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Association between *Toxoplasma gondii* exposure and paediatrics haematological malignancies: a case–control study

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Abstract

The possible association between *Toxoplasma gondii* infection and paediatric haematological malignancies in a group of patients and control subjects was evaluated in the present study. We performed an age-, gender- and residence frequency-matched case–control study of 101 blood cancer patients under 18 years of age, all of which were treated in Amirkola Pediatric Hospital. One hundred and thirty-eight control samples were gathered from the outpatient clinic in the hospital. All cases and controls were tested for the presence of anti-*Toxoplasma* IgG antibodies and then IgG-positive subjects were evaluated for IgM antibodies by enzyme-linked immunoassays. Anti-*T. gondii* IgG antibodies were found in 37 (36.6%) of the cases and 12 (8.7%) subjects in the control group (odds ratio 6.07, 95% confidence interval 2.963–12.437, $P < 0.0001$). The median and interquartile range (IQR) of IgG titre from case group (7.7 (IQR 0.25–13.5)) was higher than the control (0.2 (IQR 0.1–0.5)) ($P < 0.0001$). The frequency of anti-*T. gondii* antibodies (IgG) in lymphoblastic leukaemia (acute lymphoblastic leukaemia), Hodgkin's lymphoma and T–cell lymphoma were 33 (31.9%), 3 (50%) and 1(100%), respectively. Anti–*T. gondii* IgM was not detected in the IgG-positive patients in case group. In the case subjects, no significant difference was seen in the positive rates of *T. gondii* infection between genders (37.3% in male; 35.7% in female; $P = 0.52$) and ages groups ($P = 0.31$). This study demonstrated that *T. gondii* infection is prevalent in children with blood cancer. It also showed that toxoplasmosis may possibly be linked with an increased risk of childhood haematologic malignancies. Furthermore, these results may be helpful in research on blood neoplasia aetiology.

Introduction

Cancer is one of the most important causes of death worldwide. The total number of new cases of cancer has been reported about 14 million in 2012 and 8.8 million in 2015, respectively [1]. Furthermore, a report relies that approximately 300 000 cases of cancer are diagnosed in children and adolescents under the age of 19 years old every year and about 80 000 deaths per annum from the childhood cancer are estimated throughout the world [2]. The most common neoplasms in children are haematological malignancies, which represent about 45% of all newly diagnosed paediatric cancers [3]. In Iran, the incidence rate of haematological neoplasia is estimated as 661 per million in children under 14 years old and the most common cancer is leukaemia [4].

However, certain microbial infections have been identified as strong risk factors for specific cancers and there is a higher mortality rate among infection-related cancers, in comparison with other malignancies [5]. For example, the association between the *hepatitis C* virus and the development of different types of malignancies has been reported frequently [6]. There is also a link between parasite infections and cancers [7]. Furthermore, comparative epidemiological studies have suggested a connection between infectious agents and blood cancers in young individuals [8].

Toxoplasma gondii, an obligate intracellular coccidian parasite which is widely distributed in the world, is the most common parasitic infection in humans and all warm-blooded animals [9, 10]. Toxoplasmosis occur in humans through the ingestion tissue cysts via the undercooked meat of intermediate hosts and/or by the ingestion of water or food contaminated by oocysts from the definitive hosts [10, 11]. This infection is generally self-limiting due to efficient

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immune control, which limits the dissemination of the rapidly multiplying stage of the parasite. In contrast, it is life threatening in immunosuppressed patients [12]. Several studies have highlighted the fact that *T. gondii* infection may be associated with some specific malignancies such as brain tumours [13–16]. An ecological study demonstrated that the risk of brain cancer in humans increases in patients with *T. gondii* infection [17]. The parasite DNA was found in breast and lymph node tissues of the breast cancer patients [18] and also in lymphoma cells from patients with intraocular B-cell lymphoma [19]. Furthermore, a recent study showed a relatively high prevalence of acute and chronic toxoplasmosis in children with cancer in southwest of Iran, the results of which were obtained by serological and molecular techniques [20]. The mechanisms of how *T. gondii* initiates tumorigenesis are not clear. Latent infection of *T. gondii* may increase the host inflammation responses which boosts mutations and may affect the cancer development. Also like other intracellular pathogens, may disturb cellular barriers by oncogenic products gradually accumulating inside the cells [17]. More recent reports show that *T. gondii* can export its own miRNAs into host cell, which may affect the regulation of the hosts' gene expression, and therefore lead to the start cancer [21].

