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ORIGINAL PAPER

Depression and *Toxoplasma gondii* infection: assess the possible relationship through a seromolecular case–control study

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Abstract

Depression disorder is one of the most common psychological recognitions that characterized by sadness, low self-confidence, and disinterest in every activity. Considering evidence showing the effects of toxoplasmosis on the psychological disease, this study conducted to investigate the serological and molecular aspects of *Toxoplasma gondii* infection among patients with depression. In this study, after selecting the patients with depression and control groups under the supervision of a psychologist, the blood samples were collected and the serum samples and buffy coat were separated. The specific anti-*Toxoplasma* IgG antibodies in serum samples were evaluated using the commercial ELISA kit. Then the desired region of the *Toxoplasma* B1 gene was amplified using the specific primers. To confirm the specificity of primers to amplify the B1 gene of *Toxoplasma*, the extracted PCR product was sequenced. The overall prevalence of toxoplasmosis in patients with depression was 59.8 and 60.19% by ELISA and PCR, respectively. In the control group, the prevalence of *Toxoplasma* was 56.3 and 40.2% by serology and PCR. There was a significant correlation between the prevalence of toxoplasmosis and depression. Moreover, a significant difference was found between the variables of age, sex, kind of nutrition, level of education and toxoplasmosis among the two cases and control groups. The higher prevalence of *Toxoplasma* infection among patients with depression compared with the control group indicates the probable impact of this parasite on depression and exacerbates its symptoms, which requires special attention of specialist physicians and patient's relatives.

Keywords Depression · ELISA · PCR · Probable relation · Toxoplasmosis

Introduction

Depression is known as a unified disorder in excitement and mood. Nevertheless, it has four sets of symptoms. In addition to the excitation-mood signs, some stimulating, recognizing and physical symptoms are also introduced (Al-Hussainy et al. 2015). Toxoplasmosis is one of the most common zoonotic parasitic infections in humans and animals (Dubey 2004). As a common opportunist infection, the toxoplasmosis can create serious and sometimes deadly consequences in individuals with a weakened immune system and the fetus in pregnant women (Montoya and Liesenfeld 2004). The average seroprevalence of the toxoplasmosis in different parts of the world is 20–80%. Approximately, 30–60% of the population in developing and developed countries are suffering from toxoplasmosis (Dubey 2004; Montoya and Liesenfeld 2004). Toxoplasmosis is an immune system associated disease that is acquired via the consumption of raw or undercooked meat containing tissue cysts of parasite or having food or drinking water contaminated by oocyte excreted from cat, blood and leucocyte transfusion, organ transplants and rarely by random needle stick in laboratory and also it is transmitted from mother to her embryo congenitally (Furtado et al. 2011; Dalimi and Abdoli 2012; Fallahi et al. 2016). Clinical spectrum of *Toxoplasma gondii* infection is ranged from asymptomatic which contains

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most infected people to the intensified and serious pathologies such as CNS diseases, eye, lymph glands, heart, and other organs involvement (Walker 2005; Balasundaram et al. 2010; Sugden et al. 2016). Regarding the direct impact of parasite on the central nerve system (CNS) and since one of the anatomic organs for *Toxoplasma* localization is in the CNS, toxoplasmosis can be related to neurotic disorders such as schizophrenia, Alzheimers and depression that the *Toxoplasma* infection might play a role in the pathogenesis mechanism of this mental disorders (Sugden et al. 2016). Various studies have been conducted to evaluate the relationship between toxoplasmosis and psychopathy behaviors and interestingly some of these studies reported a significant relationship in this context (Dickerson et al. 2007; Saraei-Sahnesaraei et al. 2009; Al-Hussainy et al. 2015; Omar et al. 2015; Rashno et al. 2016; Abdollahian et al. 2017; Fallahi et al. 2017). In most cases, the examination of the relationship between toxoplasmosis and neurological disorders has been limited to the serologic evaluation of the exclusive parasite antibodies, while antibody doesn`t indicate the presence of parasite at the time of neurotic disorder. Tests that are more accurate are needed to characterize the presence of parasite at the time of the experiment. Therefore, the present study was conducted to explore the probable relationship between infection to *T. gondii* and depression in patients using serologic and molecular tests simultaneously.

