Elmer Press

Original Article J Clin Med Res. 2016;8(10):730-736

Toxoplasma gondii Infection and Premenstrual Dysphoric Disorder: A Cross-Sectional Study

Cosme Alvarado-Esquivel[a, g], Luis Francisco Sanchez-Anguiano[b], Jesus Hernandez-Tinoco[b], Alma Rosa Perez-Alamos[b], Yazmin del Rosario Rico-Almochantaf[a], Sergio Estrada-Martinez[b], Raquel Vaquera-Enriquez[c], Arturo Diaz-Herrera[c], Agar Ramos-Nevarez[d], Ada Agustina Sandoval-Carrillo[b], Jose Manuel Salas-Pacheco[b], Sandra Margarita Cerrillo-Soto[d], Elizabeth Irasema Antuna-Salcido[b], Oliver Liesenfeld[e, f], Carlos Alberto Guido-Arreola[d]

Abstract

Background: Premenstrual dysphoric disorder is a severe form of premenstrual syndrome. The influence of *Toxoplasma gondii (T. gondii)* infection on clinical features in women with this disorder has not been studied. Therefore, we determined the association of *T. gondii* infection with symptoms and signs in women suffering from premenstrual dysphoric disorder.

Methods: We performed a cross-sectional study of 151 women suffering from premenstrual dysphoric disorder. Anti-*Toxoplasma* IgG and IgM antibodies were detected in sera of the participants using enzyme-linked immunoassays (EIAs). In addition, *T. gondii* DNA was detected in whole blood of IgG seropositive participants using polymerase chain reaction. We obtained the clinical data of women with the aid of a questionnaire. The association of *T. gondii* infection with clinical characteristics of women was assessed by bivariate and multivariate analyses.

Results: Anti-*T. gondii* IgG antibodies were found in 10 (6.6%) of the 151 women studied. Of the 10 IgG seropositive women, four (40.0%) were positive for anti-*T. gondii* IgM antibodies, and one (10.0%) for *T. gondii* DNA. Mean number (25.8 ± 7.58) of premenstrual clinical characteristics in seropositive women was similar to that (29.22 ± 9.13) found in seronegative women (P = 0.25). Logistic regression showed that seropositivity to *T. gondii* was negatively associated with difficulty concentrating (OR: 0.18; 95% CI: 0.03 - 0.91; P = 0.03), and positively associated with out of control feeling or overwhelmed (OR: 9.00; 95% CI: 1.32 - 62.00; P = 0.02).

Conclusions: Results of this first study on the association of *T. gondii* infection and clinical characteristics of premenstrual dysphoric disorder suggest that this infection might be linked to some symptoms of this disorder. We report for the first time the association of *T. gondii* infection and out of control feeling or overwhelmed. Results warrant for further research on the role of *T. gondii* in premenstrual dysphoric disorder.

Keywords: *Toxoplasma gondii*; Seroprevalence; Premenstrual dysphoric disorder; Cross-sectional study

Manuscript accepted for publication August 18, 2016

[a]Faculty of Medicine and Nutrition, Juarez University of Durango State, Avenida Universidad S/N, 34000 Durango, Dgo, Mexico
[b]Institute for Scientific Research "Dr. Roberto Rivera Damm", Juarez University of Durango State, Avenida Universidad S/N, 34000 Durango, Durango, Mexico
[c]Health Center No. 2 "Dr. Carlos Santamaria", Servicios de Salud de Durango, Talpa S/N, 34170 Durango, Mexico
[d]Clinica de Medicina Familiar, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Predio Canoas S/N, 34079 Durango, Mexico
[e]Institute for Microbiology and Hygiene, Campus Benjamin Franklin, Charite Medical School, Hindenburgdamm 27, D-12203 Berlin, Germany
[f]Current address: Medical and Scientific Affairs, Roche Molecular Systems, Pleasanton, CA 94588, USA
[g]Corresponding Author: Cosme Alvarado-Esquivel, Laboratorio de Investigacion Biomedica, Facultad de Medicina y Nutricion, Avenida Universidad S/N, 34000 Durango, Dgo, Mexico. Email: alvaradocosme@yahoo.com

