Original article

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INFLUENCE OF *TOXOPLASMA GONDII* INFECTION ON SYMPTOMS AND SIGNS OF MENOPAUSE

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Some symptoms of menopause have also been described in patients with toxoplasmosis. Whether *Toxoplasma gondii (T. gondii)* infection has any influence on clinical manifestations of menopause is yet unknown. We sought to determine whether *T. gondii* exposure is associated with symptoms and signs of menopause. We performed a cross-sectional study of women attending a public health center in Durango City, Mexico. Participants were examined for the presence of anti-*Toxoplasma* IgG and IgM antibodies using enzyme-linked immunoassays. A questionnaire including 47 symptoms and signs potentially associated with menopause was applied. Association of seroprevalence for *T. gondii* with clinical characteristics of women was assessed by bivariate and multivariate analyses. Bivariate analysis showed that bouts of rapid heartbeat, breast pain, electric shock sensation, dizziness, digestive problems, low back pain, and migraine were associated with seropositivity to either IgG anti-*T. gondii* alone or both IgG and IgM anti-*T. gondii*. Breast pain was the only variable that was found to be associated with IgG seropositivity to *T. gondii* by multivariate analysis: (OR = 2.84; 95% CI: 1.35–5.90; $P = 0.005$). Our results suggest that *T. gondii* exposure may influence on the clinical manifestations of menopause. Results deserve further research.

Keywords: *Toxoplasma gondii,* seroprevalence, perimenopause, menopause, cross-sectional study

Introduction

Toxoplasma gondii (T. gondii) is a parasite that is highly disseminated around the world [1]. Infection with this parasite is usually acquired by ingesting raw or undercooked meat containing *T. gondii* tissue cysts, consumption of food or water contaminated with *T. gondii* oocysts shed by cats [2], or congenitally [3]. The clinical spectrum of *T. gondii* infection varies from asymptomatic to a severe disease with involvement of lymph nodes, eyes, and central nervous system [2–4]. Life-threatening toxoplasmosis may occur in immunocompromised individuals upon reactivation of latent disease [5]. Furthermore, infection with *T. gondii* has been linked to mental illnesses including depression [6, 7], anxiety [7], bipolar disorder [8], schizophrenia [8, 9], and cognitive impairment [10, 11]. Infection with *T. gondii* has also been linked to migraine [12].

Perimenopause is a midlife neurological transition state in women [13], and mental illnesses associated with infection with *T. gondii* may also occur or can be exacerbated during the perimenopausal period in women. In this regard, the incidence of migraine increases in the perimenopausal period [14, 15], and peri- and postmenopausal women are vulnerable to the development of depression disorders [16,

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17]. Furthermore, menopausal transition is also a period of increased vulnerability to cognitive declines [17]. Anxiety and/or depressive symptoms are often reported in premenopausal, perimenopausal, and postmenopausal women [18]. An exacerbation of bipolar mood symptoms and an increase in schizophrenic psychosis during perimenopause have been reported [19].

However, it is unclear whether *T. gondii* infection might influence the pre-, peri-, and menopausal symptoms. To the best of our knowledge, the relation of *T. gondii* exposure and menopausal clinical manifestations has not been assessed. Women at mid-age period have clinical and epidemiological importance because of the considerable morbidity rate. Therefore, we sought to determine whether *T. gondii* exposure is associated with clinical characteristics of the menopausal transition and menopause in women in Durango City, Mexico.

Materials and methods

Study design and women studied

Through a cross-sectional study design, we studied 400 mid-age women who attended general consultations in a public primary healthcare center in Durango City, Mexico. Sampling was performed from August 25 to November 9, 2015. Inclusion criteria for enrollment were women aged 38 to 56 who accepted to participate in the study. Occupation and socioeconomic status were not restrictive criteria for enrollment.

Clinical data of women

Symptoms and signs of menopause in the women studied were obtained using a face-to-face questionnaire. These clinical data included presence of irregular periods, date of last period, history of hot flashes, red skin, bouts of rapid heartbeat, night sweats, sleep problems, memory lapses, difficulty concentrating, depression, anxiety, mood changes, irritability, panic attacks, migraine, mental illness, itchy skin, burning mouth or tongue, allergy, breast pain, decrease in muscle power, joint pain, joint stiffness, low back pain, muscle tension, fatigue, tingling extremities, electric shock sensation, gum problems, urinary incontinence, urinary urgency, decreased libido, vaginal dryness, dyspareunia, vaginal infections, thyroid disease, changes in body odor, digestive problems, appetite disturbance, weight gain, obesity, arterial hypertension, dizziness, osteoporosis, hair loss, respiratory problems, and brittle nails.