Materials and methods

Study population and clinical samples

The study population contains 87 depressed people (case group) who attended Khorramabad neurological therapy centers which were selected with available sampling method. According to the American Psychiatric Association guidelines (2013), the specific criteria to select the case group include: feeling sad or having a depressed mood, loss of interest or pleasure in activities once enjoyed, changes in appetite-weight loss or gain unrelated to dieting, trouble sleeping or sleeping too much, loss of energy or increased fatigue, increase in purposeless physical activity (e.g., hand-wringing or pacing) or slowed movements and speech (actions observable by others), feeling worthless or guilty, difficulty thinking, concentrating or making decisions, and thoughts of death or suicide. Symptoms must last at least 2 weeks for a diagnosis of depression. The general medical causes (e.g., thyroid problems, a brain tumor or vitamin deficiency) that can mimic symptoms of depression were rule out. As well as, patients with chronic depression or under-treatment of depression were excluded.

On the other hands, 87 people who attended to medical diagnostic laboratories of the Khorramabad city and based on the psychiatrics consultant have not any depression criteria were selected as the control group. As far as possible, it has been tried to select a control group similar to the case group in terms of sex, age, and habitat.

After describing the objectives of the study and obtaining written consent from all participants in the study, the proper questionnaires of the study were completed. Blood samples of depressed people and control group were collected separately during 6 months in separate microtubes with and without anticoagulant near to ice (cold chain) and were transferred to the research laboratory of parasitology, Lorestan University of Medical Sciences, Khorramabad, Iran. To separation, serum and buffy coat, the blood samples were centrifuged 3–5 min at 2500*g*. The serum and buffy specimens were kept at − 20 °C until use.

Serological assessment

The *Toxoplasma*-specific IgG and IgM antibodies were assessed using a commercial ELISA kit (Pishtaz Teb Zaman Diagnostics, Tehran, Iran) based on the manufacturer's protocol. the manufactures reported the sensitivity and specificity of the kits as 100 and 99%, respectively. The level of IgG and IgM antibodies were measured at 450 and 630 nm, using a plate reader (Ao Absorbance Microplate Reader, Azure Biosystems, Inc. USA). Index value > 1.1 was regarded as positive. Index values less than 0.9 regarded as negative, while those values between 0.9 and 1.1 were regarded as equivocal. Samples within the equivocal zone were re-tested.

Separation and purification of WBCs

Due to the different inserting amounts of RBC together with buffy coat and inhibitory role and disorder of proteins especially hemoglobin and also RNA in the extraction process of DNA, it is necessary to lyse and exit the remaining RBC which has been done using washing by deionized distilled water and repeated centrifugation. In the samples in which the quantities of RBCs were more than the normal level, the globule lyses action repeated several times.

Molecular evaluation

Total genomic DNA was extracted from buffy coat samples using a Genomic DNA purification kit (DNG-PLUS, Cinnaclon Co, Iran) according to the manufactures' protocol and kept at − 20 °C until the usage time. The PCR reaction was done in a 20µL total reaction volume containing 5 µL of 10X PCR buffer, 2 mM $MgCl_2$, 250 µM of each of the four deoxynucleotide triphosphates (dNTPs), 1.25 U *Taq DNA polymerase* (Fermentas, Germany), 50 pmol of each primer (TOXO1: GGAACTGCATCCGTTCATGAG and TOXO2: TCTTTAAAGCGTTCGTGGTC targeting the B1 gene of

T. gondii) (Fallahi et al. 2015) and 5 µL of the extracted DNA in thermocycler equipment. Cycling condition was 94 °C for 5 min, followed by 30 cycles of 1 min at 94 °C, 1 min at 47 °C and 1 min at 72 °C with a final step at 72 °C for 10 min. The DNA of *Toxoplasma* tachyzoites harvested from mouse peritoneum by serial inoculations was used as positive control and doubled deionized sterile water was used as the negative control. PCR products were analyzed by electrophoresis on a 1.5% agarose gel stained with ethidium bromide solution (1 µg/ml). The PCR amplification is expected to yield a 194 bp product for positive reactions. To confirm the specificity of primers for the *T. gondii* detection, the purified PCR product was sequenced. The Basic Local Alignment Search Tool (BLAST) was used to align the sequences with the target one.