doi: http://dx.doi.org/10.14740/jocmr2699w

Introduction

The coccidian parasite *Toxoplasma gondii (T. gondii)* causes infections in humans worldwide [1]. Cats are the definitive host of *T. gondii*, whereas humans and other warm-blooded animals are intermediate hosts [2]. Most infections with *T. gondii* in humans are acquired by ingestion of food or water contaminated with *T. gondii* oocysts shed by cats, or by the ingestion of raw or undercooked meat containing tissue cysts [3]. Less frequently, infection with *T. gondii* may occur by organ transplantation [4], and blood transfusion [5]. In addition, primary infection with *T. gondii* during pregnancy may lead to vertical transmission and congenital disease [3, 6]. Infections with *T. gondii* are usually asymptomatic [3]. Subjects with clinical manifestations of infection (toxoplasmosis) may present with disease in eyes, lymph nodes and central nervous system [3, 7, 8]. Toxoplasmosis is particularly severe in immunocompromised individuals [9]. Common symptoms of toxoplasmosis include fatigue, headache, muscle aches, and difficulty concentrating [10]. Furthermore, infection with *T. gondii* has been associated with a number of psychiatric disorders including depression [11], schizophrenia [11, 12], im-

pulsive aggression [13], generalized anxiety disorder [14], and suicide attempts [15].

Premenstrual dysphoric disorder is a severe form of premenstrual syndrome with serious psychological symptoms [16]. This disorder is characterized by cognitive-affective symptoms that appear in a cyclic manner during the premenstrual period [17]. This illness has been recently designated as a disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (http://www.dsm5.org/Pages/Default.aspx). Prevalence of premenstrual dysphoric disorder varies from 1.3% to 8% [18, 19]. Symptoms of this disorder significantly impair daily functioning [20, 21], and its etiology is unclear [16, 18, 20]. It raises the question whether *T. gondii* infection plays a role in this disorder as it does in other psychiatric disorders. To our knowledge, the link of *T. gondii* infection and premenstrual dysphoric disorder has not been studied. Therefore, we sought to determine the association of *T. gondii* infection with clinical characteristics of premenstrual dysphoric disorder in a sample of women in Durango City, Mexico.

Materials and Methods

Study design and population studied

Through a cross-sectional study, we examined 151 women with premenstrual dysphoric disorder. Women studied were enrolled in two public primary healthcare centers: Centro de Salud #2 of the Secretary of Health (n = 78), and Clinic of Family Medicine of the Institute of Security and Social Services of State Workers (n = 73) in the northern Mexican city of Durango. Participants were examined from February to April 2016. Inclusion criteria for enrollment were women suffering from premenstrual dysphoric disorder, aged 30 - 40 years old, and who accepted to participate in the study. Diagnosis of premenstrual dysphoric disorder was made according to the DSM-5 criteria [22]. Occupation, civil status, and socioeconomic level of women were not restrictive criteria for enrollment. Pregnant women were not included in the study. Mean age in women examined was 35.52 ± 3.59.

Clinical data of the women studied

Signs and symptoms of women were obtained with the aid of a questionnaire. In total, 59 clinical characteristics of women were recorded including presence of irregular periods, severity of menstruation, vaginal infections, painful periods, fatigue, memory lapses, difficulty concentrating, confusion, judgment problems, suffering from mental illness, mood changes, low self-esteem, depression, guilty feeling, increase of fears, panic attacks, anxiety, tension, nervousness, irritability, aggressiveness, lack of interest in daily activities, lack of interest in social relations, out of control feeling or overwhelmed, reduced tolerance to noises and lights, dizziness, headache, migraine, allergy, breast pain, arterial hypertension, bouts of rapid heartbeat, decrease in muscle power, joint pain, low back pain, muscle tension, clumsiness, tingling extremities, electric shock sensation, bruises, edema in ankles, hands or feet, decreased libido, increased libido, dyspareunia, abdominal bloating, gas, abdominal pain, constipation, diarrhea, nauseas, abdominal inflammation, appetite disturbance, desire to eat certain food or eat a lot, weight gain, respiratory problems, presence of acne, presence of herpes labialis, sleep problems, thyroid disease, and obesity.

