

Prevalence and Risk Factors of Human Visceral Toxocariasis in Some Egyptian Patients with Eosinophilia of Unknown Origin

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Abstract: *Background:* Toxocariasis is a worldwide parasitic disease. Eosinophilia is the most outstanding characteristic of visceral larva migrans (VLM), *Objective:* this study was conducted to determine seroprevalence of toxocariasis among Egyptian patients with eosinophilia of unknown origin (EUO) and to identify the risk factors and clinical characteristics associated with VLM. *Subjects and methods:* Eosinophilic patients attended National Hepatology and Tropical Medicine Research Institute (NHTMI) were subjected to questionnaire, urine, stool analysis and serum Indirect Haemagglutination (IHA) examination to exclude patients with other parasitic infections or eosinophilia of known causes, 54 EUO patients were subjected to serologic examination for *Toxocara* IgG by ELISA. *Results:* 42.6 % were seropositive *Toxocara* IgG, 56.5%, of them were residing rural areas and 43.5% were residing urban areas, 43.5% were in contact with soil and 39.1 % were in contact with cats/dogs. Seropositivity was 60.95% in females patients and 39.1% in males patient (respecting residence, soil/contact with pets). Seropositivity was 43.5% in children and 56.5% in adults, with no significant differences. Clinical characteristics in seropositive patients with gastro-intestinal troubles (GIT troubles) were (52.2 %), bronchial asthma (30.4%), fever (21.7%), ocular troubles (21.7%), hepatosplenomegaly (34.8%), lymphadenopathy (17.4%) and myalgia (17.4%). *Conclusion:* a high prevalence of toxocariasis in EUO patients, serodiagnosis is essential in EUO, with recommendation for a large population-based survey to assess the magnitude of this disease and to identify more details about risk factors.

Key words: Toxocariasis • VLE • Eosinophilia

INTRODUCTION

Human toxocariasis is a prevalent parasitic disease caused by several species of the nematode *Toxocara* via ingestion of embryonated eggs which were shed the feces of definite dogs or cats [1]. Infection is commonly through contaminated soil, water or surfaces [2]. The larvae hatch in the small intestine, then penetrate the gut wall and are transported to the liver and lung via the blood stream, subsequently the larvae undergo further migration via the tracheal route to adulthood in the small intestine [3],

several factors that have been associated with higher rates of toxocarasis. People are more likely to be infected if they own dogs especially the children and adolescent under the age of 20 years; those are more likely to be positive for infection [4]. The incubation period can be weeks to months depending on the intensity of infection and sensitivity of the patients [5]. Clinical manifestations vary depending on the affected organ and systematically classified in four groups: Visceral larva migrans (VLM), neurological toxocariasis (NT), ocular larva migrans (OLM) and the most recently described covert

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toxocariasis [1]. The majority of infection by toxocariasis is usually asymptomatic, however in parasitized patients with anti-Toxocara antibodies, VLM is induced, it mainly affect young children and characterized by fever, hepatomegaly, coughing, wheezing, abdominal pain, hypergammaglobulinemia, leukocytosis and eosinophilia [peripheral blood eosinophil count $> 500/\text{mcL}$ ($>0.5 \times 10^9/\text{L}$)] which is one of the most outstanding characteristic of VLM in naturally infected humans [6, 7], few as 200 *Toxocara canis* larvae in small child may produce a peripheral eosinophilia of 20% to 40% for more than a year, with no other detectable symptoms, patients with 50% eosinophilia usually have symptoms might include fever, hepatomegaly, pulmonary infiltrates, cough, neurologic disturbances, endophthalmitis and hypergammaglobulinemia [8]. Due to the non-specific symptoms of this disease, its medical and public health might be underestimated [3], thus, although toxocariasis can be diagnosed tentatively based on patient's symptoms, laboratory diagnosis is required to improve the accuracy of diagnosis [2].

