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Original Article

Association between *Toxocara* Spp. Exposure and Schizophrenia: A Case-Control Study

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Abstract

Background: Toxocariasis is a zoonotic disease caused by the larvae of *Toxocara canis* or *Toxocara cati*. Patients with schizophrenia may be at higher risk of infection, possibly due to their cognitive and personal self-care impairments. We aimed to assess the association between *Toxocara* spp. exposure and schizophrenia.

Methods: This case-control study was conducted on 109 patients with schizophrenia admitted to Ibn Sina Hospital, Shiraz, Iran, and 104 age- and gender-matched healthy controls from May to September 2021. A questionnaire was obtained and serum samples were tested for IgG antibodies to *Toxocara* excretory/secretory (TES) antigens using an enzyme-linked immunosorbent assay (ELISA).

Results: Anti-*Toxocara* IgG was detected in 12 schizophrenic patients and 10 control subjects, giving respective seroprevalences of 11.0% (95% confidence interval [95% CI]=5.8–18.4%) and 9.6% (95% CI=4.7–17.0%). Univariate logistic analyses estimated an odds ratio (OR) of 1.16 (95% CI=0.44–3.16); however, it was not statistically significant (*P*=0.915). Individuals with a history of eating unwashed vegetables or fruits (23.1%, 95% CI=9.0–43.6, crude odds ratio [COR]=3.21, 95% CI=1.13–9.13) and rural residency (19.5%, 95% CI=8.8–34.9, COR=2.74, 95% CI=1.06–7.05) had significantly higher rates of seropositivity using the univariate logistic analyses. After multivariate logistic analyses, the differences were not statistically significant.

Conclusion: The toxocariasis seroprevalence among schizophrenic and healthy participants was not significantly different (11% vs. 9.6%). Since the disease severity, onset, and cognitive sequelae are not the same among schizophrenic patients, clinically matched studies with larger samples are required to address the current inconsistency between the studies.

Introduction

Toxocariasis is a zoonotic disease caused by the larvae of the dog ascarid, *Toxocara canis*, or less commonly, the cat ascarid, *T. cati* (1). Humans are accidental hosts of *Toxocara*, infected *via* ingesting infective eggs in contaminated soil or encysted larvae in the tissues of infected paratenic hosts, such as rabbits, chickens, cattle, or swine. The disease may present with visceral larva migrans (VLM), ocular larva migrans (OLM), or neurological toxocariasis. The infection may also be asymptomatic, which is known as covert toxocariasis (CT) (2). The disease affects over 1.4 billion individuals globally (3), with a seroprevalence of approximately 19 percent worldwide (4). In the setting of a compatible clinical presentation, the diagnosis can be confirmed by a specific IgG-enzyme-linked immunosorbent assay (ELISA). Nonetheless, IgG-ELISA cannot distinguish between an active, resolved, or recurrent infection (5). Western blot has higher sensitivity and specificity than ELISA and, in some circumstances, it is used to confirm positive ELISA results (6). Most individuals with mild symptoms due to toxocariasis do not require anthelminthic therapy, and symptoms usually resolve within a few weeks (7, 8). Toxocariasis is more prevalent in rural and tropical regions than in urban communities. The disease is more common in areas affected by poverty, poor housing, and limited water supplies and highly correlates with personal hygiene (9). In this regard, patients with schizophrenia, who may have problems with personal and social functioning and self-care skills, may constitute a high-risk population for toxocariasis.

Schizophrenia is ranked by the World Health Organization (WHO) as one of the top 10 illnesses contributing to the global burden of disease (10). The disease typically presents with negative symptoms, such as poverty of speech or a flat affect, and positive symptoms, such as delusions or hallucinations. Moreover, schizophrenia is also commonly associated with impairments in cognitive, social, and occupational functioning (11). Global studies indicate a prevalence of approximately 0.28% for schizophrenia (12), similar to those reported in Iran (0.25%) (13). A meta-analysis showed that the association between schizophrenia and herpes simplex virus type 2 (HSV-2), Borna disease virus (BVD), human endogenous retrovirus-W (HERV-W), *Chlamydophila pneumoniae*, *C. psittaci*, and *Toxoplasma gondii* was statistically significant (14).

