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ORIGINAL ARTICLE

Toxoplasmosis among Patients with Cancers and Blood Disorders in Iran: Serological Evaluation, Risk Factors and Comparison with Healthy Individuals

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KEYWORDS

Toxoplasmosis;
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ABSTRACT: Toxoplasma gondii is an obligate intracellular parasite that causes toxoplasmosis in humans and warm-blooded animals. In this study, we explored the risk factors and seroprevalence of Toxoplasma infection among cancer patients and patients with blood cell disorders in Iran. We collected serum samples from each participant include 600 clinically healthy individuals, 127 patients with different types of cancer, 294 patients with red blood cell disorders, and 101 patients with white blood cell disorders and tested for anti-*Toxoplasma* antibodies (IgG and IgM) using an Enzyme-Linked Immunosorbent Assay kits and analyzed the results statistically.Out of the 1122 participants ,seroprevalence of *Toxoplasmosis* among all patients with different disorders , patients with white blood cell disorders, patients with red blood cell disorders and patients with different types of cancer 9.97% , 17.82%, 11.57% and 7.09% were reported respectiveiy.Awareness campaign to educate blood cell disorders patients regarding contact with pets is salient to the reduction of the *Toxoplasma* burden. In addition, it is pertinent to screen patients with cancers to rule out *Toxoplasma* infections.

INTRODUCTION

Toxoplasma gondii is an intracellular parasite and the only agent known to cause toxoplasmosis in humans and animals. Toxoplasmosis is a disease of public concern; it was projected that about 25% of

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the global population bears the burden of the disease. [1]. Humans acquire toxoplasmosis through the ingestion of the oocyst, shed in feces of infected cats –The parasite in the infected feces may contaminate water, soil, or vegetables. Alternatively, it is acquired via ingestion of living cysts, in poorly-cooked or raw meat of intermediate hosts. Birds and rodents served as the intermediate hosts for toxoplasmosis, while cats serve as definitive hosts. [2-4]. *Toxoplasmosis* manifests as mild or asymptomatic disease in immunocompetent individuals. Although, recent evidence showed that even immunocompetent hosts could have a severe form of the disease. But can be disastrous in the immunocompromised, with attendant neurologic, ocular, or disseminated manifestations. During pregnancy, the transplacental infection may lead to severe disease in the newborn, miscarriage, or stillbirth [5-9].Immunosuppressive conditions like HIV/AIDS; those induced after a stem cell or solid organ transplants, to institute tolerance; and treatment with immunosuppressive agents (for inflammatory disorders) predispose patients to toxoplasmosis. Recent evidence proves that patients with hematologic disorders, blood cancers, and other solid tumors stand a high risk of toxoplasmosis [10-13]. Moreover, there is currently limited data that evaluated the risks and prevalence of toxoplasmosis among Iranian patients with solid tumors, blood cancers, and other blood disorders - special groups at risk of the infection. In this study, we compare the risk factors and the seroprevalence of toxoplasmosis among patients with cancers and blood disorders with healthy controls in Khuzestan Province of Iran.

MATERIALS AND METHODS

Study Population and Sample Collection

We conducted a cross-sectional study at Shahid Baghaei Hospital in Ahvaz city, Khuzestan province, Iran, from February to August 2019. The study involved 1122 participants: 600 clinically healthy individuals, 127 patients with different types of cancer, 294 patients with red blood cell disorders, and 101 patients with white blood cell disorders. We explained the objectives and protocol of the study to the participants who signed written consent. We used structured questionnaires to collect biodata of the participants and to obtain information about the risk factors such as areas of residence, history of contact with dogs/cats, and pica (a psychological disorder characterized by craving for non-nutritive substances in the environment, such as soil; paper; drywall or paint; or feces). We collected approximately 3-5 mL of venous blood samples from each participant; Blood samples were left overnight (to clot at room temperature), and then centrifuged at 1500 RPM for 10 min. We collected the serum in Eppendorf tubes, stored at 4^0C, transported (within 72h) in an icebox to Parasitology Laboratory of Tehran University of Medical Sciences, and kept at −20°C - until we analyzed them.

Serological Evaluation

We tested the serum samples for anti-*Toxoplasma* antibodies using an Enzyme-Linked Immunosorbent Assay '*Toxoplasma gondii* IgG and IgM' kits (EUROIMMUN, Germany). We calibrated the absorbance and considered positive any sample that read at least 0.38 OD units, according to the manufacturer's instructions.