Statistical analysis

The data analysis was performed using SPSS 18 software (SPSS, Chicago, IL, USA). To analyze the data, the Multivariate logistic regression, Chi-square and Fisher's exact tests were used. The odds ratios (OR) and 95% confidence intervals (CI) after adjustments were used to test the associations. For differences, the p value of <0.05 was considered statistically significant.

Results

Demographic variables

In this study, the average age of the participants was 61.9 ± 21.71. The sex ratio was 75 males and 99 females. The depression symptoms were divided into three steps: primary, medium, and advanced which contain self negative attitudes 37 people (42.5%), disappointment 41 person (47.1%), paramnesia 34 person (31.9%), grief and sorrow 45 person (51.7%), unhappiness 47 people (54%), changes in appetite and sleep 10 person (28.6%), fatigue 20 person (23%), increasing affliction and suffering 17 person (19.5%), passiveness 14 people (16.1%), lack of initiative and follow up and continuity in work 30 person (34.5%). The demographic variables and indicators of the participants in this study are shown in Table 1.

Serological assessment

In this study, the anti-*Toxoplasma* IgG antibodies were found in the serum of 52 of 87 (59.8%) patients with depression. As well as, this antibody was recognized in 49 of 87 (56.3%) serum samples of the control group. The Chi-square test showed that there is a significant relationship between the prevalence of IgG antibodies and variables of age, sex, education, and residence between the two groups of cases and controls ($p<0.001$). Also, the results of the ELISA test showed that there is not any anti-*Toxoplasma* IgM specific antibody in the two cases and control groups.

Molecular evaluation

PCR test of the *Toxoplasmas* B1 gene was positive in 53 people (60.9%) of patients with depression and 35 individuals (40.2%) of control group persons (Figs. 1, 2). The impact of age, sex, drinking water, molecular tests, the level of education and residence variables on depression analyzed using multivariate logistics regression is shown in Tables 2 and 3. Results of the multiple sequence alignment of the purified PCR products showed that the obtained partial sequences were identical to the corresponding B1 gene sequences of *Toxoplasma* reported in the GenBank database (Accession number; AF179871). The results of serological and molecular in studied patients according to the depression stage are shown in Table 4.

Discussion

In recent years, among the disorders related to *Toxoplasma gondii* psychopathy, researchers have considered mental disorders. So that the recent studies results have shown that *T. gondii* infection is related to mental illnesses such as schizophrenia, suicide, OCD and neurocognitive disorders and also other neurological disorders like Parkinson, Alzheimer, increased incidence of traffic accidents, epilepsy, headaches and migraine, mental lag and IQ (Dickerson et al. 2007; Saraei-Sahnesaraei et al. 2009; Yuksel et al. 2010; Al-Hussainy et al. 2015; Omar et al. 2015; Rashno et al. 2016; Okusaga et al. 2016; Abdollahian et al. 2017; Fallahi et al. 2017).