Laboratory tests

A serum sample from each participant was obtained and stored at −20 °C until analyzed. Serum samples were analyzed for anti-*T. gondii* IgG antibodies with the commercially available enzyme immunoassay (EIA) kit "*Toxoplasma* IgG" (International Immuno-Diagnostics, Foster City, CA, USA). Anti-*T. gondii* IgG antibody levels were expressed as International Units (IU)/ml, and results ≥ 8 IU/ml were considered positive. Serum samples positive 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 Inc., Calabasas, CA, USA). Both assays for IgG and IgM were performed following the manufacturer's instructions.

Statistical analysis

Results were analyzed with the aid of SPSS 15.0 (SPSS Inc. Chicago, Illinois), Microsoft Excel, and Epi Info 7. For calculation of the sample size, we used: a) a reference seroprevalence of 6.1% [20] as the expected frequency for the factor under study, b) 100,000 as the population size from which the sample was selected, c) a 2.5% of confidence limits, and d) a 95% confidence level. The result of the sample size calculation was 351 subjects. The association of *T. gondii* seropositivity and the clinical characteristics of women were assessed with the Pearson's χ^2 test or the two-tailed Fisher's exact test (when values were less than 5). Variables with a P value less than 0.05 in the bivariate analysis were selected for multivariate analysis. Odds ratio (OR) and 95% confidence interval (CI) were obtained by multivariate analysis using logistic regression with the Enter method. A P value <0.05 was considered statistically significant.

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 survey were explained to all participants. In addition, a written informed consent was obtained from each participant.

Results

Of the 400 women (mean age: 47.0 ± 5.3) studied, all but one showed at least one and up to 40 signs or symptoms of menopause. Anti-*T. gondii* IgG antibodies were found in 40 (10%) of the 400 women studied. Of the 40 anti-*T. gondii* IgG positive women, 14 (35.0%) had IgG levels higher than 150 IU/ml, 2 (5.0%) between 100 to 150 IU/ml, and 24 (60.0%) between 8 to 99 IU/ml. Anti-*T. gondii* IgM antibodies were found in 4 (10%) of the 40 IgG seropositive women. Seronegative women (n = 360) had from zero to 40 (mean: 17.3 ± 8.1; median: 17) signs or symptoms of menopause. Seropositive women showed from four to 35 (mean: 20.1 ± 8.4; median: 20) signs or symptoms of menopause. Mean number of signs

or symptoms of menopause was higher in seropositive women than in seronegative women (P = 0.03). Age in seronegative (mean: 47.0 ± 5.2 years) and seropositive women (mean: 47.1 ± 6.1 years) was comparable (P = 0.87).

Bivariate analysis of clinical data of menopause and IgG seropositivity to *T. gondii* showed six variables with a P value less than 0.05: bouts of rapid heartbeat, breast pain, low back pain, electric shock sensation, digestive problems, and dizziness. *Table 1* shows the correlation of selected clinical data of menopause and seropositivity to *T. gondii*. Other clinical characteristics of menopause including presence of irregular periods, date of last period, history of hot flashes, red skin, night sweats,

Table 1. Bivariate analysis of clinical data of menopause and seropositivity to *T. gondii* in the women studied

Clinical characteristics	Women tested	Prevalence of *T. gondii* infection		*P* value
	No.	No.	%	
Irregular periods				
Yes	11	9	8.1	0.43
No	126	14	11.1	
Date of last period				
Less than 1 year ago	231	20	8.7	0.08
One to 3 years ago	54	10	18.5	
More than 3 years ago	110	10	9.1	
Hot flashes				
Yes	212	27	12.7	0.05
No	188	13	6.9	
Red skin				
Yes	48	3	6.3	0.35
No	352	37	10.5	
Bouts of rapid heart beat				
Yes	190	25	13.2	0.04
No	210	15	7.1	
Night sweats				
Yes	197	24	12.2	0.15
No	203	16	7.9	
Memory lapses				
Yes	278	30	10.8	0.44
No	121	10	8.3	
Depression				
Yes	232	26	11.2	0.34
No	168	14	8.3	
Migraine				
Yes	96	13	13.5	0.18
No	304	27	8.9	
Mental illness				
Yes	19	4	21.1	0.10
No	381	36	9.4	
Breast pain				
Yes	100	21	21.0	0.00
No	299	19	6.4	

