Toxoplasma gondii seropositivity among Egyptian children with haematological malignancies

Original Article

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ABSTRACT

Background: Toxoplasmosis is caused by *T. gondii* leading to severe complications in immunocompromised patients.
Objective: The present case-control study aims at determining *T. gondii* seroprevalence among children with haematological malignancies.
Subjects and Methods: A total of 320 children were included (160 children with different types of haematological malignancies, and 160 matched controls). Anti-*T. gondii* IgM and IgG antibodies were assessed in sera from all participants using ELISA. Data included socio-demographic characteristics, predisposing factors for toxoplasmosis, and recorded type of haematological malignancy.
Results: All the recruited children were seronegative for anti-*T. gondii* IgM antibodies. The seroprevalence of anti-*T. gondii* IgG antibody in cancer patients and controls was 62.5% and 20%, respectively. Besides, children with haematological malignancies had significantly higher levels of anti-*T. gondii* IgG antibody, with the highest antibody seroprevalence rate and titer detected in children with lymphoblastic lymphoma (LL) and Burkitt's lymphoma (BL), respectively. Age ≥ 8 years, female gender, rural residence, low socio-economic standard, blood transfusion, and toxoplasmosis in other family members were recorded as significant risk factors for toxoplasmosis.
Conclusion: The high prevalence of anti-*T. gondii* IgG antibody in children with haematological malignancies necessitates routine screening for toxoplasmosis, to avoid development of severe and disseminated disease.

Keywords: children; Egypt; ELISA; leukaemia; lymphoma; risk factors; seroprevalence; *T. gondii*.

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INTRODUCTION

Childhood cancer afflicts about 400,000 children and adolescents (0-19 years old) across the world[1]. Leukaemias (34.1%) rank first to brain and nervous system tumours (18.1%), in the global burden of childhood cancer disability-adjusted life years (DALYs). Approximately, more than 90% of children who develop cancer inhabit low- and middle-income countries[2]. In Egypt, a retrospective observational cohort study conducted on a total of 15,997 children and adolescents with cancer (age 0-18 years) revealed that the youngest age group (0-4 years) was the most affected (48% of children with cancer). Solid tumours and haematological malignancies represented 59% and 41%, respectively. The most predominant cancer types were leukaemias, lymphomas, CNS tumors, and neuroblastoma[3].

Parasites were recognized as strong risk factors for certain types of cancers, such as *S. haematobium* and urinary bladder carcinoma[4], *P. falciparum* and BL[5], as well as *C. sinensis* and cholangiocarcinoma[6]. Besides, the apicomplexan *T. gondii* was linked to several types of malignancy such as leukaemias, lymphomas, myelomas, gliomas, meningiomas, neuroblastomas, breast and ovarian tumours, and lung cancer[7].

Toxoplasmosis, caused by an obligate intracellular protozoon capable of infecting a broad range of hosts, was estimated to affect populations with high risk factors in different locations; and the highest rates of infection were reported in areas with lower altitudes and humid hot climates[8]. Horizontal transmission is mostly caused by ingestion of tissue cysts in infected meat, or through consumption of food or drink contaminated with sporulated oocysts, while vertical transmission occurs due to primary acquired maternal infection throughout pregnancy[8-10].

In immunocompetent hosts, acquired infection is asymptomatic in more than 80% of cases, or is associated with fever, cervical lymphadenopathy, or myalgia. In contrast, in immunocompromised patients, toxoplasmosis is always life-threatening where toxoplasmic encephalitis is the most important presentation[11,12]. Among those patients, the disease may be caused by a newly acquired infection, reactivation following cyst rupture, donation of a cyst-containing organ from a seropositive donor to a seronegative recipient, or reactivation of dormant infection in the recipient[13-15].

It is established that toxoplasmosis elicits a powerful protective T helper 1 (Th1) immune

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response, which stimulates interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) production by T-lymphocytes. This cell-mediated immune response shields the host against pathological lesions and prevents tachyzoite multiplication[16], while humoral immune response prevents reinfection with the parasite[17]. Being an opportunistic parasite, *T. gondii* represents a critical health problem in cancer patients since treatment with anti-tumor agents can predispose patients to the reactivation of quiescent toxoplasmosis[18].