Statistical analysis

We analyzed the data using the SPSS 20.0 software package. Both dependent and independent variables were dichotomous variables. Prevalence ratio (PR) within the 95% CI, and Probability (P) value ≤ 0.05 was considered statistically significant in all the analyses.

RESULTS

Participants

The total number of the subjects involved in this study was 1122; 484(43.13%) males and 638 (56.87%) females, with the mean age of 45 years - age range between 2 to 89 years. Out of the total

participants, 436 (38.85%) were rural residents, while 686 (61.15%) lived in urban areas. About a third 399 (35.56%) of the participants had a history of contact with pets (cats and dogs), and 133 (11.87%) had a positive response to pica.

Toxoplasmosis Seroprevalence and Risk factors

The results of the current study show that the overall seroprevalence of toxoplasmosis among all patients with different disorders was 9.97% (52 of 522), while among the healthy individuals was 11.17% (67 of 600). Of the 101 sera from patients with white blood cell disorders, 18 (17.82%) were positive for anti-toxoplasmosis IgG, among which 03 (0.99%) had a positive history of pica and 08 (07.92%) had a positive history of contacts with dogs and cats. Further analysis showed that contact with animal pets (cats and dogs) is a statistically significant risk factor for toxoplasmosis among patients with white cell disorders (Table 1). Table 2 shows the prevalence of toxoplasmosis IgG seropositivity among patients with red blood cell disorders (11.57%) compared to healthy individuals (09.86%). We found that pica and contact with animal pets have a statistically significant association with toxoplasmosis among both patients with red blood cell disorders and healthy individuals. The prevalence of toxoplasmosis IgG-seropositivity among cancer patients (7.09%) compared to healthy individuals is shown in Table 3. The statistical evaluation showed the absence of a significant association between the location of residence, pica, or contact with animal pets and toxoplasmosis in patients with different types of cancer. Analysis of age and sex distribution among patients with white blood cell disorders showed a lack of statistically significant association between gender and *Toxoplasma* infection-Table 4. Similarly, gender was not a significant risk factor for *Toxoplasma* seropositivity in patients with red blood cell disorders or patients with cancers, as shown respectively in Table 5 and Table 6. Furthermore, of all the subjects (1122), only 2 had simultaneous IgG and IgM anti-*Toxoplasma* gondii (0.18%). Figure 1 summarizes the results of the comparison between *Toxoplasma* infection (IgG and IgM seropositive) among all patients and healthy individuals.

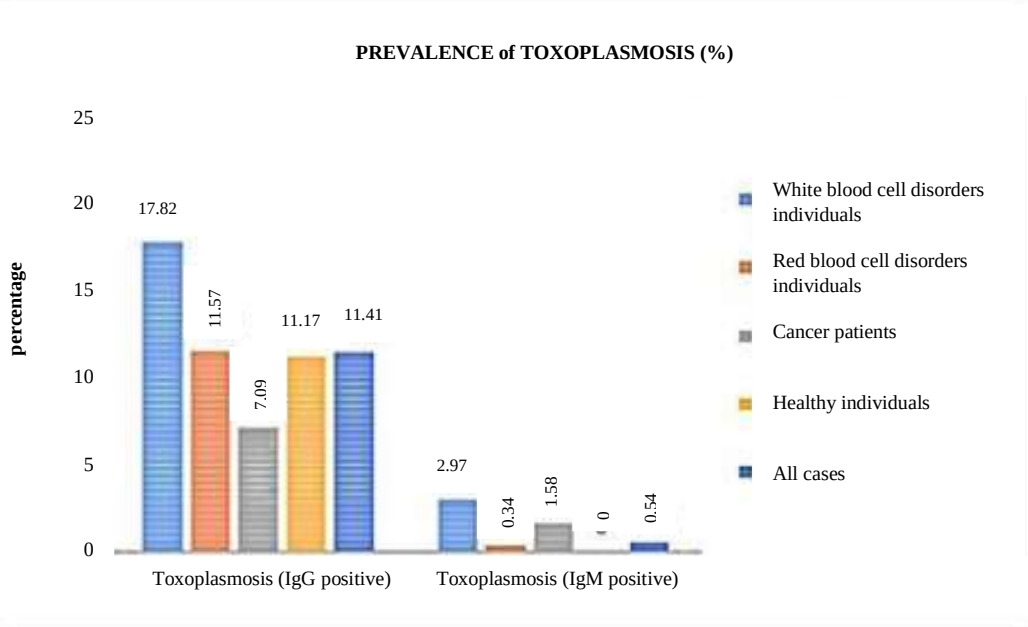

Table 1. Prevalence of toxoplasmosis (IgG positive) in individuals with white blood cell disorders compared to healthy individuals

