocompromised patients [2, 5, 6]. Seroprevalence of *T. gondii* is high in psychiatric patients in general [7, 8]. A number of mental illnesses have been linked to *T. gondii* infection including schizophrenia [9, 10], anxiety [11], and cognitive impairment [12–14]. There is controversy about an association of *T. gondii* infection and mood disorders. In a study of psychiatric patents in Cuba, researchers found the highest percentage of reactivity to the toxoplasmin intradermal test among patients with depressive mental disorders [15]. A case of depression with *T. gondii* seropositivity who responded to antidepressant treatment only after adequate treatment for *T. gondii* was reported [16]. However, in the Third National Health and Nutrition

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Survey in the USA, researchers did not find an association between *T. gondii* seroprevalence and history of major depression or dysthymia [17]. On the other hand, *T. gondii* antibody titers have been linked to suicide attempts in patients with recurrent mood disorders [18]. Therefore, we sought to determine the association between *T. gondii* infection and depression in patients attended in a public psychiatric hospital in Durango City, Mexico.

Materials and methods

Study design and patients studied

Through an age- and gender-matched case–control study design, we examined 89 psychiatric patients suffering from depression attended in a public psychiatric hospital in Durango, Mexico and 356 control subjects without depression from the general population of the same city. This study was performed from August to November 2015. Inclusion criteria for enrollment of cases were: 1) patients suffering from depression attended in the Hospital of Mental Health "Dr. Miguel Vallebueno" of the Secretary of Health in Durango City; 2) aged 17 years and older; and 3) who accepted to participate in the study. Gender was not a restrictive criterion for enrollment. Of the 89 cases, 64 (71.9%) were females and 25 (28.1%) were males. Mean age in cases was 38.65 ± 12.93 (range 17–78) years old. The diagnosis of depressive disorder was classified using the International Classification of Diseases (ICD-10) (http://www.who.int/classifications/icd/en/). Control subjects were matched with cases for gender and age. Controls were randomly selected from the general population of Durango City. Controls considered themselves as healthy without depression. Inclusion criteria for enrollment of controls were: 1) subjects of the general population of Durango City without depression; 2) aged 17 years and older; and 3) who accepted to participate in the study. Of the 356 controls, 260 (73.0%) were females and 96 (27.0%) were males. Mean age in controls was 38.66 ± 12.89 (range 17–80) years old. No statistically significant differences in age ($P = 0.99$) and gender ($P = 0.83$) between cases and controls were found.

*Detection of anti-*T. gondii *antibodies*

Serum samples from participants were obtained and stored at −20 °C until analyzed. Anti-*T. gondii* IgG antibodies were determined in sera with the commercially available enzyme immunoassay (EIA) kit "*Toxoplasma* IgG" (Diagnostic Automation/Cortez Diagnostics Inc., Woodland Hills, CA, USA). Anti-*T. gondii* IgG antibody levels were expressed as International Units (IU)/ml, and results ≥8 IU/ml were considered positive. Seropositive for anti-*T. gondii* IgG antibodies were further analyzed for anti-*T. gondii* IgM antibodies by the commercially available EIA "*Toxoplasma* IgM" kit (Diagnostic Automation/Cortez Diagnostics Inc.). All IgG and IgM assays were performed according to the instructions of the manufacturer.

Statistical analysis

We performed the statistical analysis with the aid of the software SPSS 15.0 (SPSS Inc., Chicago, Illinois) and Epi Info 7. For calculation of the sample size, we used a 95% confidence level, a power of 80%, a 1:4 proportion of cases and controls, a reference seroprevalence of 6.1% [19] as the expected frequency of exposure in controls, and an odds ratio of 3.3. The result of the sample size calculation was 67 cases and 268 controls. The student's *t* test was used to compare the age among the groups. The association of *T. gondii* infection and depression was assessed with the two-tailed Pearson's Chi-square test or the Fisher's exact test (when cell values were less than 5). We calculated the odds ratio (OR) and 95% confidence interval (CI), and statistical significance was set at a *P* value of <0.05.

Ethical aspects

This study was approved by The Ethics Committee of the General Hospital of the Secretary of Health in Durango City, Mexico. The purpose and procedures of this case–control study were explained to all participants, and a written informed consent was obtained from all of them.