Diagnosis of *T. gondii* in immunocompromised patients is of extreme importance, because infection can be lethal or result in dissemination. Thus, we ran this study to assess the prevalence of toxoplasmosis in Egyptian children with haematological malignancies, through detection of anti-*T. gondii* IgM and IgG antibodies in serum using ELISA, and to reveal any association between toxoplasmosis and demographics as well as lifestyle parameters.

SUBJECTS AND METHODS

This case-control study was conducted at Medical Parasitology Department, Faculty of Medicine, and Pediatric Oncology Unit, Oncology Center, Mansoura University Hospital over a period of one year (August 2021-2022).

Study design: The current study is an observational analytical study, where the exposure (acquiring toxoplasmosis) was assessed after the outcome (development of haematological malignancy). Evaluation was based on measurement of the serological IgM and IgG antibody response by ELISA, in view of the socio-demographic characteristics.

Study target population: The study was carried out on 172 males and 148 females, aged 8 months-17 years, divided into two groups. Group I included 160 children suffering from haematological malignancies (leukaemia and lymphoma). Group II included 160 age-, sex- and residence-matched apparently healthy children who were recruited from health screenings at the hospital. Exclusion criteria included children who 1) had haematological malignancies related to HIV infection, 2) were subjected to bone marrow transplant procedure, 3) had received immunotherapy before blood sampling, and 4) had other types of malignancy.

Collected data included socio-demographic characteristics such as age, sex, residence, and socio-economic standard. Predisposing factors for toxoplasmosis as contact with cats, dogs or farm animals, exposure to soil, consumption of raw milk or meat, unwashed fruits or vegetables, lack of hand hygiene behaviour, history of maternal toxoplasmosis, affection of other family members, and blood transfusion or long term oral steroid use, were also registered. The underlying type of haematological malignancy was recorded.

Assessment of *T. gondii* IgM and IgG antibodies using ELISA[19]: Two ml of venous blood were collected from each participant enrolled in the study, allowed to clot, and centrifuged for 10 min at 3000 rpm. Sera were transferred to clean eppendorf tubes and stored at -20°C. All samples were thawed at room temperature before use for detection of anti-*T. gondii* IgM and IgG. Commercially available ELISA kits: Toxo (*Toxoplasma* Antibody) IgM ELISA kit (Prechek Bio Inc., Korea), and Elecsys® Toxo IgG (Roche Diagnostics, Switzerland), were used. The optical density values of IgM and IgG antibody titres were read using an automatic ELISA reader at 450 nm, and the results were interpreted according to the manufacturer's guidelines.

Statistical analysis: Data were recorded and analyzed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent, while quantitative data were described using median, minimum, and maximum for non-parametric data, and mean and standard deviation for parametric data. After testing normality using Kolmogrov-Smirnov test, qualitative data were analyzed using Chi-Square test for comparing two or more groups, and Monte Carlo test as correction for Chi-Square test when more than 25% of cells had a count less than five in tables (> 2*2). Quantitative data were analyzed using Student's *t*, and Mann-Whitney U tests to compare two independent groups for parametric data, and non-parametric test, respectively. Significance of the obtained results was judged at the 0.05 level. For prediction of independent variables of binary outcome, binary stepwise logistic regression analysis was used. Significant predictors in the univariate analysis were entered into a regression model using forward Wald method. Adjusted odds ratios and their 95% confidence interval were calculated.

Ethical consideration: The enrollment of human cases and use of their data and samples in the study were in accordance with the guidance of the Committee of Research Ethics, Mansoura Faculty of Medicine-Institutional Research Board (MFM-IRB, R.18.03.105). Informed written consent was obtained from parents or guardian after assuring confidentiality. *Toxoplasma*-seropositive children were referred to the physician for treatment of toxoplasmosis.

RESULTS

Characteristics of the study participants: Children group with haematological malignancies included a gender-equal number of 80 with a mean age of 7.13± 4.77 years. The control group involved 92 males (57.5%) and 68 females (42.5%), with a mean age

of 6.29±3.17. No significant difference was detected between both groups (*P*=0.178 and 0.07, respectively).