Toxocara larvae possess the capability to pass the blood-brain barrier (BBB), thereby gaining access to the central nervous system (CNS) and causing "neurotoxocariasis." The disease may manifest with a diverse range of neurological presentations, such as encephalitis, meningitis, myelitis, cerebral vasculitis, and even asymptomatic CNS infection (15). Furthermore, some previous studies have brought up the idea that disorders affecting mental and cognitive functions may lead to increased susceptibility to parasitic infections such as toxocariasis, possibly through deteriorations in self-hygiene and self-care skills (16).

Alvarado-Esquivel showed that 4.7% of patients with psychiatric disorders had positive anti-*Toxocara* IgG, while only 1.1% of control individuals were seropositive (17). Similarly, studies from eastern China and Italy indicated higher anti-*Toxocara* seroprevalence rates in psychiatric patients (18, 19). In a Turkish hospital, toxocariasis seroprevalence was as high as 45.9% among patients with schizophrenia, while it was only 2% in the healthy control group (20). In addition, toxocariasis seroprevalence was significantly higher among hospitalized patients with schizophrenia in two other case-control studies in Egypt and Iran (21, 22). However, due to various environmental and clinical factors, such as geographical variations, different lifestyles, cultures, and clinical severity of schizophrenia, the definite relationship between schizophre-

nia and toxocariasis is not yet clear, and there are conflicting reports on the associations between toxocariasis and schizophrenia.

In light of these considerations, this case-control study was carried out to assess the associations between *Toxocara* spp. exposure and schizophrenia, as well as possible contamination routes for toxocariasis in Fars Province, southern Iran.

Materials & Methods

Ethical approval

The Research Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran, approved this study under the terms of the Declaration of Helsinki and with the ethical code IR.SUMS.MED.REC.1400.049. All participants and their legal guardians were voluntarily enrolled in the study and informed about the purpose and methodology of the study. Written, informed consent was obtained from all participants and their legal guardians.

Participants and study design

From May to September 2021, 109 patients diagnosed with schizophrenia disorder and 104 age- and gender-matched healthy controls were included in the study. The cases were included from patients admitted to Ibn Sina Hospital, Shiraz, Iran, with the diagnosis of schizophrenia made by experienced psychiatrists of the hospital (23). The diagnostic criteria for schizophrenia were based on the 5th version of the Guidelines for Diagnosis and Statistics of Mental Disorders (DSM-V) (24). Briefly, typical presentations may include delusions, hallucinations, disorganized speech or behavior, and negative symptoms.

The control group comprised healthy individuals undergoing routine check-ups at laboratories in Shiraz. After obtaining a brief neurological and psychiatric history, individuals with any history of these disorders were excluded from the control group. Participants with known immunodeficiency disorders and those with blood samples showing hemolysis were also excluded.

Sample collection and questionnaire

A four-milliliter venous blood sample was taken from all cases and controls and tested for IgG antibodies to *Toxocara* excretory/secretory (TES) antigens using an ELISA kit. A questionnaire, including patients' gender, age, occupation, residency, suicide history, educational status, and factors associated with toxocariasis, including contact with soil or gardening, having pets (dogs or cats), dietary habits, including consumption of raw or undercooked meat, unwashed vegetables or fruits, and unsanitary water, was obtained.

Preparation of Toxocara excretory-secretory antigens

Zibaei et al. (25) illustrated the preparation of TES antigens. Briefly, *T. cati* eggs were harvested from female worms and embryonated in a 2.5% formalin/ringer solution for 30 days at 25 °C. On RPMI medium, the second-stage larvae were cultivated, and culture supernatant containing TES antigen was extracted, concentrated, and stored at -20 °C until use.