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Prevalence of toxoplasmosis (IgG Positive)				
With blood cell disorders				
Multiple myeloma	09 (08.91%)	02 (01.98%)	1	
Acute myeloid (or myelogenous) leukemia (AML)	18 (17.82%)	03 (02.97%)	0.98	
Chronic myeloid (or myelogenous%) leukemia (CML)	09 (08.91%)	02 (01.98%)	1	
Acute lymphocytic (or lymphoblastic%) leukemia (ALL)	31 (30.7%)	04 (03.96%)	0.74	
Chronic lymphocytic leukemia (CLL)	14 (13.86%)	03 (02.97%)	1.02	
Hodgkin's lymphoma	11 (10.89%)	02 (01.98%)	0.82	
Non Hodgkin's lymphoma	06 (05.94%)	01 (0.99%)	1.05	
burkitt's lymphoma	03 (02.97%)	01 (0.99%)	1.21	
Total	101 (100%)	18 (17.82%)		
Healthy individuals				Pv>0.05
Total	101 (100%)	23 (22.78%)	1.01	
Pica				
With blood cell disorders				Pv>0.05
Yes	08 (07.92%)	03 (0.99%)	1	
No	93 (92.08%)	15 (04.95%)	0.62	
Healthy individuals				Pv>0.05
Yes	39 (39.61%)	06 (05.95%)	1	
No	62 (61.39%)	17 (16.83%)	0.57	
Contact with dog and cat				
With blood cell disorders				Pv≤0.05
Yes	21 (20.8%)	08 (07.92%)	1	
No	80 (79.2%)	10 (09.90%)	0.26	
Healthy individuals				*Pv>0.05*
Yes	58 (57.42%)	16 (15.84%)	1	
No	43 (42.58%)	07 (06.94%)	0.82	
Location				
With blood cell disorders				*Pv>0.05*
Urban area	77 (76.24%)	12 (11.87%)	1	
Rural area	24 (23.76%)	06 (05.95%)	1.21	
Healthy individuals				*Pv≤0.05*
Urban area	66 (65.35%)	10 (09.90%)	1	
Rural area	35 (34.65%)	13 (12.88%)	1.43	

Table 2. Prevalence of toxoplasmosis (IgG positive) in individuals with red blood cell disorders compared to healthy individuals

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Prevalence of toxoplasmosis (IgG positive)				
Red blood cell disorders				
Major Thalassemia	38(12.93%)	06(02.04%)	1	
Minor Thalassemia	71(24.15%)	08(0.08%)	0.92	
Sickle cell anemia	07(02.38%)	01(0.34%)	0.96	
Iron-deficiency anemia	169(57.48%)	19(06.46%)	0.84	
Aplastic anemia	05(1.70%)	00	0	
Megaloblastic anemia	04(01.36%)	00	0	
Total	294(100%)	34(11.57%)		
Healthy individuals				Pv>0.05
Total	294(100%)	29(09.86%)	0.65	
Pica				
Red blood cell disorders				Pv≤0.05
Yes	29(09.86%)	10(03.40%)	1	
No	265(90.14%)	24(08.16%)	0.33	
Healthy individuals				Pv≤0.05
Yes	12(04.08%)	07(02.38%)	1	
No	282(95.92%)	22(07.48%)	0.11	
Contact with dog and cat				
Red blood cell disorders				Pv≤0.05
Yes	92(31.3%)	16(05.44%)	1	
No	202(68.7%)	18(06.12%)	0.24	
Healthy individuals				Pv≤0.05
Yes	141(52.04%)	19(06.46%)	1	
No	153(47.96%)	10(03.40%)	0.29	
Location				
Red blood cell disorders				Pv>0.05
Urban area	218(74.15%)	27(09.18%)	1	
Rural area	76(25.85%)	07(02.38%)	0.93	
Healthy individuals				Pv>0.05
Urban area	100(34.01%)	13(04.42%)	1	
Rural area	194(65.99%)	16(05.44%)	0.66	