Anti-*T. gondii* antibody assay: Seroprevalence of specific IgG antibody was significantly higher (*P*<0.001) in children with haematological malignancies (100/160; 62.5%) than in controls (32/160; 20%, with odds ratio (OR) = 6.67; 95% CI: 4.03-11.02). Moreover, the level of specific IgG antibody (median=38.0; 0.10-650.0) was significantly higher (*P*=0.01) in children with haematological malignancies, compared to their matched controls (median=0.166; 0.10-220.0) (Table 1). Sera from both studied groups were negative for specific IgM antibody.

Analysis of socio-demographic characteristics and risk factors in relation to anti-*T. gondii* IgG antibody seropositivity: The socio-demographic characteristics and risk factors of the recruited children and their correlation with *T. gondii* IgG seroprevalence are presented in table (2). A significantly higher seroprevalence of specific IgG was found in females

Table 1. Seropositivity of anti-*T. gondii* IgG antibody in the studied groups.

	Group I (No=160)	Group II (No=160)	Statistical analysis	
	No. (%)	No. (%)	*P* value	Odds ratio (95% CI)
***T. gondii* IgG serology**				
Positive	100 (62.5)	32 (20)	X^2=59.63	6.67 (4.03-11.02)
Negative (r)	60 (37.5)	128 (80)	*P* < 0.001*	
***T. gondii* IgG ELISA titre**				
Median	38.0	0.166	Z=2.56	
Minimum-maximum	0.10-650.0	0.10-220.0	*P* = 0.01*	

Group I: Children with haematological malignancy; **Group II:** Control children; **r:** Reference group, X^2: Chi-Square test, **Z:** Mann Whitney U test; ***:** Significant (*P*<0.05).

Table 2. Analysis of socio-demographic data and risk factors in relation to anti-*T. gondii* IgG seropositivity in the studied groups.

	Group I (No=160)				Group II (No=160)			
	No.	IgG N (%)	*P*	Odds ratio (95% CI)	No.	IgG N (%)	*P*	Odds ratio (95% CI)
Age groups (Y)								
< 8 y	104	64 (61.5)	0.732	1.125	116	85 (73.3)	**<0.001***	13.2
≥ 8 y	56	36 (64.3)		(0.57-2.21)	44	43 (97.7)		(3.87-110)
Sex								
Male	80	44 (55)	**0.05***	1.91	92	76 (82.6)	0.424	0.684
Female (r)	80	56 (70)		(0.99-3.65)	68	52 (76.5)		(0.31-1.49)
Residence								
Urban (r)	98	54 (55.1)	**0.015***	2.34	85	66 (77.6)	0.428	1.37
Rural	62	46 (74.2)		(1.17-4.69)	75	62 (82.7)		(0.63-3.01)
SES								
Low	95	71 (74.7)	**<0.001***	4.26 (2.14-8.48)	84	68 (81)	0.327	0.80 (0.36-1.70)
Intermediate (r)	61	25 (41)		1	69	53 (76.8)		
High	4	4 (100)		Undefined	7	7 (100)		
Cats at household	36	24 (66.7)	0.56	1.26 (0.58-2.76)	0			
Dogs at home	32	20 (62.5)	1.0	1.0 (0.46-2.23)	0			
Contact with farm animals	128	84 (65.6)	0.102	1.91 (0.87-4.18)	56	4 (7.1)	**0.003***	0.21 (0.07-0.63)
Exposure to soil	64	40 (62.5)	1.0	1.0 (0.52-1.92)	4	0	0.585	
Consumption of raw milk	8	4 (50)	0.474	0.58 (0.14-2.42)	0			
Consumption of raw meat	36	16 (44.4)	**0.018***	0.38 (0.18-0.81)	0			
Consumption of unwashed raw vegetables or fruits	32	20 (62.5)	1.0	1.0 (0.45-2.23)	0			
Lack of hand hygiene behaviour	68	40 (58.8)	0.409	0.76 (0.40-1.45)	144	28 (19.4)	0.598	0.72 (0.22-2.42)
Blood transfusion	36	36 (100)	**<0.001***		0			
Maternal toxoplasmosis	20	16 (80)	0.08	2.67 (0.85-8.39)	0			
Toxoplasmosis in other family member	8	8 (100)	**0.02***		0			
Long term oral steroid use	12	8 (66.7)	1.0	1.21 (0.35-4.23)	0			