In Egypt, high prevalence of toxocariasis indicated by anti- *Toxocara* antibodies has been recorded by many researchers, seroprevalence of *Toxocara* IgE antibodies has been reported as 7.7% among the general population [3, 9]. Santo, Chieffi and Pereze [4] detected seropositive toxocariasis 6.6% among suspected children and 18% among adults. Patients with bronchial asthma, hepatomegaly, hepatosplenomegaly, neurological disorders, gastrointestinal troubles and dermatitis are thought to be prone to toxocariasis [8]. Diagnosis of toxocariasis is essentially clinical, based on the lesion morphology of the affected organ and also the supportive laboratory data such as ELISA titers, other diagnostic methods are imaging studies including ultrasound, computed tomography fluorescein angiography [6].

Misdiagnosis due to the non-specific clinical presentation, may lead to prolonged morbidity and development of health complications, therefore it is necessary to establish an early diagnosis and start appropriate treatment [1].

Objective: This study was conducted to determine seroprevalence of toxocariasis among Egyptian patients with EUO and to identify the risk factors and clinical characteristics associated with VLM to be the gate way for early, definitive diagnosis and treatment to limit the health hazards and complications of this zoonotic infection.

MATERIALS AND METHODS

Type of the Study: The study is a cross sectional study that conducted on EUO patients attending National Hepatology and Tropical Medicine Research Institute NHTMI from December 2019 to April 2020.

Subjects: The study was conducted on EUO patients (males and females), aged from 2-60 years. Adult patients participated in the study provided verbal or written informed consent and children less than 18 years of age verbal or written informed consent by parents or guardians.

Exclusion Criteria: All subjects with malignancy, allergic, viral hepatitis A,B,C, autoimmune diseases (by patients history, laboratory reports), or infected with other helminthes as *Ascaris lumbricoides*, *Ancylostoma duodenal*, *Enterobius vermicularis*, *Schistosoma* and *Fasciola*, by parasitological examination of urine and stool samples and serum examination for detection of *Fasciola* or *Schistosoma* serum antibodies by indirect haemagglutination test (IHA) as described later in laboratory examinations were excluded from the study.

Inclusion Criteria: Patients proved to be free from malignancy, allergic, autoimmune, hepatitis A, B, C and parasitic infections that may cross react with *Toxocara* infection were included in the study.

Procedures

Each Patient Was Subjected To: A- questionnaire forms contained epidemiological data including: name, age, gender, address, contact with pets, geophagia, complaint, history for allergic, malignancy, hepatitis A, B, C or autoimmune diseases other diseases, medical drugs, these revealed 130 EUO patients whom subjected to laboratory examinations as following:

Samples Collection:

- Fresh Urine and stool samples were collected from each EUO patients 130 patients in a dry, clean, sterile and labeled containers and examined as the following:
- Blood samples collection: - Five ml of venous blood were collected using vacutainer tubes from only 54 patients (with identical inclusion criteria), samples were centrifuged for 15 min to separate sera, each serum sample was divided into 2 sub-samples and each was preserved in CRYO tube and were stored at

-20°C until used (1st sub-sample used for detection of serum antibodies for *Fasciola hepatica* and *Schistosoma mansoni* / *Schistosoma haematobium* by using Indirect Haemagglutination test (IHA), the 2nd sub-sample used for detection of *Toxocara* IgG by ELISA.

Procedures and Examination:

- Complete urine analysis (macroscopic, chemical and microscopically)
- Macroscopic stool examination to identify fecal consistency, visible worms, blood, mucous, pus.
- Microscopic stool examination by using direct smear and simple concentration techniques [10, 11] to detect presence of other parasitic infections, 76 positive intestinal parasitic patients were excluded to eliminate cross reactions.
- Serological examinations by IHA TEST:-The test was done using commercially available kits by FUMOZE DIAGNOSTICS -FRANCE. All test procedures and interpretation guided by manufacturers as the following:
 - For schistosomiasis, titer ≥ 1 : 160 indicates significant reaction, with presumption of acute infection.
 - For fascioliasis, titer ≥ 1 : 320 indicates significant reaction in favor of acute infection.