Detection of anti-*T. gondii* IgG and IgM antibodies

A serum sample from each woman was obtained. Serum samples were stored at -20 °C until analyzed. Anti-*T. gondii* IgG antibodies were detected in serum samples with the commercially available enzyme immunoassay (EIA) kit "*Toxoplasma* IgG" (Diagnostic Automation/Cortez Diagnostics Inc., Woodland Hills, CA, USA). This kit was also used to quantitate the IgG levels. Anti-*T. gondii* IgG antibody levels were expressed as International Units (IU)/mL. A cut off of ≥ 8 IU/mL of IgG was used for seropositivity. Sera reactive 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 EIAs were performed following the instructions of the manufacturer.

Detection of T. gondii DNA

Whole blood of women with anti-*T. gondii* IgG antibodies was analyzed to detect *T. gondii* DNA by nested-polymerase chain reaction (PCR). DNA of whole blood was extracted following a protocol describe elsewhere (http://www.protocol-online.org/prot/Protocols/Rapid-Extraction-of-High-Quality-DNA-from-Whole-Blood-Stored-at-4-C-for-Long-Period-4175.html). Primers directed against the B1 gene of *T. gondii* and a PCR protocol previously described [23] were used. Sensitivity and specificity of this test were previously examined [24]. Amplification products were analyzed by electrophoresis using 2% agarose gels, stained with ethidium bromide, and visualized using ultraviolet illumination.

Statistical analysis

Results were analyzed with the aid of the software SPSS 15.0 (SPSS Inc. Chicago, IL), Microsoft Excel, and Epi Info 7. For calculation of the sample size, we used: 1) a reference seroprevalence of 6.1% [25] as the expected frequency for the factor under study, 2) 100,000 as the population size from which the sample was selected, 3) a 4.0% of confidence limits, and 4) a 95% confidence level. The result of the sample size calculation was 137 subjects. The association of *T. gondii* infection and the clinical characteristics of women was assessed with the Pearson's Chi-squared test or the two-tailed Fisher's exact test (when values were five or less). In the multivariate analysis, we included only variables with a P value ≤ 0.20 obtained

Table 1. Results of Bivariate Analysis of a Selection of Clinical Data and Seropositivity to *T. gondii*

Characteristics	No. of women tested	Prevalence of *T. gondii* infection		P value
		No.	%	
Irregular periods				
Yes	100	9	9	0.16
No	50	1	2	
Sleep problems				
Yes	85	4	4.7	0.33
No	66	6	9.1	
Difficulty concentrating				
Yes	109	4	3.7	0.02
No	41	6	14.6	
Judgment problems				
Yes	59	2	3.4	0.31
No	91	8	8.8	
Mood changes				
Yes	145	9	6.2	0.29
No	5	1	20	
Low self-esteem				
Yes	114	5	4.4	0.06
No	37	5	13.5	
Guilty feeling				
Yes	80	3	3.8	0.19
No	71	7	9.9	
Increase of fears				
Yes	83	3	3.6	0.11
No	68	7	10.3	
Anxiety				
Yes	103	5	4.9	0.29
No	48	5	10.4	
Tension				
Yes	111	6	5.4	0.45
No	40	4	10	
Nervousness				
Yes	119	7	5.9	0.44
No	32	3	9.4	
Irritability				
Yes	124	7	5.6	0.38
No	27	3	11.1	
Lack of interest in social relations				
Yes	92	8	8.7	0.31
No	59	2	3.4	
Out of control feeling or overwhelmed				
Yes	86	8	9.3	0.18
No	65	2	3.1	

Table 1. Results of Bivariate Analysis of a Selection of Clinical Data and Seropositivity to *T. gondii* - *(continued)*