Table 1. *(cont'd)*

Clinical characteristics	Women tested	Prevalence of *T. gondii* infection		*P* value
	No.	No.	%	
Decrease in muscle power				
Yes	195	23	11.8	0.25
No	204	17	8.3	
Joint pain				
Yes	274	30	10.9	0.35
No	126	10	7.9	
Low back pain				
Yes	240	30	12.5	0.04
No	159	10	6.3	
Muscle tension				
Yes	231	25	10.8	0.41
No	167	14	8.4	
Tingling extremities				
Yes	195	24	12.3	0.09
No	203	15	7.4	
Electric shock sensation				
Yes	86	14	16.3	0.02
No	314	26	8.3	
Decreased libido				
Yes	187	23	12.3	0.13
No	206	16	7.8	
Vaginal dryness				
Yes	132	17	12.9	0.15
No	263	22	8.4	
Vaginal infections				
Yes	110	15	13.6	0.11
No	285	24	8.4	
Digestive problems				
Yes	270	33	12.2	0.03
No	129	7	5.4	
Appetite disturbance				
Yes	217	25	11.5	0.27
No	182	15	8.2	
Dizziness				
Yes	180	25	13.9	0.02
No	217	15	6.9	
Hair loss				
Yes	223	25	11.2	0.38
No	175	15	8.6	

Table 2. Multivariate analysis of selected clinical characteristics of menopause and their association with *T. gondii* infection

Characteristics	Odds ratio	95% confidence interval	*P* value
Bouts of rapid heart beat	1.30	0.62–2.7	0.48
Breast pain	2.84	1.35–5.9	0.005
Low back pain	1.27	0.56–2.91	0.56
Electric shock sensation	1.34	0.63–2.85	0.44
Digestive problems	1.54	0.62–3.79	0.34
Dizziness	1.19	0.55–2.55	0.65

sleep problems, memory lapses, difficulty concentrating, depression, anxiety, mood changes, irritability, panic attacks, migraine, mental illness, itchy skin, burning mouth or tongue, allergy, decrease in muscle power, joint pain, joint stiffness, muscle tension, fatigue, tingling extremities, gum problems, urinary incontinence, urinary urgency, decreased libido, vaginal dryness, dyspareunia, vaginal infections, thyroid disease, changes in body odor, appetite disturbance, weight gain, obesity, arterial hypertension, osteoporosis, hair loss, respiratory problems, and brittle nails showed *P* values equal to or higher than 0.05 by bivariate analysis. Further analysis by logistic regression of variables with *P* less than 0.05 obtained by bivariate analysis showed that only the variable breast pain was associated with seropositivity to *T. gondii* (OR = 2.84; 95% CI: 1.35–5.90; *P* = 0.005) *(Table 2)*.

Concerning the association of clinical data of menopause and seropositivity to both IgG and IgM anti-*T. gondii*, bivariate analysis showed only five variables with a *P* value less than 0.05: bouts of rapid heartbeat, migraine, breast pain, electric shock sensation, and dizziness. *Table 3* shows the correlation of selected clinical data of menopause and seropositivity to both IgG and IgM anti-*T. gondii*. Other clinical characteristics of menopause did not show an association with seropositivity to both IgG and IgM ($P > 0.05$). Prevalence of high (>150 IU/ml) IgG antibody levels was significantly ($P = 0.03$) higher in women who reported vaginal infections (7/110; 6.4%) than in those without this clinical manifestation (6/285; 2.1%). In addition, prevalence of high IgG antibody levels was significantly ($P = 0.04$) higher in women who reported digestive problems (13/270; 4.8%) than in those without this clinical manifestation (1/129; 0.8%). Due to a small number of cases with high IgG antibody levels and IgM seropositivity, no further regression analysis with these variables was performed.

Table 3. Bivariate analysis of clinical data of menopause and seropositivity to both IgG and IgM anti-*T. gondii* in the women studied

Characteristics	Women tested	Prevalence of *T. gondii* infection		*P* value
	No.	No.	%	
Bouts of rapid heart beats				
Yes	190	4	2.1	0.03
No	210	0	0	
Migraine				
Yes	96	4	4.2	0.002
No	304	0	0	
Breast pain				
Yes	100	3	3	<0.001
No	299	1	0.3	
Low back pain				
Yes	240	4	1.7	0.07
No	159	0	0	
Electric shock sensation				
Yes	86	3	3.5	0.01
No	314	1	0.3	
Dizziness				
Yes	180	4	2.2	0.02
No	217	0	0	