The possible link between *T. gondii* infection and blood cancer including leukaemia in children has not been well understood [21]. Therefore, the present study aimed to investigate the possible association between the *Toxoplasma* infection and haematological neoplasia, and associated risk factors in children and adolescents.

Methods and materials

Study design

In a case–control study format, seroprevalence and the associated risk factors of *T. gondii* infection were evaluated in 101 patients suffering from haematological neoplasms (case group) who were treated in the haematology–oncology ward of Amirkola Pediatric Hospital, Amirkola, Iran, and 138 children without any history of malignancy who were admitted to the outpatient clinic of the hospital were included in the study as a control group. The control subjects were frequency-matched with cancer patients by age, gender and residence. The current study was carried out from March 2016 to August 2017. All participants in both case and control groups were included in our study under the supervision of a paediatrician. Inclusion criteria for enrolment of cases were: (i) patients suffering from haematological malignancies in the affiliated Hospital of Babol University of Medical Sciences in Amirkola, Amirkola, Iran; (ii) aged under 18 years old; and (iii) who agreed to contribute in the study.

Ethical aspects

The purpose of this study was explained to the parents of each participant and they gave their written and informed consent. This work was approved by the ethical committee of Babol University of Medical Sciences, Babol, Iran (MUBABOL.REC. 1395.24).

Sample collection

Two millilitres of venous blood was taken from each participant and the serum was separated after clot formation by centrifugation at 2500 rpm for 5 min. The sera were collected in Eppendorf tubes and then transported in an icebox to Parasitology–Mycology Department, Faculty of Medicine, Babol University of Medical Sciences, where they were kept at −20 °C until tested.

Socio-demographic, clinical and behavioural data

Socio-demographic data including age, gender, residence and parents' education level were obtained for all patients using a questionnaire form. Clinical data explored in patients included the type of blood cancer and a history of blood transfusion. Behavioural data included consumption of raw/undercooked meat, eating of raw vegetables and fruit, exposure to soil and animal contact. These variables were selected based on the literature [1]. Data were obtained from the parents of the patients, physicians and medical examination records.

Serological analysis

First, the sera were evaluated for the presence of IgG antibodies against *T. gondii* by commercially available enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN, Germany) based on the manufacturer's instructions. Second, all IgG-positive serum samples were assessed for IgM antibodies to *T. gondii* using an ELISA kit (EUROIMMUN). The optical density of IgG and IgM antibody titres was read at 450 nm by an automatic ELISA reader and the results were interpreted according to the kit's guidelines. The negative samples had IgG titres of <8 IU/ml. A sera IgG titre higher than 11 IU/ml and between 8 and 11 IU/ml were considered positive and border line, respectively. The sensitivity and specificity of the test are 99.9% and 100%, in that order.

Statistical analysis

SPSS v. 22.0 software (SPSS Inc., Armonk, NY, USA) was used to analyse the results. Age values and IgG titre were reported as median values and interquartile ranges (IQRs), and were compared by Mann–Whitney *U* test. The association between the characteristics of the subjects and *T. gondii* infection was carried out by χ^2 test and Fisher's exact test. Odd ratios (OR) and 95% confidence intervals (CIs) were calculated by logistic regression and $P < 0.05$ was considered statistically significant. Furthermore, multivariable analyses were applied to evaluate the association between the features of the studied population and the *T. gondii* infection.

Results

The median and IQR of age among case and control groups were (6 (IQR 4–9)) and (5 (IQR 3–7)), respectively, indicating no significant difference between the two groups ($P = 0.154$). The demographic factors including age, gender and place of residence were frequency-matched between groups but the level of parents education was not matched. The demographic characteristics of the participants included in this study are shown in Table 1. These data showed that 81.2% of the cases reported a blood transfusion, while only 2.9% of the subjects in the control group reported a blood transfusion ($P < 0.0001$). Animal and soil contact were more prevalent in the control group than the case group ($P = 0.045$ and $P = 0.047$, respectively).