Characteristics	No. of women tested	Prevalence of *T. gondii* infection		P value
		No.	%	
Reduced tolerance to noises and lights				
Yes	89	4	4.5	0.31
No	62	6	9.7	
Joint pain				
Yes	96	8	8.3	0.32
No	55	2	3.6	
Low back pain				
Yes	117	9	7.7	0.45
No	34	1	2.9	
Tingling extremities				
Yes	96	4	4.2	0.17
No	55	6	10.9	
Decreased libido				
Yes	81	7	8.6	0.34
No	68	3	4.4	
Dyspareunia				
Yes	42	1	2.4	0.28
No	108	9	8.3	
Presence of acne				
Yes	85	4	4.7	0.33
No	65	6	9.2	

*Sum may not add up to 151 because of missing values.

in the bivariate analysis. We calculated odds ratio (OR) and 95% confidence interval (CI) using logistic regression with the Enter method. A P value less than 0.05 was considered statistically significant.

Ethical aspects

This study was approved by the Ethics Committees of the General Hospital of the Secretary of Health, and the Institute of Security and Social Services of State Workers in Durango City, Mexico. Participation of women was voluntary. The purpose and procedures of this study were explained to all participants, and a written informed consent was obtained from all of them.

Results

Anti-*T. gondii* IgG antibodies were found in 10 (6.6%) of the 151 women with premenstrual dysphoric disorder studied. Of the 10 anti-*T. gondii* IgG positive women, five (50.0%) had IgG levels > 150 IU/mL, two (20.0%) between 100 and 150 IU/mL, and three (30.0%) between 8 and 99 IU/mL. Anti-*T. gondii* IgM antibodies were found in four (40.0%) of the 10 IgG seropositive women. DNA of *T. gondii* was detected in one (10.0%) of the 10 women with IgG antibodies against *T. gondii*. IgG levels in this women were 146 IU/mL.

Women seropositive to anti-*T. gondii* IgG antibodies showed from 13 to 40 (mean: 25.8 ± 7.58) signs or symptoms, whereas seronegative women (n = 141) had from 7 to 48 (mean: 29.22 ± 9.13) signs or symptoms. Mean number of clinical characteristics in seropositive women was similar to that found in seronegative women (P = 0.25).

Concerning clinical characteristics, bivariate analysis showed seven variables potentially ($P \leq 0.20$) associated with IgG seropositivity to *T. gondii*: irregular periods, difficulty concentrating, low self-esteem, guilty feeling, increase of fears, out of control feeling or overwhelmed, and tingling extremities. Other clinical characteristics studied showed P values higher than 0.20 by bivariate analysis. Results of bivariate analysis of a selection of clinical characteristics of women and IgG seropositivity to *T. gondii* are shown in Table 1. Further analysis by logistic regression of variables with $P \leq 0.20$ obtained by bivariate analysis showed that seropositivity to *T. gondii* was negatively associated with difficulty concentrating (OR: 0.18; 95% CI: 0.03 - 0.91; P = 0.03), and positively associated with out of control feeling or overwhelmed (OR: 9.00; 95% CI: 1.32 - 62.00; P = 0.02) (Table 2).

Bivariate analysis showed that the prevalence of high (> 150 IU/mL) IgG levels to *T. gondii* was significantly (P =

Table 2. Results of the Multivariate Analysis of Clinical Characteristics and IgG Seropositivity to *T. gondii*

Characteristics	Odds ratio	95% confidence interval	P value
Irregular periods	7.91	0.75 - 82.5	0.08
Difficulty concentrating	0.18	0.03 - 0.91	0.03
Low self-esteem	0.48	0.08 - 2.57	0.39
Guilty feeling	0.45	0.08 - 2.46	0.36
Increase of fears	0.58	0.11 - 3.10	0.53
Out of control feeling or overwhelmed	9.00	1.32 - 62.0	0.02
Tingling extremities	0.40	0.08 - 1.86	0.24