Table 3. Prevalence of toxoplasmosis (IgG positive) in patients with different types of cancer compared to healthy individuals

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Prevalence of toxoplasmosis (IgG positive)				
types of cancer				
Brain cancer	04(3.15%)	01(0.79%)	1	
Skin cancer	07(5.51%)	00	0	
Breast cancer	42(33.08%)	05(03.93%)	0.74	
Colorectal cancer	12(9.45%)	01(0.79%)	0.65	
Pancreatic cancer	04(3.15%)	00	0	
Testicular cancer	03(2.36%)	00	0	
Liver cancer	19(14.96%)	01(0.79%)	0.36	
Lung cancer	06(4.72%)	00	0	
Soft tissue sarcoma	02(1.57%)	00	0	
Esophageal cancer	08(6.3%)	00	0	
Ovarian cancer	09(7.09%)	00	0	
Gastric cancer	11(8.66%)	01(0.79%)	0.71	
Total	127(100%)	09(07.09%)		
Healthy individuals				Pv>0.05
Total	127(100%)	15(11.58%)	0.76	
Pica				
Cancer patients				Pv>0.05
Yes	09(7.09%)	01(0.79%)	1	
No	118(92.91%)	08(06.32%)	0.98	
Healthy individuals				Pv>0.05
Yes	25(19.68%)	01(0.79%)	1	
No	102(80.32%)	14(11.06%)	1.03	
Contact with dog and cat				
Cancer patients				Pv>0.05
Yes	36(28.35%)	04(03.16%)	1	
No	91(71.65%)	05(03.95%)	0.75	
Healthy individuals				Pv>0.05
Yes	27(21.26%)	06(04.74%)	1	
No	100(78.74%)	09(07.11%)	0.82	
Location				
Cancer patients				Pv>0.05
Urban area	96(75.59%)	07(05.53%)	1	
Rural area	31(24.41%)	02(01.58%)	0.95	
Healthy individuals				Pv≤0.05
Urban area	89(70.08%)	04(03.16%)	1	
Rural area	38(29.92%)	11(08.69%)	4.56	

Table 4. Prevalence of toxoplasmosis (IgG positive) among individuals with withe blood cell disorders, based on age and sex

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Age				
03-22	12(11.88)	03(16.67)	1	
23-42	22(21.78)	04(22.22)	0.81	
43-62	48(47.53)	09(50)	0.83	
63 or more	19(18.81)	02(11.11)	0.44	
Total	**101(100)**	**18(100)**		
Sex				**Pv>0.05**
Male	41(40.59)	12(66.66)	1	
Female	60(59.41)	06 (33.34)	0.36	

Table 5. Prevalence of toxoplasmosis (IgG positive) among individuals with red blood cell disorders, based on age and sex

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Age				
05-24	109(37.08)	09(26.47)	1	
25-44	101(34.36)	10(29.41)	1.15	
45-64	55(18.70)	07(20.59)	2.62	
65 or more	29(9.86)	08(23.53)	4.17	
Total	**294(100)**	**34(100)**		
Sex				**Pv>0.05**
Male	116(39.46)	19(55.89)	1	
Female	178(60.54)	15(44.11)	0.61	

Table 6. Prevalence of toxoplasmosis (IgG positive) among Patients with different types of cancer, based on age and sex

Variables	Samples N (%)	Positivity N (%)	Prevalence Ratio	P-value
Age				
02-21	05(3.94)	01(11.11)	1	
22-41	19(14.96)	01(11.11)	0.26	
42-61	54(42.52)	03(33.33)	0.20	
62 or more	49(38.58)	04(44.45)	0. 48	
Total	**127(100)**	**09(100)**		
Sex				**Pv>0.05**
Male	49(38.58)	02(22.22)	1	
Female	78(61.42)	07(77.78)	2.15	