Group I: Children with haematological malignancy; **Group II:** Control children; **No.:** Number examined; **N:** Number positive; **r:** Reference group, **SES:** Socio-economic standard; **Test of significance:** Chi-Square test; ***:** Significant (*P*<0.05).

and children living in rural areas and those having low socio-economic standard in group with haematological malignancy, and in age group ≥ 8 years in the control group. In haematological malignancy group, 100% of patients who had history of blood transfusion or presence of toxoplasmosis in other family members were seropositive for specific IgG antibody.

Clinical findings and seroprevalence of anti-*T. gondii* IgG antibody in children with hematological malignancies: Table (3) shows the clinical presentations and their relation to the seroprevalence of chronic toxoplasmosis. A statistically significant association was detected between specific IgG seroprevalence and lymphadenopathy as well as anaemia (P<0.001 and =0.02, respectively); while no significant association was found with hepatomegaly, splenomegaly, or fever.

Types of haematological malignancies and seroprevalence of anti-*T. gondii* IgG antibody: Whereas children with T-cell ALL (T-ALL) had the lowest specific IgG seroprevalence (12/32; 37.5%), the highest specific IgG seropositivity was found in children with LL (20/20; 100%), followed by BL (20/24; 83.3%), and precursor B-cell ALL (pre-BALL) (48/84; 57.1%), (Table 4). In addition, the highest titre of specific IgG antibody was found in children with BL (median=67.50; 0.10-560.0) and LL (median=42; 38-650.0).

Multivariate regression analysis: In control children, multivariate regression analysis showed that age ≥ 8 years (OR 22.75, 95% CI 2.95-175.12, P=0.001) was significantly associated with toxoplasmosis (Table 5).

Table 3. Clinical findings and seroprevalence of anti-*T. gondii* IgG antibody in the selected children with haematological malignancies.

	No.	*T. gondii* IgG		*P* value	Odds ratio (95% CI)
		Seropositive N (%)	Seronegative N (%)		
Lymphadenopathy					
Positive	44	8 (18.2)	36 (81.8)	**<0.001***	0.06 (0.02-0.14)
Negative	116	92 (79.3)	24 (20.7)		
Hepatomegaly					
Positive	108	72 (66.7)	36 (33.3)	0.117	1.71 (0.87-3.37)
Negative	52	28 (53.8)	24 (46.2)		
Splenomegaly					
Positive	100	64 (64)	36 (36)	0.618	1.18 (0.61-2.29)
Negative	60	36 (60)	24 (40)		
Fever					
Positive	116	76 (65.5)	40 (34.5)	0.201	1.58 (0.78-3.21)
Negative	44	24 (54.5)	20 (45.5)		
Anaemia					
Positive	100	56 (56)	44 (44)	**<0.02***	0.46 (0.23-0.93)
Negative	60	44 (73.3)	16 (26.7)		

Group I: Children with haematological malignancy; **Group II:** Control children; **No.:** Number examined; **N:** Number positive; **r:** Reference group, **Test of significance:** Chi-Square test; ***:** Significant (P<0.05).

Table 4. Types of haematological malignancies and seroprevalence of anti-*T. gondii* IgG antibody in the selected Egyptian children.

Type of hematological malignancy	No.	*T. gondii* IgG seroprevalence				*T. gondii* IgG ELISA titre	
		Positive N (%)	Negative N (%)	*P* value	Odds ratio (95% CI)	Median (Min-Max)	*P* value
ALL	116	60 (51.7)	56 (48.3)				
T-ALL	32	12 (37.5)	20 (62.5)	**0.001***	0.28 (0.12-0.61)	0.125 (0.10-77)	
Pre-BALL	84	48 (57.1)	36 (42.9)	0.14	0.62 (0.32-1.18)	32 (0.10-650)	
NHL	44	40 (91)	4 (9)				**<0.001***
BL	24	20 (83.3)	4 (16.7)	**0.02***	3.5 (1.13-10.79)	67.50 (0.10-560)	
LL	20	20 (100)	0	**0.002***		42 (38-650)	

ALL: Acute lymphoblastic leukaemia; **T-ALL:** T-cell acute lymphoblastic leukaemia; **Pre-BALL:** Precursor B-cell acute lymphoblastic leukaemia; **NHL:** Non-Hodgkin lymphoma; **BL:** Burkitt's lymphoma; **LL:** Lymphoblastic lymphoma; **N:** Number positive; **Test of significance:** Chi-Square test; ***:** Significant (P<0.05).