0.02) lower in women with difficulty concentrating (1/109: 0.9%) than in those without this clinical feature (4/41: 9.8%). Whereas prevalence of high IgG levels was higher, but not statistically significant (P = 0.07), in women suffering from out of control feeling or overwhelmed (5/86: 5.8%) than in those without this clinical characteristic (0/65: 0%). Concerning the association of clinical data and seropositivity to both anti-*T. gondii* IgG and IgM antibodies, bivariate analysis showed no significant associations. DNA of *T. gondii* was found in only one woman who was seropositive to anti-*T. gondii* IgG antibodies. Due to a limited number of cases with high IgG levels, seropositivity to IgM, and positivity to *T. gondii* DNA, no further regression analysis of the association of these laboratory results and the clinical variables was performed.

Discussion

Premenstrual dysphoric disorder is a clinical entity of unclear pathogenesis [18]. This psychiatric disorder is currently affecting up to 8% of women at reproductive age and focuses on psychological symptoms, whereas physical symptoms prevail in premenstrual syndrome [21]. Infection with *T. gondii* leads to a wide parasite spread in the host from the intestine to many organs in the body including the brain [26]. Infection with *T. gondii* has been associated with psychiatric disorders in general [27, 28], and it has been linked to changes in behavior [29, 30]. To our knowledge, the association between *T. gondii* infection and signs and symptoms of premenstrual dysphoric disorder was not assessed previously. Therefore, the present work aimed to determine whether infection with *T. gondii* was associated with clinical characteristics of premenstrual dysphoric disorder in a sample of women in the northern Mexican city of Durango. We observed that women with *T. gondii* IgG antibodies had a similar mean number of signs or symptoms to seronegative women. Nevertheless, multivariate analysis showed that seropositivity to *T. gondii* is associated with specific clinical characteristics of premenstrual dysphoric disorder in particular. Interestingly, IgG seropositivity to *T. gondii* was associated with the clinical manifestation of out of control feeling or overwhelmed. It is not clear why infection with *T. gondii* was associated with this psychological symptom in women with premenstrual dysphoric disorder. We did not find any report in the medical literature about the association of *T. gondii* and the clinical manifestation of out of control feeling or overwhelmed. The subjective sense of being overwhelmed or out of control has been recognized as a diagnostic symptom of premenstrual dysphoric disorder for about 20 years [31]. In a retrospective study of Brazilian college students, researchers found that out of control feeling or overwhelmed were major symptoms of premenstrual dysphoric disorder [32]. Brazil has a high (64.9%) prevalence of *T. gondii* infection among women of childbearing age [33], and our finding raises the question whether *T. gondii* might be linked to these symptoms in Brazilian women with premenstrual dysphoric disorder. In a study in Casablanca, Morocco, researchers found that the subjective sense of being overwhelmed or out of control was present in 55.7% of women with premenstrual dysphoric disorder studied [34]. We may hypothesize that *T. gondii* in brain may lead to psychological symptoms as out of control feeling or overwhelmed in women suffering from premenstrual dysphoric disorder. Infection with *T. gondii* may cause changes in neurotransmitters, i.e., dopamine and serotonin, that could lead to mood and behavioral changes [11, 35]. On the other hand, in the present study, infection with *T. gondii* was negatively associated with difficulty concentrating. This finding suggests a protective effect of *T. gondii* on this clinical characteristic. Nevertheless, this finding may also suggest that *T. gondii* was not an important factor for this symptom in women with premenstrual dysphoric disorder. Difficulty concentrating has been linked to *T. gondii* infection in immunocompetent adult patients suffering from acute toxoplasmic lymphadenitis [10]. Difference in results among the studies might be explained by difference in the characteristics of the patients studied including clinical diagnosis of patients, duration of infection (acute vs. chronic), and gender.

This study has limitations including small sample size of women with premenstrual dysphoric disorder and a low frequency of anti-*T. gondii* IgG, IgM and PCR positivity. In addition, criteria for diagnosis of this disorder have been recently described, and it is unclear whether this disorder requires further characterization. For the above reasons results of the present study should be interpreted with care.