Discussion

To the best of our knowledge, the association between *T. gondii* infection and signs and symptoms of menopause has not been studied yet. Therefore, this work aimed to determine whether seropositivity to *T. gondii* was associated with clinical data of menopause in a sample of mid-age women in Durango City, Mexico. Remarkably, we found that women seropositive for *T. gondii* suffered from a significantly higher mean number of signs or symptoms of menopause than seronegative women. It is not clear why seropositive women had more clinical manifestations of menopause than seronegative women did. The pathogen *T. gondii* has a remarkable ability to disseminate throughout the body of infected hosts to cause disease [21]. Dissemination of *T. gondii* to the central nervous system may lead to a number of neurological or psychiatric manifestations that resemble those observed in menopausal women. For instance, cognitive impairment [10, 11], migraine [12], and mood disorders [6–8] seen in patients with *T. gondii* infection are also considered as clinical manifestations of menopause. Perimenopause is usually linked to a reproductive transition; however, clinical manifestations of perimenopause are neurological in nature [13]. Therefore, the increased number of clinical manifestations of menopause in *T. gondii* infected women can be a cumulative effect of infection and the menopausal state. Intriguingly, bivariate analysis showed a number of clinical data associated with seropositivity to *T. gondii*. Bouts of rapid heartbeats were associated with IgG and IgM seropositivity to *T. gondii*. Infection with *T. gondii* may disseminate to heart leading to disease [22]. Therefore, *T. gondii* infection might have influenced the frequency of women with bouts of rapid heartbeats. Breast pain was also associated with IgG and IgM seropositivity to *T. gondii* in the women studied. The association of IgG positivity remained significant following multivariate analysis. We are not aware of any report of this association in the medical literature. It is not clear why women with breast pain had a significantly higher rate of *T. gondii* exposure than those without this clinical manifestation. Breast pain is a common symptom in women [23, 24]. Breast pain may be related to underlying diseases of the breast itself but can also arise from other diseases affecting the chest wall [25]. The etiology and optimal treatment of breast pain remain undefined [25]. Therefore, further research to elucidate the role of *T. gondii* infection in breast pain is needed. Electric shock sensation and dizziness were more frequently observed in IgG and IgM seropositive women than in seronegative women. We are not aware of any report of the association of *T. gondii* and electric shock sensation. The etiology of electric shock sensation in menopause remains poorly understood. Electric shock sensation is a symptom of neuropathy [26], and *T. gondii* might be causing neuropathy since this parasite disseminates to the nervous system and resides in neurons of infected hosts [21]. For its part, the association of dizziness with *T. gondii* exposure found in the women studied confirms previous observations in other population groups in Mexico including migrant agricultural workers [27] and people of the Huichol ethnic group [28]. The frequency of IgM seropositivity to *T. gondii* was higher in women with migraine than in those without this clinical feature. Migraine has been linked to perimenopause [14, 15] as well as to *T. gondii* infection [12]. Therefore, it is possible that infection with *T. gondii* could have contributed to increasing the frequency of migraine in menopausal women. High IgG levels were associated with digestive problems and vaginal infections. Digestive disorders are rarely reported in *T. gondii*-infected individuals. Infection with *T. gondii* has been linked to colitis with diarrhea [29] and abdominal pain [30]. On the other hand, it is not clear whether *T. gondii* infection might be involved in vaginal infections. Experimental vaginal infection with *T. gondii* has been demonstrated in goats [31]; however, it is unknown whether *T. gondii* can cause vaginal pathology. Further research to determine the role of *T. gondii* in vaginal infections is needed.

Our study has limitations: first, a small sample size of women studied, and second, only one health center of Durango City participated. Further studies with larger samples sizes and a higher number of health centers should be conducted. This study was performed in a few months period, and it is not clear whether seasonal variation on seroprevalence might have influenced the results. Very little is known about the seasonal variation of *T. gondii* seroprevalence in humans. In a study in Serbia, researchers observed that most symptomatic acute infections occurred between October and March [32]. However, in a Chinese study, researchers did not find a variation in seroprevalence of IgM anti-*T. gondii* with seasons in normal populations [33].

Conclusions

This is the first study that demonstrates an association of *T. gondii* infection with some clinical manifestations of menopause. Results suggest that women with *T. gondii* exposure may suffer from a broader spectrum of signs or symptoms of menopause than seronegative women. Therefore, the association of *T. gondii* infection with clinical manifestations of menopause deserves further research.

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