Enzyme-linked immunosorbent assay

ELISA microplates were coated according to the reference method (25). Briefly, at a concentration of 5 µg/mL (measured using the Bradford method), antigens were coated and blocked on 96-well flat-bottom microplates (Corning, USA). One hundred µl of diluted (1:100) serum samples were added to the plates and incubated for one hour at 37 °C. Finally, after incubation with anti-human IgG conjugated with horseradish peroxidase (HRP) (Sigma-Aldrich, USA), ortho-phenylenediamine dihydrochloride (OPD) (Sigma-Aldrich, USA) substrate was added to the wells, and reactions were stopped using a 20% sulfuric acid solution. The optical density (OD) was then measured at 490 nm using an automated ELISA reader (Biotek, USA). The specificity and sensitivity of the test are reported at 96.7% and 97.0%, respectively (25).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) Software, version 16.0 (Chicago, IL, USA), was used to analyze the data (IBM, USA). Frequencies (%) and 95% confidence intervals (95% CI) were used to look for factors associated with toxocariasis seroprevalence. The crude odds ratio (COR), adjusted odds ratios (AOR), and 95% CI were used to test the strength of the associations between the predictors and outcome variables. Uni- and multivariate logistic regression analyses were employed to control the effect of potential confounding factors. *P*-values less than 0.05 were considered statistically significant.

Results

General characteristics of the participants

A total of 213 participants were included in the study, of which 140 (65.7%) were male and 73 (34.3%) were female. Out of 109 patients with schizophrenia, 67 (61.5%) were male and 42 (38.5%) were female, with a mean age of 36.53±12.51 years. Out of 104 healthy individuals in the control group, 73 (70.2%) were male and 31 (29.8%) were female, with a mean age of 38.21±14.26 years. There were no significant differences in terms of gender and age between the cases and controls (*P*=0.18 and 0.13, respectively) (**Tables 1** and **2**).

Seroprevalence of toxocariasis

The overall seroprevalence of anti-*Toxocara* IgG antibodies among cases and controls was 10.3% (95% CI=6.6–15.2). Anti-*Toxocara* IgG was detected in 12 schizophrenic patients and 10 control subjects, giving respective seroprevalences of 11.0% (95% CI=5.8–18.4%) and 9.6% (95% CI=4.7–17.0%) (Table 2).

Univariate logistic regression

The seroprevalence of toxocariasis in schizophrenic patients was 1.16 times higher (95% CI=0.44-3.16) than that of the control group; however, it was not statistically significant (*P*=0.915). Subgroup analyses found that individuals with a positive history of contact with contaminated soil had the highest seroprevalence of anti-*Toxocara* antibodies (23.5%, 95% CI=6.8–49.9), followed by individuals with a positive history of eating unwashed vegetables or fruits (23.1%, 95% CI=9.0–43.6). The seroprevalence of toxocariasis among rural residents was 2.74 times higher (95% CI=1.06–7.05) than that of urban residents (19.5% vs. 8.1%, *P*=0.037). Moreover, this seroprevalence in individuals with a positive history of eating unwashed vegetables or fruits was 3.21 times higher (95% CI=1.13-9.13) than that of those who denied eating unwashed vegetables or fruits (23.1% vs. 8.6%, *P*=0.029). However, the differences in seroprevalence based on the other variables were not statistically significant (*P*>0.05) (Table 1).

Multivariable logistic regression

The seroprevalence of toxocariasis in schizophrenic patients was also insignificantly higher than that of healthy controls even after adjusting the effect of the multiple variables, including age, gender, education, location of residency, history of contact with dogs or cats, owning a pet (dog or cat), consumption of contaminated water, eating unwashed vegetables or fruits, contact with contaminated soil, suicide history, and occupation (*P*>0.05) (Table 2).