Conclusions

Results of this first study on the association of *T. gondii* infection and clinical characteristics of premenstrual dysphoric disorder suggest that this infection might be linked to some

symptoms of this disorder. We report for the first time the association of *T. gondii* infection and out of control feeling or overwhelmed. Results warrant for further research on the role of *T. gondii* in premenstrual dysphoric disorder.

Financial Support

This study was financially supported by Secretary of Public Education, Mexico (grant no. DSA/103.5/14/11311).

Competing Interests

The authors declare that no competing interests exist.

References

1. Dubey JP. History of the discovery of the life cycle of Toxoplasma gondii. Int J Parasitol. 2009;39(8):877-882.
2. Innes EA. A brief history and overview of Toxoplasma gondii. Zoonoses Public Health. 2010;57(1):1-7.
3. Montoya JG, Liesenfeld O. Toxoplasmosis. Lancet. 2004;363(9425):1965-1976.
4. Saadatnia G, Golkar M. A review on human toxoplasmosis. Scand J Infect Dis. 2012;44(11):805-814.
5. Foroutan-Rad M, Majidiani H, Dalvand S, Daryani A, Kooti W, Saki J, Hedayati-Rad F, et al. Toxoplasmosis in Blood Donors: A Systematic Review and Meta-Analysis. Transfus Med Rev. 2016;30(3):116-122.
6. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis and treatment. Expert Rev Anti Infect Ther. 2012;10(7):815-828.
7. Maenz M, Schluter D, Liesenfeld O, Schares G, Gross U, Pleyer U. Ocular toxoplasmosis past, present and new aspects of an old disease. Prog Retin Eye Res. 2014;39:77-106.
8. Parlog A, Schluter D, Dunay IR. Toxoplasma gondii-induced neuronal alterations. Parasite Immunol. 2015;37(3):159-170.
9. Machala L, Kodym P, Maly M, Geleneky M, Beran O, Jilich D. [Toxoplasmosis in immunocompromised patients]. Epidemiol Mikrobiol Imunol. 2015;64(2):59-65.
10. Wong WK, Upton A, Thomas MG. Neuropsychiatric symptoms are common in immunocompetent adult patients with Toxoplasma gondii acute lymphadenitis. Scand J Infect Dis. 2013;45(5):357-361.
11. Henriquez SA, Brett R, Alexander J, Pratt J, Roberts CW. Neuropsychiatric disease and Toxoplasma gondii infection. Neuroimmunomodulation. 2009;16(2):122-133.
12. Alvarado-Esquivel C, Urbina-Alvarez JD, Estrada-Martinez S, Torres-Castorena A, Molotla-de-Leon G, Liesenfeld O, Dubey JP. Toxoplasma gondii infection and schizophrenia: a case control study in a low Toxoplasma seroprevalence Mexican population. Parasitol Int. 2011;60(2):151-155.
13. Coccaro EF, Lee R, Groer MW, Can A, Coussons-Read M, Postolache TT. Toxoplasma gondii infection: relationship with aggression in psychiatric subjects. J Clin Psychiatry. 2016;77(3):334-341.
14. Markovitz AA, Simanek AM, Yolken RH, Galea S, Koenen KC, Chen S, Aiello AE. Toxoplasma gondii and anxiety disorders in a community-based sample. Brain Behav Immun. 2015;43:192-197.
15. Arling TA, Yolken RH, Lapidus M, Langenberg P, Dickerson FB, Zimmerman SA, Balis T, et al. Toxoplasma gondii antibody titers and history of suicide attempts in patients with recurrent mood disorders. J Nerv Ment Dis. 2009;197(12):905-908.
16. Robinson LL, Ismail KM. Clinical epidemiology of premenstrual disorder: informing optimized patient outcomes. Int J Womens Health. 2015;7:811-818.
17. Hantsoo L, Epperson CN. Premenstrual Dysphoric Disorder: Epidemiology and Treatment. Curr Psychiatry Rep. 2015;17(11):87.
18. Rapkin AJ, Lewis EI. Treatment of premenstrual dysphoric disorder. Womens Health (Lond). 2013;9(6):537-556.
19. Schatz DB, Hsiao MC, Liu CY. Premenstrual dysphoric disorder in East Asia: a review of the literature. Int J Psychiatry Med. 2012;43(4):365-380.
20. Leminen H, Paavonen J. [PMS and PMDD]. Duodecim. 2013;129(17):1756-1763.
21. Dennerstein L, Lehert P, Heinemann K. Epidemiology of premenstrual symptoms and disorders. Menopause Int. 2012;18(2):48-51.
22. Epperson CN, Steiner M, Hartlage SA, Eriksson E, Schmidt PJ, Jones I, Yonkers KA. Premenstrual dysphoric disorder: evidence for a new category for DSM-5. Am J Psychiatry. 2012;169(5):465-475.
23. Roth A, Roth B, Hoffken G, Steuber S, Khalifa KI, Janitschke K. Application of the polymerase chain reaction in the diagnosis of pulmonary toxoplasmosis in immunocompromised patients. Eur J Clin Microbiol Infect Dis. 1992;11(12):1177-1181.
24. Khalifa Ke-S, Roth A, Roth B, Arasteh KN, Janitschke K. Value of PCR for evaluating occurrence of parasitemia in immunocompromised patients with cerebral and extracerebral toxoplasmosis. J Clin Microbiol. 1994;32(11):2813-2819.
25. Alvarado-Esquivel C, Estrada-Martinez S, Pizarro-Villalobos H, Arce-Quinones M, Liesenfeld O, Dubey JP. Seroepidemiology of Toxoplasma gondii infection in general population in a northern Mexican city. J Parasitol. 2011;97(1):40-43.
26. Harker KS, Ueno N, Lodoen MB. Toxoplasma gondii dissemination: a parasite's journey through the infected host. Parasite Immunol. 2015;37(3):141-149.
27. Alvarado-Esquivel C, Alanis-Quinones OP, Arreola-Valenzuela MA, Rodriguez-Briones A, Piedra-Nevarez LJ, Duran-Morales E, Estrada-Martinez S, et al. Seroepidemiology of Toxoplasma gondii infection in psychiatric inpatients in a northern Mexican city. BMC Infect Dis. 2006;6:178.
28. Cong W, Dong W, Bai L, Wang XY, Ni XT, Qian AD,