Results

Of the 89 cases of depression included in the study, 69 (77.5%) suffered from a depressive episode (ICD-10 code F32) and 20 (22.5%) from recurrent depressive disorders (ICD-10 code F33). *Table 1* shows the diagnoses of the patients studied and their correlation with *T. gondii* seroprevalence. Anti-*T. gondii* IgG antibodies were found in 11 (12.4%) of the 89 cases and in 22 (6.2%) of the 356 controls. The seroprevalence of *T. gondii* infection was significantly higher in cases than in controls (OR = 2.14; 95% CI: 1.00–4.59; $P = 0.04$). Of the 11 anti-*T. gondii* IgG positive cases, four (36.4%) had IgG levels higher than 150 IU/ml, one (9.1%) between 100 and 150 IU/ml, and six (54.5%) between 8 and 99 IU/ml. In comparison, of the 22 anti-*T. gondii* IgG positive controls, 11 (50.0%) had IgG levels higher than 150 IU/ml, one (4.5%) between 100 and 150 IU/ml, and ten (45.5%) between 8 and 99 IU/ml. The frequency of high (>150 IU/ml) anti-*T. gondii* IgG levels was similar in cases and controls (OR = 1.47; 95% CI: 0.45–4.74; $P = 0.51$). Seroprevalence of *T. gondii* infection did not vary with the types of depression diagnoses *(Table 1)*. Patients with a depressive episode (ICD-10 code F32) had a similar seroprevalence of *T. gondii* than patients with recurrent depressive disorders (ICD-10 code

Table 1. Correlation of depression diagnoses and seroprevalence of *T. gondii* infection in the patients studied

Diagnoses	No. tested	*T. gondii* infection		*P* value
		No.	%	
Mild depressive episode (F32.0)	39	6	15.4	0.70
Moderate depressive episode (F32.1)	26	2	7.7	
Severe depressive episode (F32.2)	4	0	0.0	
Mild recurrent depressive disorder (F33.0)	13	3	23.1	
Moderate recurrent depressive disorder (F33.1)	3	0	0.0	
Severe recurrent depressive disorder (F33.2)	3	0	0.0	
Recurrent depressive disorder in remission (F33.4)	1	0	0.0	

F33) (8/69: 11.6% vs. 3/20: 15.0%; $P = 0.70$). Patients with mild forms of depression had the highest seroprevalence of *T. gondii* infection (mild depressive episode: 15.4%; mild recurrent depressive disorder: 23.1%). However, patients with mild depression had a comparable seroprevalence of *T. gondii* infection compared to patients with moderate, severe or in remission depression (9/52: 17.3% vs. 2/37: 5.4%; $P = 0.11$).

Anti-*T. gondii* IgM antibodies were found in four (19%) of 21 anti-*T. gondii* IgG seropositive controls; none of the 11 anti-*T. gondii* IgG seropositive cases had anti-*T. gondii* IgM antibodies. There was not a statistically significant difference in the frequency of IgM seropositivity among cases and controls ($P = 0.27$).

When results of the seroprevalence of *T. gondii* infection were collapsed by sex and age, we observed that seroprevalence did not vary with sex but with age groups. Patients aged 30 years old and younger had a significantly higher seroprevalence of *T. gondii* infection than controls of the same age group ($P = 0.001$) *(Table 2)*. Seroprevalence did not vary between cases and controls in the age groups of 31–50 years and older than 50 years.