Table 1: Univariate logistic regression analyses of toxocariasis seroprevalence in the cases and controls

Variables	***Total***		***Univariate logistic regression***	
	No. (%)	Seropositive No. (%, [95%CI])	COR (95%CI)	*P*-value
Group				
Schizophrenia	109 (51.2)	12 (11.0, [5.8-18.4])	1.16 (0.44-3.16)	
Control	104 (48.8)	10 (9.6, [4.7-17.0])	1	0.915
Age				
≤30 yrs.	81 (38.3)	6 (7.4, [2.8-15.4])	1	
>30 yrs.	131* (61.7)	16 (12.2, [7.1-19.1])	1.74 (0.61-5.66)	0.379
Gender				
Male	140 (65.7)	12 (8.6, [4.5-14.5])	1	
Female	73 (34.3)	10 (13.7, [6.8-23.8])	1.69 (0.62-4.53)	0.351
Education				
Illiterate	13 (6.1)	1 (7.7, [0.2-36.0])	0.80 (0.09-6.85)	0.836
Secondary and high school	96 (45.1)	11 (11.5, [5.9-19.6])	1.24 (0.49-3.14)	0.655
University	95* (44.8)	9 (9.5, [4.4-17.2])	1	
Residency				
City	172 (80.8)	14 (8.1, [4.5-13.3])	1	
Rural	41 (19.2)	8 (19.5, [8.8-34.9])	2.74 (1.06-7.05)	0.037**
Having a dog or cat as a pet				
Yes	35 (16.4)	5 (14.3, [4.8-30.3])	1.58 (0.54-4.60)	0.403
No	178 (83.6)	17 (9.6, [5.7-14.9])	1	
Contact with dog or cat				
Yes	89 (41.8)	9 (10.1, [4.7-18.3])	0.96 (0.39-2.36)	0.930
No	124 58.2)	13 (10.5, [5.7-17.3])	1	
Eating unwashed vegetables or fruits				
Yes	26 (12.2)	6 (23.1, [9.0-43.6])	3.21 (1.13-9.13)	0.029**
No	187 (87.8)	16 (8.6, [5.0-13.5])	1	
Contact with garden soil or gardening				
Yes	17 (8)	4 (23.5, [6.8-49.9])	3.04 (0.90-10.32)	0.074
No	196 (92)	18 (9.2, [5.5-14.1])	1	
Unsanitary water consumption				
Yes	28 (13.1)	4 (14.3, [4.0-32.7])	1.55 (0.48-4.96)	0.463
No	185 (86.9)	18 (9.7, [5.9-14.9])	1	
Suicide history				
Yes	13 (6.1)	3 (23.1, [5.0-53.8])	2.86 (0.72-11.29)	0.134
No	200 (93.9)	19 (9.5, [5.8-14.4])	1	
Occupation				
Employee	32 (15)	3 (9.4, [2.0-25.0])	0.66 (0.15-3.02)	0.594
Homeworker	57 (26.8)	5 (8.8, [2.9-19.3])	0.62 (0.17-2.29)	0.469
Student	37 (17.4)	5 (13.5, [4.5-28.8])	1	
Others	83* (39)	8 (9.6, [4.3-18.1])	0.68 (0.21-2.25)	0.530
Total	213 (100)	22 (10.3, [6.6-15.2])		

In the variable marked with *, the number of participants is less than the total due to missing data. ** statistically significant

Table 2: Multivariate logistic regression analyses of toxocariasis seroprevalence in the cases and controls