DISCUSSION

Over recent years, potential links between *Toxoplasma* infection and different types of cancer have attracted the attention of lots of researchers. However, relationships between toxoplasmosis and blood disorders have not been exhaustively researched. The current study aimed at determining the risk factors and the seroprevalence of toxoplasmosis among patients with cancers and

blood disorders in comparison with healthy individuals in Khuzestan Province of Iran. The principal findings of the current study were the seroprevalence of anti-*T. gondii* IgG among all patients – with white blood cell disorders, red blood cell disorder, and cancer patients – was 9.97% (52 of 522); the seroprevalence among the healthy individuals was 11.17% (67 of 600); among the entire study population was 11.41% (128 of 1122). Patients with disorders such as cancers, white blood cell disorders, red blood cell disorder constitute a group at risk of *T.gondii* infections due to their deranged immune status. Researchers reported different seroprevalence rates of *T.gondii* infections among several groups at risk in different parts of Iran. In a systematic review and meta-analysis, Ahmadpour et al. reported an overall seroprevalence rate of *Toxoplasma* infection in Iranian immunocompromised patients to be 50.01%; however, they also recorded significant heterogeneity among study groups; 55.1% among transplant recipients, 50.05% among HIV/AIDS, and 45.06% among cancer patients [14]. Also, a recent study reported an anti-*Toxoplasma* IgG seroprevalence of 27.7% among hemodialysis patients [15]; Another registered 41.51% among cancer patients in Iran [11]. Similarly, systematic review and meta-analysis estimated a prevalence rate (41%) among Iranian pregnant women [16]. Reports from other parts of the world revealed disparate IgG seroprevalence rates among particular groups; 20% among cancer patients from Egypt [12]; 87.4% among HIV-positive individuals in Ethiopia [17]; and 13% among non-stem cell transplant patients with hematological malignancies in India [18]. Although there is limited evidence to link gender and age to toxoplasmosis, studies have shown that heterogeneity between study groups; methods used for diagnosis; different sample sizes; environmental factors such as temperature, rainfall, and altitude; lifestyle and personal hygiene can influence toxoplasmosis seroprevalence. These factors could explain the discrepancies in the above reported local and international prevalence rates.

In the current study, we found the seroprevalence of anti-*T. gondii* IgG in patients with white blood cell (WBC) disorders (17.82%) higher than in patients with red blood cell disorders (11.57%), patients with cancers (7.09%), and the healthy control (11.17%). White blood cell (leukocyte) disorders probably contribute to the development of toxoplasmosis or may have an association with *T.gondii* infection – further studies need to prove that. Apart from the disturbed immune system, patients with WBC malignancy (leukemia) are prone to multiple blood/blood product transfusion, which increases the risk of transmission of toxoplasmosis. Previous studies demonstrated the possibility of transmission of toxoplasmosis by leukocyte transfusion from donors with elevated anti-*T.gondii* antibody titers [19]. Recently, several reports indicated that leukemic patients are at increased risk of acute toxoplasmosis from reactivation of latent infection [20-22]. Moreover, an evidence-based meta-analysis showed that *T. gondii* infection might be associated with increased leukemia risk among Chines population (OR=3.05; 95%CI=1.83–5.08) [23]. Besides, another case-control study evaluated serum anti-*Toxoplasma* IgG-positive children with blood cancers and demonstrated a possible link between toxoplasmosis and an increased risk of childhood hematologic malignancies in Iran [24].Red blood cell disorders predispose individuals to opportunistic infections. Hemoglobinopathies are classical types of Red blood cell disorders. Apart from the increased risks of transfusion-related toxoplasmosis, patients with sickle cell anemia and other severe forms of beta-thalassemia carried higher risks of hemolysis, splenectomy, and recurrent vasoocclusive events which disturb their immune balance and expose them to other opportunistic infections - toxoplasmosis inclusive [25]. The Iranian population is extremely heterogeneous due to the presence of many multiethnic groups - the frequencies and severity of red blood cell disorders also differ among groups. However, Mediterranean thalassemia has the highest frequency in most parts of the country [26]. In a hospital-based study, β-thalassemia accounts