Laboratory urine, stool and blood examinations, results detected 54 EUO patients free from *Ascaris lumbricoides*, *Ancylostoma duodenale*, *E. vermicularis*, *Fasciola*, Schistosomiasis, those 54 patients (identical to inclusion criteria) were subjected to the following:

Serodiagnosis for Toxocara IgG by ELISA: All the 54 serum samples were examined for IgG *Toxocara canis* antibodies by ELISA technique using commercially available kits by RIDA screen Toxocara IgG k7421, R - Biopharma ACT, Germany, the test is based on E/S antigens of *Toxocara* larvae, sensitivity of the test is 100% and 98% specificity, all test procedures and interpretation guided by manufacturers' protocol, where level above 200 IU/ml considered positive result.

Clinical Examination: General, chest, heart, abdomen

Radiological Examination: By abdominal U.S.

Statistical Analysis: Qualitative data was expressed in numbers and percentages, chi-square test for comparison of qualitative data and test the association by odds ratio.

Mean and SD for quantitative data N.B. the level of significance was P value < 0.05 .

RESULTS

Results showed that there were 50% patients suffered from gastrointestinal troubles, 24% had bronchial asthma and 20.45% had fever or myalgia, 16.7 % had ocular troubles or hepatosplenomegaly and 13% had lymphadenopathy. All these troubles were more detected insignificantly among seropositive patients in contrast to seronegative group except for myalgia which is more among the seronegative patients. Seropositive patients were more than 2 times at high risk of developing with hepatosplenomegaly (Table 2).

All clinical manifestations among seropositive patients were more in children than adult except lymphadenopathy and ocular troubles without statistical significant difference (Table 3).

Concerning clinical manifestations it was found that bronchial asthma, myalgia, fever, GIT troubles and hepatosplenomegaly were more in children than adults without statistical significant difference except GIT manifestations as 73.9% of children had it versus 32.3% of adults OR= 5.9 (Table 4)

DISCUSSION

Human toxocariasis is a common worldwide helminthic zoonosis that may elicit various symptoms, authors in different studies considered it as one of the different main causes of peripheral eosinophilia, in 2002 [12] found that there was 97 apparently healthy individuals suffering from over 10% eosinophilia (more than 500 cells in the peripheral blood) and 60% of them were seropositive for toxocariasis by ELISA and Immunoblot techniques, in [4] demonstrated that there was 28/80 patients (71.8%) with peripheral blood eosinophilia combined by seropositive result for toxocariasis, also they found that the percent of eosinophilic patients were at 149 greater risk of toxocariasis. In Egypt, authors detected the kinetics of IgE production and eosinophilia in experimental murine toxocariasis [13-15], this come in agreement with our results as there was 23 eosinophilic patients (42.6%) were *Toxocara* seropositive, on contrary, Kim *et al.* [16] did not find seropositive toxocariasis in eosinophilic individuals (more than or equal to 10% WBCs).

Some authors demonstrated the high seropositive results for toxocariasis in adults due to the habits of eating raw or uncooked animal tissues that may contain

Table 1: Distribution of subjects with EUO enrolled in the study according to their demographic characteristics.

	EUO patients					
Studied groups	Toxocara seropositive		Toxocara seronegative		Chi square Test c2	Total sample
Characteristics	No.23 (42.6%)		No.31 (57.4%)		& P value	No.54
Age -Range	3-57		2-60		Mann-Whitney	Mean ±SD
- Mean rank	27.4		27.7		p=0.9	25.7±15.6
	No.	%	No.	%		No. (%)
Age groups:-						14 (25.9)
≤10	6	26.1	8	25.9		9 (16.7)
11-20	4	17.4	5	16.1	χ ² p=0.9	17 (31.5)
21-30	8	34.8	9	29		14 (25.9)
31or more	5	21.7	9	29		
Groups :-					χ ² p=0.7	
Children	10	43.5	13	41.9		23(42.6)
Adult	13	56.5	18	58.1		31(57.4)
Sex:- -Male	9	39.1	18	58.1	χ ²	27(50)
-Female	14	60.9	13	41.9	p=0.2	27(50)
Contact with dogs/cats:-						
-Yes	9	39.1	9	29	χ ²	18(33.3)
-No	14	60.9	22	71	p=0.4	36(66.7)
Contact with soil						
-Yes	10	43.5	14	45.2	χ ²	24(44.4%)
-No	13	56.5	17	54.8	p=0.9	30(55.6%)
Location						
-Urban	10	43.5	16	51.6	χ ²	26(48.1%)
-Rural	13	56.5	15	48.4	p=0.6	28(51.9%)