In this study anti-*Toxoplasma*, IgG antibodies frequency was 59.8% in patients with depression and 56.3% in the control group. The role of antibodies in *Toxoplasma*-infected neuropsychiatric disorders was first studied in 1953 (Torrey et al. 2007). A positive antibody titer shows the presence of the parasite in the central nervous system and other organs. Tissue cysts containing bradyzoites may be torn and parasites become free that cause antibody titers to remain high. In the current research according to the Chi-square test, assuming all other variables being constant, the risk of depression in the people with positive serology tests is 1.5 times more than people with negative serology tests that there was not a statistically significant relationship ($p>0.05$). Assuming all other variables constant, the risk of depression in men is almost 4.7 times more than women that according to $p=0.001$ there was a significant relationship. Also assuming all other variables

Table 1 Demographic variable abundance and population indicators in two studied groups

Variable	Condition	Group				*p* value
		Case group (patients with depression)		Control group (healthy people)		
		Statistical indicators				
		No.	%	No.	%	
Sex	Male	49	56.3	26	29.9	0.701
	Female	38	43.7	61	70.1	
	Total	87	100	87	100	
Residence	City	65	74.7	50	57.5	0.001
	Village	22	25.3	37	42.5	
	Total	87	100	87	100	
Education	Illiterate	36	16.4	13	5.9	0.001
	Elementary	59	26.8	26	11.8	
	Secondary	44	20	35	15.9	
	High Schooler	64	29.1	106	48.2	
	Collegiate	17	7.7	40	18.2	
	Total	87	100	87	100	
Nutrition	Vegetable	2	2.3	0	0	0.001
	Meaty	18	20.7	12	13.8	
	Both	67	77	75	86.2	
	Total	87	100	87	100	
Age	≤30	12	13.79	15	17.24	0.105
	31–60	53	60.91	47	54.2	
	>60	22	25.28	25	28.73	
	Total	87	100	87	100	
Drinking water	Well	2	2.3	6	6.9	0.149
	Pipe	93.1	81	97.7	93.1	
	Total	87	100	87	100	

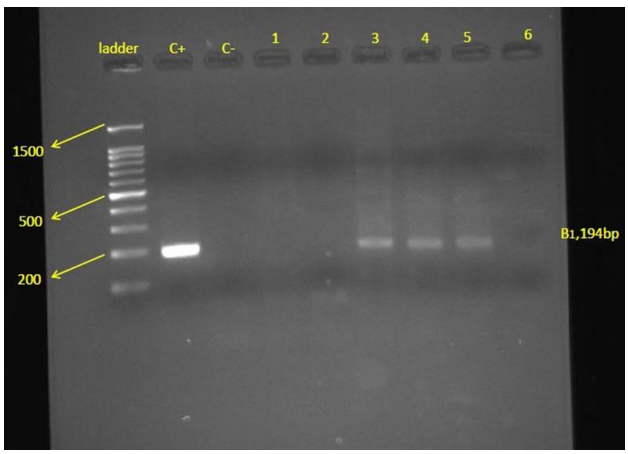

Fig. 1 PCR test results of the controls group samples (ladder = 100 bp marker, C+ = positive control, C− = negative control, 1–6 sample wells = 6 DNA sample of control group people that were randomly selected)

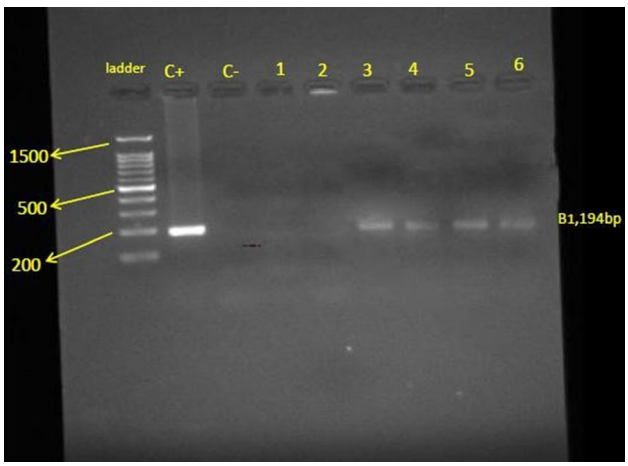

Fig. 2 PCR test results on case group samples (ladder = 100 bp marker, C+ = positive control, C− = negative control, 1–6 sample wells = 6 DNA sample of case group people that were randomly selected)