Anti-*T. gondii* antibodies (IgG) were detected in the sera of 37 out of 101 cancer patients, with an overall seroprevalence of

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Table 1. Socio-demographic characteristics and *Toxoplasma gondii* exposure among children with blood cancers and without any history of malignancy attending to Amirkola Children Hospital, Amirkola, Iran

Variable	Case (101)	Control (138)	OR	CI	*P*-value
Level of parents education					
High school graduated	65 (64.4)	61 (44.2)	0.439	0.259–0.744	0.002
Tertiary education	36 (35.6)	77 (55.8)			
Eating raw vegetables					
No and low	36 (35.6)	32 (23.2)	0.545	0.309–0.961	0.036
Medium and high	65 (64.4)	106 (76.8)			
Eating undercooked meat					
Yes	30 (29.7)	52 (37.7)	1.431	0.827–2.476	0.217
No	71 (70.3)	86 (62.3)			
Blood transfusion					
Yes	82 (81.2)	4 (2.9)	0.007	0.002–0.021	0.0001
No	19 (18.8)	134 (97.1)			
Animal contact					
Yes	10 (9.9)	27 (19.6)	2.214	1.018–4.813	0.045
No	91 (90.1)	111 (80.4)			
Soil contact					
Yes	27 (26.7)	54 (39.1)	1.762	1.009–3.078	0.047
No	74 (73.3)	84 (60.9)			
T. gondii exposure					
Yes	37 (36.7)	12 (8.7)	6.07	2.963–12.437	0.0001
No	64 (63.3)	126 (91.3)			
Median and IQRs of IgG titre	7.7 (0.25–13.5)	0.2 (0.1–0.5)	–	–	0.0001

36.6%. Twelve out of 138 (8.7%) cases in the control group were positive for anti-*T. gondii* antibodies (IgG). This difference was statistically significant and showed that the chance of haematological malignancies was higher in seropositive cases (OR 6.07, 95% CI 2.963–12.437, $P < 0.0001$). The median and IQR of IgG titre from the case group (7.7 (IQR 0.25–13.5)) was higher than the control (0.2 (IQR 0.1–0.5)) ($P < 0.0001$) (Table 1).

The frequencies of IgG antibodies against *T. gondii* and the associated risk factors among case and control groups are presented in Table 2. Among the case group, the frequency of IgG antibodies against *T. gondii* had a higher rate in patients aged under 4 years and those living in rural areas. Statistical analysis using χ^2 test showed that no significant difference was observed between the presence of anti-*T. gondii* antibodies and behavioural and demographic characteristics among the case and control groups.

Our findings showed that toxoplasmosis was more prevalent in patients with a history of blood transfusion than cases without a history of blood and/or blood product transfusion. The results of the single variable analysis showed that toxoplasmosis was more prevalent in patients with a history of blood transfusion than cases without a history of blood and/or blood product transfusion (OR 4.74, 95% CI 2.43–9.24, $P < 0.0001$) and also in patients with cancer (OR 6.07, 95% CI 2.97–12.44, $P < 0.0001$). In the multivariable analysis, only cancer was significantly related to toxoplasma infection (OR 4.57, 95% CI 1.46–14.31, $P = 0.009$). None of the behavioural characteristics and demographic data were significant (Table 3).

The frequency of anti-*T. gondii* antibodies (IgG) in lymphoblastic leukaemia (acute lymphoblastic leukaemia), Hodgkin's lymphoma and T-cell lymphoma was 33 (31.9%), 3 (50%) and 1 (100%), in that order (Table 4).

Anti-*T. gondii* IgM was not detected in IgG-positive patients in the case group. In the control group, the frequency of positive and borderline IgM antibodies against *T. gondii* were 1 (8.3%) and 3 (25%), respectively.

Discussion

The potential association between parasitic protozoan infections and cancer has been documented by clinical and epidemiological investigations [8]. The Apicomplexan parasite, *T. gondii* is considered to be associated with ocular tumours, meningioma, leukaemia and lymphoma [8, 13, 14]. In this frequency-matched case–control study, the results showed a higher seroprevalence rate of anti-*T. gondii* IgG antibodies in patients with haematological neoplasms under 18 years of age (36.6%) in comparison with the control subjects (8.7%), with a statistically significant difference ($P < 0.0001$). The possible explanations are: (1) patients with cancer are more sensitive to this parasite because they are immunocompromised and *T. gondii* is the most common protozoan parasite causing opportunistic infections in