Table 2: Comparison of results of Toxocara canis IgG -ELISA in subjects with EUO according to their clinical characteristics

	EUO patients Total N0.54 (100%)					
Studied groups Characteristics	Toxocara seropositive No.23 (42.6%)		Toxocara seronegative No.31 (57.40%)		Test of significance & P value	Total sample No.54
Lymphadenopathy:-						
-Yes	4	17.4	3	9.7	χ^2	7(13.0%)
-No	19	82.6	28	90.3	p=0.4	47(87.0%)
Ocular troubles:-						
-Yes	5	21.7	4	12.9	χ^2	9(16.7%)
-No	18	78.3	27	88.1	p=0.4	45(83.3%)
Bronchial asthma:-						
-Yes	7	30.4	6	19.4	χ^2	13(24.1%)
-No	16	69.6	25	80.6	p=0.3	41(75.9%)
Myalgia:-						
-Yes	4	17.4	7	22.6	χ^2	11(20.4%)
-No	19	82.6	24	77.4	p=0.6	43(79.6%)
Fever:-						
-Yes	5	21.7	6	19.4	χ^2	11(20.4%)
-No	18	78.3	25	80.6	p=0.8	43(79.6%)
Gastrointestinal troubles:-						
-Yes	12	52.2	15	48.4	χ^2	27(50.0%)
-No	11	67.8	16	51.6	p=0.8	27(50.0%)
Hepatomegaly or hepatosplenomegaly:-						
-Yes	8	34.8	1	3.2	χ^2 p=0.002*	9(16.7%)
-No	15	65.2	30	96.8	OR=2.7	45(83.3%)

Table 3: Comparison of results of *Toxocara canis* -IgG -ELISA in seropositive children and adults according to their clinical characteristics.

Studied groups	Seropositive Total No.23 (100%)				
Characteristics	Children No.10 (43.48%)		Adult No.13 (56.52%)		Test of significance & P value
Lymphadenopathy:-					
-Yes	1	10	3	23.1	χ^2
-No	9	90	10	76.9	p=0.4
Ocular troubles:-					
-Yes	1	10	4	30.8	χ^2
-No	9	90	9	69.2	p=0.2
Bronchial asthma:-					
-Yes	3	30	4	30.8	χ^2
-No	7	70	9	69.2	p=0.9
Myalgia:-					
-Yes	2	20	2	15.4	χ^2
-No	8	80	11	84.6	p=0.8
Fever:-					
-Yes	3	30	2	15.4	χ^2
-No	7	70	11	84.6	p=0.4
Gastrointestinal troubles:-					
Yes	6	60	6	46.2	χ^2
No	4	40	7	53.8	p=0.5
Hepatomegaly or hepatosplenomegaly:-					
-Yes	4	40	4	30.8	χ^2
-No	6	60	9	69.2	p=0.6

Table 4: Distribution of subjects with EUO enrolled in the study according to their age groups and clinical presentation

Studied groups Characteristics	Age groups				Test of significance & P value
	Children No.23		Adult No.31		
Lymphadenopathy					
-Yes	2	8.7	5	16.1	χ^2
-No	21	91.3	26	83.9	p=0.4
Ocular troubles					
-Yes	3	13	6	19.4	χ^2
-No	29	87	25	80.6	p=0.5
Bronchial asthma:-					
-Yes	7	30.4	6	19.4	χ^2
-No	16	69.6	25	80.6	p=0.3
Myalgia					
-Yes	6	26.1	5	16.1	χ^2
-No	17	73.9	26	83.9	p=0.4
Fever					
-Yes	7	30.4	4	12.9	χ^2
-No	16	69.6	27	87.1	p=0.1
Gastrointestinal troubles					
-Yes	17	73.9	10	32.3	χ^2 p=0.002*
-No	6	26.1	21	67.7	OR=5.9
Hepatomegaly or hepatosplenomegaly					
-Yes	4	17.4	5	16.1	χ^2
-No	19	82.6	26	83.9	p=0.9