Discussion

Currently, there are fragmentary and sometimes conflicting results about the association of *T. gondii* infection and depression [15–17]. This study aimed to determine whether *T. gondii* seropositivity is associated with depression in Durango City, Mexico. Results of our study show that psychiatric patients suffering from depression have a significantly higher seroprevalence of *T. gondii* infection than control subjects without depression in the general population of the same city. Thus, results of this gender- and age-matched case–control seroprevalence provide further support for the association of *T. gondii* infection with depression as reported in other studies. In a study of 70 women veterans, significant associations between *T. gondii* seropositivity and the Center for Epidemiologic Studies Depression score, Profile for Mood States – depression, and total mood disturbance score were found [20]. In a study of pregnant women in the USA, prenatal depression was associated with higher *T. gondii* titers in infected women [21]. In addition, the report of a 32-year-old male suffering from depression with *T. gondii* seropositivity who responded to antidepressant treatment only after adequate treatment for *T. gondii* [16] supports the potential role of *T. gondii* in depression. In addition, patients suffering from bipolar disorder with positive serology to *T. gondii* treated with antipsychotic and/or mood stabilizers having known in vitro anti-Toxoplasmic activity had less depressive episodes than patients treated with drugs having no anti-Toxoplasmic activity [22]. On the other hand, researchers did not find a significant OR (1.21; $P = 0.28$) supporting the asso-

Table 2. Comparison of seropositivity rate to *T. gondii* according to sex and age between cases and controls

	Cases			Controls			*P* value
		Seroprevalence of *T. gondii* infection			Seroprevalence of *T. gondii* infection		
Characteristics	No. tested	No.	%	No. tested	No.	%	
Sex							
Male	25	4	16.0	96	6	6.3	0.21
Female	64	7	10.9	260	16	6.2	0.18
Age (years old)							
30 or less	28	5	17.9	111	1	0.9	0.001
31–50	46	5	10.9	185	17	9.2	0.77
>50	15	1	6.7	60	4	6.7	1.0

ciation of the presence of anti-*T. gondii* IgG antibodies and major depression in a meta-analysis [9]. Similarly, in the Third National Health and Nutrition Survey in the USA, no association between *T. gondii* seroprevalence and history of major depression was found [17]. These studies examined the association of *T. gondii* infection with major depression. However, in the present study, we examined the association of infection with mild, moderate, and severe forms of depression and did not find an association of *T. gondii* infection with severe depression. Instead, we found an association of infection with mild depression. However, since the present study only included a limited number of cases of severe depression (n = 15), further research with a larger number of cases with severe depression to elucidate the association of this disease with infection should be conducted.

In the present study, seroprevalence of *T. gondii* infection was similar in male and female patients suffering from depression. In contrast, young patients (30 years old and younger) but not other age groups suffering from depression had a significantly higher seroprevalence than controls of the same age group. Of interest, the seroprevalence (17.9%) found in young patients suffering from depression is remarkably high in Durango City, and seroprevalence of *T. gondii* infection in patients with depression did not follow the typical increase with age. On the contrary, seroprevalence decreased from 17.9% in the youngest group to 6.7% in the oldest group (51 years and older). In addition, the seroprevalence in young patients with depression is much higher than those reported in subjects of the same age in other population groups in the same city studied; for instance, seroprevalences of *T. gondii* infection in subjects 30 years and younger were 4.3% in workers with occupational exposure to animals [23], 5.4% in fruit and vegetable workers [24], and 8% in meat workers [25].

Of note, none of the cases seropositive to *T. gondii* had IgM antibodies, suggesting that depression might be associated with latent infection. It is not clear how *T. gondii* causes depression. Tachyzoites of *T. gondii* invade a number of cells in brain [26]. It is possible that *T. gondii* causes mood disorders through changes in the levels of brain dopamine and serotonin [21]. The *T. gondii* genome contains two aromatic aminoacid hydroxylases that could affect dopamine and/or serotonin biosynthesis [27]. *T. gondii* could cause depression by affecting the tryptophan metabolism and the hypothalamic–pituitary–adrenal axis [27].

This study has limitations. The sample size of cases with depression was small. In addition, we studied only patients who sought medical care at the Hospital of Mental Health, and thus, results cannot be extrapolated to the general population. Comparison of *T. gondii* seroprevalence between depressed patients and patients suffering from psychiatric diseases other than depression is still needed. Further studies with a larger sample size of cases with depression and with population groups other than psychiatric inpatients (i.e., pregnant women, general population) to determine the association of *T. gondii* exposure and depression should be conducted.

Conclusions

Results of the present study suggest an association between *T. gondii* exposure and depression. Young depressed patients had the highest seroprevalence of *T. gondii* infection. Further studies to confirm our results and to determine the epidemiology of *T. gondii* exposure in young depressed patients should be conducted.

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