for 53.1% of hemoglobinopathies seen at hematologic clinics in Kermanshah Province, Western Iran [27]. In the current study, the seroprevalence of anti-*T. gondii* IgG in patients with red blood cell disorders was 11.57%. Moghimi et al. investigated 250 participants in Yazd province, Iran, and reported 16% as the seroprevalence of anti-*T. gondii* IgG among patients with thalassemia major [28]. Recently, a similar study (involving 235 thalassemia major patients and 235 healthy controls) from Shahrekord, west of Iran, reported a higher prevalence rate (51.9%) of anti-*Toxoplasma* IgG among thalassemia patient compared to (34.8%) the control group [29]. Internationally, studies that evaluated the serum anti-*Toxoplasma* antibodies reported prevalence rates of 53.6% for IgG and 23.2% for IgM among thalassemia children in Egypt [30]. Additionally, serum anti-*T.gondii* IgG was 16.8% among thalassemia patients in Iraq [31]; 19.4% among thalassemia major patients in Turkey [32]; and 43.5% among patients with sickle cell disease, 18.1% among patients with homozygous beta-thalassemia, and 50% among patients with heterozygous beta-thalassemia in Brazil [33]. Pertinent to our findings, in most of the studies, there is no significant difference between age or gender and the prevalence of serum antibodies but with a positive history of contact with cats.Fighting infections is an important challenge in cancer patients due to their weakened immune systems; opportunistic parasitic infections are the usual hallmarks of terminal cancer diseases. Many researchers dwelled their investigations to find any association between cancer diseases and *Toxoplasma gondii* infections. The seroprevalence and odds ratio of *Toxoplasma* infection among cancer patients worldwide was estimated at 30.8% and 3.1, respectively, using the random-effects model meta-analysis [34]. In a previous study, Arefkhah et al. reported the seroprevalence of *T. gondii* infection among cancer patients and hemodialysis patients as 13% and 27.7%, respectively, in southwest Iran, compared to 15.9% in healthy control [15]. In the current study, the overall prevalence rate of anti-*T. gondii* IgG among cancer patients was 7.11% which is lower than the rate reported in Iraq (49.0%), Turkey (63.0%), China (35.56%), and Egypt (20% for IgG and 4% for IgM,)[12,35-37]. Besides, our results showed the seroprevalence of anti-*Toxoplasma* IgG among patients with specific cancer types to be 5.51% for brain cancer; 3.39% for breast cancer; 0.79% each for colorectal cancer, liver cancer, and gastric cancer; 0% each for skin cancer, pancreatic cancer, testicular cancer, lung cancer, soft tissue sarcoma, esophageal cancer, and ovarian cancer. Similarly, serum anti-*Toxoplasma* IgG prevalence rates (among patients with specific cancers disease) higher than our findings were reported in Iraq: breast cancer (56.6%), rectal cancer (54.0%), thyroid cancer (44.6%), and leukemia cancer (36.0%) [36]; China: lung cancer patients (60.94%), cervical cancer patients (50%), brain cancer patients (42.31%), and endometrial cancer patients (41.67%)[37]; Egypt: (96.1%) breast cancer, (80%) squamous cell carcinoma of bone, (69.2%) brain tumor, (35%) liver tumor, (25%) bladder cancer, and (16.7%) [38]. The above discrepancies in rates may be linked to different geographical factors, eating habits, livestock handling practices, nature of their study conducted, and genetic susceptibilities of the study population.

CONCLUSIONS

The prevalence rate of anti-*Toxoplasma* IgG among patients with leukocytes disorders is high and significantly associated with contact with pets. We determine that pica and contact with pets have a significant association with *Toxoplasma* infection among patients with red blood cell disorders but not cancer patients. As such, minimal contact with animal pets can substantially minimize the rate of *Toxoplasma* infection among patients with blood disorders. It is pertinent to screen patients with cancers: particularly brain tumors, to rule out *Toxoplasma* infections.

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Compliance with Etical Standards

All stages of sampling of the participants in this study were performed according to the ethical protocols of the hospital and all individuals received written consent. In addition, it was emphasized that all patient information should be recorded confidentially.

ETHICAL CONSIDRATION

All the participants were provided with written informed consent by themselves or their guardians before any laboratory analysis or physical examination. A code was assigned for each of the patients and the data were kept totally confidential. The study protocol was approved by the Ethics Committee of zahedan University of Medical Sciences (reference number: IR.ZAUMS.REC . 1399.486).

Conflict of interest

The authors declare that they have no conflict of interest that affects this study.

Author's contribution

Study concept and design: Vahid Raissi. Collecting samples and preparing for experiment: Maryam Fasihi Karami, Mohammad Zareie, Zahra Babaei Samani. Analysis and interpretation of data:Gita Alizadeh, Omid Raiesi and Fatemeh Bayat. Drafting of the manuscript: Muhammad I. Getso and Soudabeh Etemadi.

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