Table 5. Multivariate regression analysis for independent predictors of positive *T. gondii* IgG serology in the control group.

	Independent predictors	*P* value	Odds ratio (95% CI)
Control children (No.=160)	**Age** **<8 (r)** **≥8**	**0.003***	22.75 (2.95-175.12)

(r): Reference group; ***:** Significant (P<0.05).

DISCUSSION

The intracellular apicomplexan, *T. gondii*, is responsible for the neglected tropical disease toxoplasmosis[20]. About two thirds of the world population are infected with *T. gondii*[8]. High *Toxoplasma* seroprevalence has been documented in patients with variable cancer types[7].

Undiagnosed toxoplasmosis in cancer patients can result in severe toxoplasmosis[21]. Consequently, those patients should be periodically screened for toxoplasmosis. To the best of our knowledge, this is the first study investigating *T. gondii* seropositivity in a sample of children suffering from haematological malignancies in Egypt and highlighting the possible risk factors for toxoplasmosis in this cohort of children.

The immune response associated with malignancy and its specific treatment becomes compromised predisposing the affected children to opportunistic infections[22]. In our study the significantly higher IgG seropositivity in children with haematological malignancies can be attributed to their higher susceptibility to acquiring toxoplasmosis, or due to reactivation of a dormant infection. The high prevalence is the result of a suppressed cellular immunity, owing to bone marrow affection[23,24] and the use of immunosuppressant therapy and steroids in the treatment regimens[25]. Immunosuppressed patients are more susceptible to reactivation of latent toxoplasmosis because of the opportunistic nature of *T. gondii*[26]. Our study recorded the significant 100% association of specific anti-*Toxoplasma* IgG positivity with LL, 83.3%, with BL, and 57.1% with precursor B-cell ALL (pre-BALL). In accordance, Huang *et al*.[27] suggested that toxoplasmosis could be considered as a risk factor for the development of cancer.

Concerning the age of children in our study, comparison of insignificant specific IgG seroprevalence in group I children with malignancies who are < 8 years old, with the significant seroprevalence in group II children of the same age may be attributed to the competent immune system response of the latter group of children to exposure to sources of infection[28].

The recorded higher seroprevalence in children residing in rural areas or those with low socio-economic standard could be attributed to poor educational attainment. Education is expected to lower the risk of exposure to sources of infection owing to the implementation of hygienic practices, particularly those associated with food[29] and the use of untreated or treated (boiled and/or refined) water, contact with fresh water for recreation, and sanitation coverage[30,31].

It is well known that *Toxoplasma* transmission is closely associated with contact with cats, through ingestion of oocysts in contaminated soil, water, and food. Moreover, acquisition of infection has been linked to consumption of infected raw meat containing tissue cysts[8]. However, our findings showed no significant association between positive *T. gondii* IgG serology and contact with cats, dogs, or farm animals, exposure to soil, consumption of raw milk or meat, or unwashed raw vegetables or fruits, or poor hand hygiene. Similarly, two other studies[32,33] reported no significant association between *T. gondii* seroprevalence and the assessed risk factors in children with haematological malignancies. In contrast, Alvarado-Esquivel *et al*.[34] and Cong *et al*.[35] documented that exposure to soil, contact with cats, and consumption of improperly cooked meat are risk factors for toxoplasmosis in cancer patients. Diversity of published results could be attributed to different dietary habits and other lifestyle variables of the studied populations, as well as the assessment of different age groups exposed to variation in frequency of infection exposure.