encapsulated larvae [17], while Glickman and Schantz [18] reported that the age of VLM patients were children aged between 2 and 7 years old, also [19, 20] demonstrated that there was significant association between age and seropositivity for toxocariasis especially for ages less than 10 years old due to big frequency of geophagia in children, EL-Shazly *et al.* [9] and Nihal *et al.* [21] found that there is no relation between age groups and the rate of *Toxocara* seropositivity, this come in agreement with our results as there was no statistical significant differences between age groups in relation to seropositivity (43.5% in children /56.5%in adults) or seronegative results (41.9% in children /58.1% in adults).

It was detected by Antonios *et al.* and Kanafani and Skoury [1, 22] that there was a predominance of toxocariasis in males patients due to their social behaviors while Shazly *et al.* [9] and Nihal *et al.* [21] reported that there is no relation between seropositivity and sex differences and neither age groups or gender seemed to be important factor in relation to seropositivity, this comes in agreement with our results as there was 39.1% seropositive males and 60.9% seropositive females with no statistical significant differences.

In [23] estimated that soil contaminated with *Toxocara* eggs may represent 90% of the investigated areas worldwide due to the high survival ability of the eggs in the soil even in harsh conditions, so the higher contact with this contaminated soil on squares showed significant association with *Toxocara* seropositive, this comes in agreement with our results that obtained an association between soil contact and seropositivity as there was 43.5 % patients with soil contamination and 56.5% without soil contact among seropositive patients, on contrary [24] found that there was no association between playground/contact with dogs or puppies, no hands washing before meals, eating unwashed vegetables or fruits and consumption of raw or uncooked meat and seropositivity. El Tras *et al.* Roddie *et al.* [25, 26] found that direct human to dog contact could be the route of human infection and *Toxocara* eggs has been recovered from infected dog's hair, this comes in agreement with our results that obtained a significant differences between prevalence of seropositivity and frequent contact with pets were there was 39.1% seropositive patients in contact with pets and 60.9% seropositive with no contact with pets.

In 2008, Antonios *et al.* [1] detected a high rate of seropositivity for *Toxocara* antibodies in rural areas population more than urban, also, Magnaval *et al.* [27] found that the seropositive rate of toxocariasis was 2-5

years in apparently healthy urban adults while it was 14.2% to 37% in rural areas, in Egypt, El-Shazly *et al.* [9], Kanafani and Skoury [22] detected that there were a higher prevalence of *Toxocara* seropositive in rural than urban patients, this comes in agreement with our results that revealed that seropositivity in rural residence was 56.5 %, to be more than seropositivity among urban areas that was 43.5 % respectively, this comes in contrary with the result obtained in 2008 by Alavi and Sephidgaran [28] in Iran who detected that there was a similar result of seropositive prevalence in both rural and urban patients.

Several authors reported the high prevalence of *Toxocara* seropositivity even among asymptomatic individuals, Alderete *et al.* [3], Ismail and Osama Khalafallah [29] found that *Toxocara* seropositive were generally asymptomatic, in 2017, Iddawela *et al.* [30] detected that the most common symptoms encouraging people to seek medical advice were: fever, breathing difficulty, enlarged lymph nodes and the significance association between seropositivity and lymph node pathology especially cervical and generalized lymphadenopathy, Mazur-Melewska *et al.* [31] and Cooper [32] identified lymphadenopathy as a most frequently clinical feature among seropositive *Toxocara* infected children, our results obtained 17.4 % seropositive patients with lymphadenopathy and 10.0 % of them were children and 23.0% were adults with no statistical significance differences. There are number of prior studies detected a significant relation between *Toxocara* seropositivity and muscular pain as well as arthralgia and myalgia. In 2007, Finstere and H.Auer [33] detected that there was a peripheral nervous system involvement that occurs as a result of *Toxocara* infection (radiculitis or inflammation of the cranial nerves or skeletal muscles) which is however rarely seen in human beings, in the current study, myalgia was detected in 22.6% of seronegative cases and in 17.4% of seropositive cases respectively, myalgia was detected more among seropositive children (20%) than in seropositive adults (15.4%) but without statistical significance.