Variables	***Schizophrenia***		***Control***		***Multivariate logistic regression***	
	No. (%)	Seropositive No. (%, [95%CI])	No. (%)	Seropositive No. (%, [95%CI])	AOR (95%CI)	*P*-value
Age						
≤30 yrs.	47 (43.1)	5 (10.6, [3.5-23.1])	34 (32.7)	1 (2.9, [0.1-15.3])	1.21 (0.45-3.33)	0.841
>30 yrs.	62 (56.9)	7 (11.3, [4.7-21.9])	69* (66.3)	9 (13.0, [6.1-23.3]		
Gender						
Male	67 (61.5)	7 (10.4, [4.3-20.3])	73 (70.2)	5 (6.8, [2.3-15.3])	1.11 (0.41-3.03)	0.999
Female	42 (38.5)	5 (11.9, [4.0-25.6])	31 (29.8)	5 (16.1 [5.5-33.7])		
Education						
Illiterate	9 (8.3)	1 (11.1, [0.3-48.2])	4 (3.8)	0	1.17 (0.42-3.35)	0.923
Secondary and high school	57 (52.3)	7 (12.3, [5.1-23.7])	39 (37.5)	4 (10.3, [2.9-24.2])		
University	43 (39.4)	4 (9.3, [2.6-22.1])	52* (50)	5 (9.6, [3.2-21.0])		
Residency						
City	70 (64.2)	4 (5.7, [1.6-14.0])	102 (98.1)	10 (9.8, [4.8-17.3])	0.68 (0.18-2.25)	0.668
Rural	39 (35.8)	8 (20.5, [9.3-36.5])	2 (1.9)	0		
Having a dog or cat as a pet						
Yes	12 (11)	4 (33.3, [9.9-65.1])	23 (22.1)	1 (4.3, [0.1-21.9])		
No	97 (89)	8 (8.2, [3.6-15.6])	81 (77.9)	9 (11.1, [5.2-20.0])	1.24 (0.46-3.42)	0.813
Contact with dog or cat						
Yes	59 (54.1)	8 (13.6, [6.0-25.0])	30 (28.8)	1 (3.3, [0.1-17.2])		
No	50 (45.9)	4 (8.0, [2.2-19.2])	74 (71.2)	9 (12.2, [5.7-21.8])	1.19 (0.43-3.33)	0.893
Eating unwashed vegetables or fruits						
Yes	25 (22.9)	6 (24.0, [9.4-45.1])	1 (1)	0		
No	84 (77.1)	6 (7.1, [2.7-14.9])	103 (99)	10 (9.7, [4.8-17.1])	0.78 (0.24-2.40)	0.819
Contact with garden soil or gardening						
Yes	16 (14.7)	4 (25.0, [7.3-52.4])	1 (1)	0		
No	93 (85.3)	8 (8.6, [3.8-16.2])	103 (99)	10 (9.7, [4.8-17.1])	0.93 (0.32-2.70)	0.999
Unsanitary water						

consumption						
Yes	26 (23.9)	4 (15.4, [4.4-34.9])	2 (1.9)	0		
No	83 (76.1)	8 (9.6, [4.3-18.1]0	102 (98.1)	10 (9.8, [4.8-17.3])	1.05 (0.36-3.04)	0.999
Suicide history						
Yes	13 (11.9)	3 (23.1, [5.0-53.8])	0 (0)	0	0.97 (0.33-2.80)	0.999
No	96 (88.1)	9 (9.4, [4.4-17.1])	104 (100)	10 (9.6, [4.7-17.0])		
Occupation						
Employee	18 (16.5)	0	14 (13.5)	3 (21.4, [4.7-50.8])	1.30 (0.47-3.69)	0.744
Homeworker	15 (13.8)	1 (6.7, [0.2-31.9])	42 (40.4)	4 (9.5, [2.7-22.6])		
Student	23 (21.1)	5 (21.7, [7.5-43.7])	14 (13.5)	0		
Others	53 (48.6)	6 (11.3, [4.3-23.0])	30* (28.8)	2 (6.7, [0.8-22.1])		
Total	109 (100)	12 (11.0, [5.8-18.4])	104 (100)	10 (9.6, [4.7-17.0])	1.16 (0.44-3.16)	0.915

In the variable marked with *, the number of participants is less than the total due to missing data.

Discussion

In the present study, we investigated the association between *Toxocara* spp. exposure and schizophrenia. Several previous studies have raised the idea that patients with psychiatric disorders, compared to control healthy groups, may have a higher risk for toxocariasis (17-19). Cognitive and behavioral impairments accompanying schizophrenia may place the patients at higher risk of various infections, particularly parasitic ones such as toxocariasis (11). This heightened vulnerability could potentially arise from declines in personal hygiene and self-care behaviors (16).