In the current study, all patients with history of blood transfusion had positive anti-*T. gondii* IgG antibody, denoting that blood transfusion is a risk factor for transmission of toxoplasmosis[8]. Hence, vulnerable clinical groups as cancer patients are at a high risk for toxoplasmosis by the transfused blood. Similar findings were also archived by Kalantari *et al*.[32] and Zhou *et al*.[33]. Besides, the significant association between presence of toxoplasmosis in other family members and positive *T. gondii* serology in children with haematological cancers potentially points to food-related behaviours or common exposure to other sources of toxoplasmosis.

In China, lower *T. gondii* IgG seroprevalence of 19.1% was recorded by Duan *et al*.[36] in children with malignant lymphoma. Zhou *et al*.[33] also reported lower seropositivity of 14.2% for *T. gondii* IgG in children with leukaemia, and seroprevalence of 18.1% in children with ALL. These lower seroprevalence rates compared to ours can be explained by different climatic and environmental conditions, besides differences in habits across cultures. Higher prevalence rates are classically reported for tropical regions, while lower prevalence rates are recorded for colder regions[31]. In Iran, Kalantari *et al*.[32] assessed *T. gondii* seroprevalence in children and adolescents with hematological malignancies, and detected IgG seroprevalence of 36.6%. The authors also reported IgG seroprevalence of 31.9% in patients with ALL, which parallels our findings (37.5%).

Three studies from Egypt reported the seropositivity of *T. gondii* in adult patients with different types of malignancies. Ali *et al*.[37] conducted a case-control study on cancer patients receiving chemotherapy, and documented seropositivity of 5.8% and 40% for *Toxoplasma* IgM and IgG antibodies, respectively, in the subgroup of patients with haematological malignancies. On the other hand, Mostafa *et al*.[38] reported seropositivity of 12.5% for

T. gondii IgG in patients with lymphoma, and Abdel Malek *et al*.[39] documented seropositivity of 12% for *Toxoplasma* IgG in patients with haematological origin tumours (leukaemias, lymphomas, or multiple myelomas) treated with chemotherapy. These differences can be attributed to lower number of patients in the studied subgroups. Higher *T. gondii* IgG seropositivity of 48.21% was documented by Kholib-Jati *et al*.[40] in patients with lymphoma, leukaemia, and multiple myeloma. This discrepancy can be explained by different climatic conditions. As with our results, Mostafa *et al*.[38] and Abdel Malek *et al*.[39] also reported IgM 0% seroprevalence.

Several theories have been postulated for the association between toxoplasmosis and malignancy as prevention of apoptosis[41], T-cell exhaustion phenomenon which interferes with the host ability to deal with intracellular pathogens or tumours[42], enhancement of the motility of dendritic cells and macrophages essential for limiting the spread of parasites and tumours[43], induction of cancer through alteration of gene expression in the host cell by microRNAs[27], and accumulation of oncogenic mutations as a result of disturbed traditional cell barriers[44].

The limitations of the current study included: the small number of participants that resulted in some indecisive associations; the unavailability of therapeutic history (anti-cancer or anti-*Toxoplasma* medications); and lack of testing of sera for anti-*T. gondii* antibodies before blood transfusion.

In conclusion, our findings showing that toxoplasmosis is prevalent in children with haematological malignancies applies to the reported sample of children and should not be taken to represent Egypt as a whole. However, it revealed that more attention should be paid to cancer patients through periodic screening for toxoplasmosis to prevent severe infection and dissemination. Future studies are needed to determine the seroprevalence of toxoplasmosis in pediatric patients with other types of malignancy. Furthermore, the possibility of acquiring toxoplasmosis through blood transfusion should be considered. Therefore, blood should be routinely screened for anti-*T. gondii* antibodies before donation.

Author contribution: El-Beshbishi SN conceived the study. El-Beshbishi SN and ElBlihy AA designed the research work. ElBlihy AA carried out acquisition of data, and Abd Elmabood S performed the clinical assessment. ElBlihy AA and Alhusseiny SM conducted the laboratory investigations. El-Beshbishi SN, ElBlihy AA, and Alhusseiny SM conducted data analysis, and Abd Elmabood S assisted in interpretation of results. Alhusseiny SM drafted the manuscript, and El-Beshbishi SN critically revised the manuscript for intellectual content. All authors revised and approved the final manuscript.

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