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Table 2. Seroprevalence and encountering particular risk factors of *Toxoplasma* infection in 101 patients with haematological malignancies and 138 individuals without cancer

	T. gondii infection in cases (101)			*T. gondii* infection in controls(138)			Total		
Variable	No. tested	*N* (%)	*P*-value	No. tested	*N* (%)	*P*-value	No. tested	*N* (%)	*P*-value
Age									
<4	37	17 (45.9)	0.307	56	6 (10.7)	0.517	93	23 (24.7)	0.410
4–10	49	16 (32.7)		67	4 (6.0)		116	20 (17.2)	
>10	15	4 (26.7)		15	2 (13.3)		30	6 (20)	
Gender									
Male	59	22 (37.3)	0.520	75	8 (10.7)	0.279	134	30 (22.4)	0.519
Female	42	15 (35.7)		63	4 (6.6)		105	19 (18.1)	
Residency									
Urban	60	20 (30.3)	0.266	81	5 (6.2)	0.172	141	25 (17.8)	0.254
Rural	41	17 (41.5)		57	7 (12.2)		98	24 (24.5)	
Level of parents education									
High school	88	29 (32.9)	0.048	61	7 (11.4)	0.233	149	36 (24.2)	0.339
Tertiary education	13	8 (61.5)		77	5 (6.5)		90	13 (14.4)	
Eating undercooked meat									
Yes	30	9 (30.0)	0.252	52	6 (11.5)	0.267	82	15 (18.3)	0.614
No	71	28 (39.4)		86	6 (7)		157	34 (21.7)	
Eating raw vegetables									
Yes	36	11 (30.6)	0.234	32	2 (6.3)	0.442	68	13 (19.1)	0.859
No	65	26 (40)		106	10 (9.4)		171	36 (21.1)	
Blood transfusion									
Yes	82	32 (39.0)	0.222	4	0 (0.00)	0.692	86	32 (37.2)	0.0001
No	19	5 (26.3)		134	12 (9.0)		153	17 (11.1)	
Animal contact									
Yes	10	5 (50.0)	0.277	27	3 (11.1)	0.428	37	8 (21.6)	0.827
No	91	39 (42.9)		111	9 (8.1)		192	48 (25)	
Soil contact									
Yes	27	8 (29.6)	0.260	54	6 (11.1)	0.305	81	14 (17.3)	0.403
No	74	29 (39.2)		84	6 (7.1)		158	35 (22.2)	

Statistical analysis was performed by χ^2 test.

immunocompromised individuals [22] and/or (2) possible role of this parasite in the induction of cancer in humans. Although, the mechanisms underlying the association between cancer and toxoplasmosis are not clearly understood, but T-cell exhaustion phenomenon may affect the inability of the host to control intracellular pathogen infections or tumours [23]. There is evidence that *T. gondii* is able to increase the motility of the host's dendritic cells and macrophages, which may affect both the spread of parasites and progression of tumorous diseases [24]. Furthermore, *T. gondii* may manipulate gene expression in the host cell by miRNAs and thus could cause cancer onset [21]. However, toxoplasmosis has frequently been described to be linked with some particular neoplasms such as acute and chronic leukaemias, lymphoma or multiple myeloma [13, 25]. Also, other cancer patients with solid tumours in the breast, ovary and lung, who were under chemotherapy, have been associated with toxoplasmosis [13, 26].

In relation to the socio-demographic features of the patients, the seroprevalence of *T. gondii* was only significantly associated with the level of education of the parents ($P = 0.05$), and there was no significant association between other socio-demographic data and toxoplasmosis. These findings are supported by the results obtained from a recent study where no significant relationship exist between *Toxoplasma* seroprevalence and demographic characteristics in cancer patients [16, 27]. However, our findings are in contrast with the documented data indicating that the seropositivity rate of *T. gondii* is related to age and place of residence [28–30]. Further studies with large sample sizes in different areas and along with molecular techniques should be developed to confirm this association and explore the potential molecular

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Table 3. The logistic regression analysis for the factors that influence *Toxoplasma* infection in cancer patients compared with control subjects