Table 2 Impact of different variables on depression using a multivariate logistic regression model and serology assay

Variable	Group	Odd ratio	95% confidence interval for odd ratio	*p* value
Sex	Female	Reference	–	–
	Male	4.7	(2.1, 10.85)	< 0.001
Drinking water	Pipe	Reference	–	–
	Well	3.9	(0.6, 25.03)	0.15
Serology test	Negative	Reference	–	–
	Positive	1.5	(0.69, 3.44)	0.282
Age	–	1.06	(1.03, 1.1)	< 0.001
Education	Bachelor	Reference	–	–
	Associate degree	0.8	(0.1, 6.04)	0.81
	Diploma	0.23	(0.4, 1.34)	0.1
	Cycle	1.54	(0.29, 8.14)	0.6
	Elementary	0.57	(0.1, 3.23)	0.52
	Illiterate	2.35	(0.27, 19.8)	0.43
Residence	Village	Reference	–	–
	City	2.47	(1.01, 6.08)	0.047

Table 3 Impact of different variables on depression using a multivariate logistic regression model and molecular assay

Variable	Group	Odd ratio	95% confidence interval for odd ratio	*p* value
Sex	Female	Reference	–	–
	Male	3.97	(1.67, 9.38)	0.002
Drinking water	Pipe	Reference	–	–
	Well	2.76	(0.19, 39.3)	0.305
Molecular test	Negative	Reference	–	–
	Positive	6.07	(2.23, 16.5)	0.001
Age	–	1.08	(1.04, 1.12)	0.001
Education	Bachelor	Reference	–	–
	Associate degree	0.279	(0.03, 2.6)	0.263
	Diploma	0.109	(0.016, 0.75)	0.025
	Cycle	0.681	(0.107, 4.32)	0.684
	Elementary	0.396	(0.064, 2.4)	0.321
	Illiterate	1.72	(0.165, 18)	0.684
Residence	Village	Reference	–	–
	City	4.34	(1.6, 11.7)	0.004

constant, for each year increase in age, the risk of depression increases 6% that according to $p < 0.001$ this increase was significant. Assuming all other variables constant, the odds ratio of depression for people living in urban areas was almost 2.5 times more than people living in the villages that based on $p < 0.047$ this result was significant. It could be due to more contact with cats and more consumption of meat products contaminated by tissue cysts in these regions.

Some researchers have shown that the serum positive cases for toxoplasmosis in a patient with schizophrenia are 3 times more than healthy people (Hinze-Selch et al. 2007; Mahmoud and Hasan 2009; Alipour et al. 2011). The relationship between toxoplasmosis and the pathophysiology of neuropsychiatric disorder have been checked in different studies including; imbalance in the dopamine and dopaminergic signal change by the dependence of parasite to microglia cell, toxic-free radical increasing by parasite behavioral changes in *Toxoplasma* infection, inhibition of *Toxoplasma* in culture with many antipsychotic drugs and more exposure to people with neuropsychiatric disorder with cat during childhood (Mortensen et al. 2007; Prandovszky et al. 2011; Karabulut et al. 2015). Schizophrenics in the acute phase of the disease have high Th1-related cytokine responses. *Toxoplasma* infection that induces Th1 response to balance dopamine and serotonin neurotransmitters system also led to the neuropsychiatric symptoms. Antipsychotic drugs reduce symptoms by modulating this pathway and reducing dopamine in the brain and they involved in host defense against infection, they also prevent the proliferation of *Toxoplasma* and reduce the titer (Hinze-Selch et al. 2007; Mahmoud and Hasan, 2009; Alipour et al. 2011).