Zhu XQ. Seroprevalence and associated risk factors of Toxoplasma gondii infection in psychiatric patients: a case-control study in eastern China. Epidemiol Infect. 2015;143(14):3103-3109.
29. Kamerkar S, Davis PH. Toxoplasma on the brain: understanding host-pathogen interactions in chronic CNS infection. J Parasitol Res. 2012;2012:589295.
30. Fekadu A, Shibre T, Cleare AJ. Toxoplasmosis as a cause for behaviour disorders - overview of evidence and mechanisms. Folia Parasitol (Praha). 2010;57(2):105-113.
31. Severino SK. Premenstrual dysphoric disorder: controversies surrounding the diagnosis. Harv Rev Psychiatry. 1996;3(5):293-295.
32. Teng CT, Filho AH, Artes R, Gorenstein C, Andrade LH, Wang YP. Premenstrual dysphoric symptoms amongst Brazilian college students: factor structure and methodological appraisal. Eur Arch Psychiatry Clin Neurosci. 2005;255(1):51-56.
33. Fernandes GC, Azevedo RS, Amaku M, Yu AL, Massad E. Seroepidemiology of Toxoplasma infection in a metropolitan region of Brazil. Epidemiol Infect. 2009;137(12):1809-1815.
34. McHichi alami K, Tahiri SM, Moussaoui D, Kadri N. [Assessment of premenstrual dysphoric disorder symptoms: population of women in Casablanca]. Encephale. 2002;28(6 Pt 1):525-530.
35. Fond G, Capdevielle D, Macgregor A, Attal J, Larue A, Brittner M, Ducasse D, et al. [Toxoplasma gondii: a potential role in the genesis of psychiatric disorders]. Encephale. 2013;39(1):38-43.