	Single variable analysis			Multivariable analysis		
Factors	OR	CI 95%	*P*-value	OR	CI 95%	*P*-value
Cancer						
Yes	6.07	2.963–12.437	0.0001	4.566	1.457–14.306	0.009
No						
Age						
<4	1.31	0.478–3.612	0.185	1.84	0.243–1.139	0.288
4–10	0.83	0.302–2.302	0.725	0.97	0.176–1.675	0.956
>10						
Gender						
Male	1.31	0.687–2.480	0.415	1.35	0.650–2.801	0.422
Female						
Residency						
Urban	1.51	0.800–2.830	0.205	1.77	0.810–3.887	0.152
Rural						
Level of parents education						
High school	0.72	0.381–1.360	0.311	1.12	0.519–2.429	0.769
Tertiary education						
Eating undercooked meat						
Yes	1.24	0.628–2.429	0.541	1.18	0.536–2.591	0.683
No						
Eating raw vegetables						
Yes	1.3	0.556–2.289	0.738	1.53	0.682–3.430	0.303
No						
Blood transfusion						
Yes	4.74	2.432–9.240	0.0001	1.81	0.588–5.543	0.302
No						
Animal contact						
Yes	0.92	0.393–2.170	0.854	0.55	0.192–1.583	0.268
No						
Soil contact						
Yes	1.36	0.685–2.708	0.379	1.29	0.566–2.953	0.542
No						

Table 4. The rates of seropositivity of anti-*T. gondii* antibodies (IgG) in different haematological cancer paediatric

Types of blood cancer	Number of patients	Seropositive IgG* *N* (%)	Mean (s.d.) IgG titre**
Acute lymphoblastic leukaemia (ALL)	94	33 (35.1)	25.1 ± 63.3
Hodgkin's lymphoma	6	3 (50)	39.4 ± 76.8
T-cell lymphoma	1	1 (100)	12.9

*$\chi^2 = 1.27$, $P = 0.59$; **df = 100, $P = 0.85$

mechanisms. Regarding the behavioural characteristics of patients, the present study showed that soil exposure, animal contact, consumption of raw vegetables and raw/undercooked meat were not associated with the seroprevalence of *T. gondii* in both studied groups. These findings are not in line with some previous studies and indicated that consumption of raw/undercooked meat, contact with cats, contact with soil and consumption of raw vegetables are important risk factors for *T. gondii* infection in humans [28, 31]. The possible explanation for these differences could be related to dietary habits of the population surveyed as they were under 18 years of age and tend to eat less raw meat or vegetables compared with adults.

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Then again, in this study, there was a higher seroprevalence rate of anti-*T. gondii* IgG antibodies in patients with a history of blood transfusion (39% *vs.*26.3%), but this difference was not statistically significant in the patient group ($P = 0.22$). Nevertheless, with respect to blood transfusion history, the different prevalence of anti-*T. gondii* antibodies between the patient group and the control group was statistically significant (OR 4.74, 95% CI 2.432–9.240, $P < 0.0001$), suggesting that blood transfusion may be a major risk factor for *T. gondii* infection in childhood haematological malignancies. It has been reported that the seropositivity of *T. gondii* is related to the positive history of blood transfusion in cancer patients [30, 32].

In a study, by Ghasemian *et al.*, it was reported that the seroprevalence of anti-*T. gondii* antibodies in haematologic cancer patients was much higher than individuals with different types of malignancies under 20 years of age in Ahvaz, southern Iran [33]. This is associated with many factors, such as types of study patients, local customs and habits. Based on our best knowledge, there is a very little information about toxoplasmosis in childhood cancers, particularly haematological malignancies. However, in this study, physical examination of the cancer patients did not find any manifestations of acute *Toxoplasma* infection due to reactivation of the parasite or recent infection. Since clinical symptoms of toxoplasmosis are often non-specific, this infection is often overlooked in the process of clinical diagnosis and treatment [34]. Nevertheless, in immunosuppressed patients, undetected *T. gondii* infection may result in severe toxoplasmosis, and therefore, cancer patients should be periodically evaluated for this infection to prevent the possibility of severe toxoplasmosis [35].

In conclusion, the present study demonstrated that *T. gondii* infection is prevalent in children and adolescents with haematological malignancies in the north of Iran. It also indicated that toxoplasmosis might have an association with an increased risk of paediatric blood cancers. Therefore, clinicians should take more care of immunosuppressed patients, particularly cancer patients, and the parasitological investigations of these patients should be regularly performed to prevent the possibility of severe toxoplasmosis. Furthermore, these results may be helpful in the research on blood neoplasia aetiology.

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