In our study, the difference between the seroprevalence of toxocariasis among schizophrenic patients and the control group was insignificant. A meta-analysis of six case-control studies concluded that, compared to healthy controls, patients with schizophrenia are four times at higher risk of being seropositive for or having exposure to *Toxocara* (26). Nevertheless, in this analysis, high heterogeneity for various factors, such as age and gender, was observed. Moreover, the characteristics and definitions of the control groups were neither consistent nor clear between the included studies. Similar studies have addressed higher but inconsistent rates among schizophrenic patients. For instance, Kaplan et al. reported the seroprevalence of toxocariasis in patients with schizophrenia as high as 45.9%, while it was 2% in the control group (20). Toxocariasis seroprevalence in hospitalized schizophrenic patients from Egypt and Ahvaz, Iran, was reported at 23.3% and 14%, while it was 2.2% and 4.3% in the control group, respectively (21, 22). Another explanation for the variations in the seroprevalence among our findings and other studies could be related to the geographic patterns of the infection, local cultures and lifestyles, environmental exposures, and socioeconomic statuses in different societies (4, 9, 27, 28).

The overall seroprevalence of toxocariasis in our study was 10.3%, similar to the overall seroprevalence of toxocariasis in Iran, estimated at 11% by a recent meta-analysis (29). In contrast, Sadjjadi et al. reported a seroprevalence of 25.6% for toxocariasis among schoolchildren in Shiraz (30). In another study among street sweepers in Shiraz city, this percentage was 26.3% (31). There are some possible explanations for the difference between the results obtained from our study and those

from others. Theoretically, these two populations of schoolchildren and street sweepers are more likely to be exposed to soil, a significant environmental source of *Toxocara* exposure (31). Additionally, the exploratory activities of children, such as tasting anything around them, eating soil, and contact with dogs and cats, are other possible explanations (30). In contrast, our study participants mainly consisted of young adults, of whom only a minority (8%) declared a history of soil contact.

We found that people who lived in rural areas and those who consumed unwashed vegetables or fruits had significantly higher rates of *Toxocara* spp. seropositivity, using univariate logistic analyses. However, in the multivariate logistic analyses, the difference was not statistically significant. Agricultural activities, exposure to contaminated soil, and contact with stray animals in rural areas may contribute to the greater incidence of toxocariasis among rural inhabitants (9). Furthermore, consumption of unwashed or improperly washed vegetables is a significant risk factor for *Toxocara* infection, as a prior Iranian study has revealed that regional vegetables are moderately contaminated with *Toxocara* eggs (32). Our results showed an insignificantly higher rate of *Toxocara* seropositivity among those with a history of unsanitary water consumption. It is possible that, due to the low number of seropositive cases, our analysis failed to establish a statistically significant association for this variable. Additionally, as shown by other studies (23), older ages and female gender are other risk factors for toxocariasis; nonetheless, we believe that our insignificant results regarding these variables were due to the small sample size and low number of seropositive cases.

Our study showed that dog and cat ownership were not associated with higher rates of toxocariasis in schizophrenic patients. However, it is a controversial issue among studies. Similar to our research, it was not associated with *Toxocara* infection in several studies from various countries (33-35). Nonetheless, other studies have found dog and cat ownership to be associated with toxocariasis (36, 37). It could be postulated that other possible confounding factors, such as animal age (38) and whether the animal is allowed to roam outside the house, may also play a role.

This study has a few limitations. Studies with a larger population are required to eliminate the possible effects of other confounding factors, such as psychiatric and environmental factors. We employed TES-ELISA to identify anti-*Toxocara* IgG antibodies, but ELISA kits using TES antigen preparations have shown varying and suboptimal sensitivities and specificities. Additionally, TES-ELISA may cross-react with serum antibodies against helminths other than *Toxocara* spp. (39). Another limitation of this study is the lack of a comprehensive psychiatric assessment of mood, cognition, and behaviors in schizophrenic patients. The severity, subtypes, and duration of schizophrenia from the onset may affect patients' cognitive, social, and personal functioning. Future studies should recognize these clinical factors as well.

Conclusion

The seroprevalence of toxocariasis among schizophrenic patients was 11%, which was not significantly higher than that of healthy individuals (9.6%). Since the disease severity, onset, and cognitive sequelae are not the same among schizophrenic patients, clinically matched, controlled studies with larger sample sizes are required to address the current inconsistency between the studies. Future studies in schizophrenia population should strive to mitigate the influence of confounding factors such as lifestyle habits, geographic disparities, socioeconomic status, and the clinical severity of schizophrenia.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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