The serological method for the detection of *Toxoplasma* has flaws and it is not an exact method, for example, antibodies in serum may be related to a few years ago. Sometimes, the IgM antibody could be survive in the serum for 9 months and the infection may be related to the past, but ELISA test shows positive amount of IgM that it would not be accurate representative to show the acute phase of disease. In another similar condition, in immunocompromised patients that are in the acute phase of the disease, but still have not produce the antibody and the ELISA test become negative. For these reasons, the serology test is not an accurate way of detecting the *Toxoplasma* infection and we used a molecular method, the PCR, for an accurate diagnosis of infection. Because with this method parasite DNA has been detected and DNA presence means the presence of parasite itself and as long as the parasite is in the blood it can be detected and tracked as well. For this purpose, *Toxoplasma* B1 gene-specific primers were used. This gene is the most well-known gene sequence with high sensitivity and 35 times repeat in the genome of this parasite (Fallahi et al. 2014).

In this study, the PCR test for *Toxoplasma* was positive in 60.9% of patients with depression and 40.2% of the control group. Based on the chi-square test and assuming other conditions are constant, the odds ratio for depression in people who are positive *Toxoplasma* was almost 6 times more than those whose tests were negative, that according to ($p < 0.001$ this increase was significant. Assuming all other variables constant, for each unit increase in age, the

Table 4 Results of serological and molecular in studied patients according to the depression stage

Type of test	Depression stage					
	Primary		Medium		Advance	
	No.	%	No.	%	No.	%
Serological test	19	36.5	24	46.2	9	17.3
Molecular test	29	54.7	23	43.4	1	1.9
Total	32	36.8	40	46	15	17.2

Table 5 Comparison of the results of molecular and serological tests in two cases and controls groups

Case and control group	Molecular+/serological+		Molecular−/serological+		Molecular+/serological−		Molecular−/serological−	
	No.	%	No.	%	No.	%	No.	%
	53	52.5	48	47.5	35	47.9	38	52.1

risk of depression increases 8% that this increase was significant ($p < 0.001$). Assuming all other variables constant the risk of depression in men is almost 3.97 against women that according to $p = 0.002$ there was a significant relationship. Kind of nutrition according to $p < 0.001$ had a significant relationship with the molecular test result. Assuming all other variables constant the odds ratio for depression for people living in the urban areas was almost 4.34 times more than people living in the villages that according to $p < 0.001$ it had a significant relationship with the molecular test result. This suggests that most patients who are living in urban area have higher *Toxoplasma* outbreak possibility, due to more exposure to cats or consumption of meat food products. Kind of drinking water according to $p = 0.305$ has not had a significant relationship with the molecular test. Based on the Hosmer and Lemeshow test and according to $p = 0.917$, the model has a good fit to the data. In this study, after comparing the molecular and serological tests, it has been found that 35 persons (47.9%) have a negative serological and positive molecular test this suggests that the serological test may not be an accurate measure for *Toxoplasma* infection and only is suitable for primary screening of suspects (Table 5). This finding indicates the presence of parasite DNA in blood samples of these people and, therefore, is reagent of the acute phase of the illness. The inverse of the previous state was also observed in the number of subjects. Therefore, those 48 persons (47.5%) whose serological test result was positive had a negative molecular test. This finding indicates that may be a long time has passed from infection, the parasite is limited by the immune system, and the chronic phase of the disease is established. However, parasites specific antibodies can remain in people's blood for a long time and the result of the serology test becomes positive despite the lack of active infection.

Conclusion

According to the results of the ELISA test, it can be concluded that most patients with depression were infected with toxoplasmosis before catching to depression, because none of them showed anti-*Toxoplasma* IgM antibodies titer in their serum. It is always necessary for clinicians to bear the risks of reactivation of a latent infection of *Toxoplasma* in people with depression and it's consequences in mind. The higher *T. gondii* prevalence in patients with depression than the control group shows the possible impact of this parasite on causing depression and intensifying its symptoms that requires special attention of physicians and the patient relatives. As PCR technique has higher sensitivity and specificity than the serology method for early diagnosis of toxoplasmosis in people with depression, in addition to conventional serological methods it is recommended to use other sensitive and reliable methods such as PCR.

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Compliance with ethical standards

Conflict of interest The author declares no conflict of interest.

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