It was detected by Chia-Kwung *et al.* [34] and Sharghi *et al.* [35] that histopathological examination revealed the presence of vitreous hemorrhage, granulomatous lesion and multiple retinal hemorrhage with or without larvae in OLM and demonstrated that ocular toxocariasis incidence has been estimated at just 1 /10000 annually, this comes in agreement with our results as there was 21.7 % seropositive patients with ocular troubles (30.8 % adult and 10.0 % children without significant difference).

Several cases of pericardial effusion and pleural effusion associated with seropositive results for toxocariasis have been reported by Zibaei [36] and Wickramasinghe *et al.* [37] also, they have shown the ability of toxocariasis to be the cause of myocarditis and increase the vulnerability of episodic wheezing in some patients due to the immune reaction to the inhaled allergens set up by *Toxocara canis*, in 2013, El-Tantawy *et al.* [38] detected that there was positive correlation between toxocariasis and bronchial asthma especially in children, Jayasena *et al.* [39] found that there was 22.5% of the total seropositive population had difficulty in breathing as a common symptom of infection, Chieffi and Ueda [20] detected the relation between prevalence of positivity for *Toxocara* IgG (6.2% in children and 18% in adults) and respiratory symptoms or PUO respectively due to attributed to more outdoor activity in adults, in 2014 Woodhall *et al.* [40] proved that anti -*Toxocara* antibody titer can remain positive for several years and considered as indicator of active toxocariasis, this findings may help in explanation of the associative relation between active infection and clinical conditions such as bronchial asthma, ankylosing spondylitis and psychiatric illness, this comes in agreement with our results where there was 30.4 % seropositive patients had bronchial asthma (30.0 % were children and 30.8 % were adults respectively with no significance differences, many authors detected that there was 20.9% of the seropositive subjects were suffering of fever and it is a prominent symptom of toxocariasis regardless of the age group of patients [41-43], this come in agreement with our results as fever was 21.7% in seropositive patients (30.0% in children and 15.4 % in adult) without significant difference.

In several studies, authors demonstrated the association between toxocariasis and hepatomegaly that can make toxocariasis diagnosis more likely especially when it is associated with pica or multisystem involvement [30, 44] who found that 6.17% of studied seropositive patients were hepatosplenomegaly [30, 44]. In 2011, Stoics *et al.* [45] found that the liver is the most common affected organ as a result of toxocariasis infection and this comes in association with granuloma formation and hepatitis, concluding that hepatic toxocariasis should be included in the differential diagnosis of multiple liver nodules particularly in case of eosinophilia, Mohamed *et al.* [46] and Coskum and Akinci [47] found that there is a difficulty in radiological differentiation of hepatic toxocariasis which looks like

multiple hypoechoic lesions with regular borders that can be mistaken for tumor lesions. In our study, patients with hepatomegaly/ splenomegaly were more than 2 times at higher risk of developing toxocariasis than those with other manifestations meaning that patients with seropositive were more than 2 times at a higher risk of developing hepatosplenomegaly, also incidence of hepatomegaly or hepatosplenomegaly was 40.0 % in children and 30.8 % in adults with no significant difference, GIT troubles were 52.2 % in seropositive patients (60.0 % children and 46.2 % adults) with no significant differences.

CONCLUSION AND RECMENDATIONS

The prevalence of toxocariasis was high in EUO patients and serodiagnosis of *Toxocara* antibodies is essential for evaluation of EUO. So, clinicians have to consider toxocariasis infection as a common cause of eosinophilia especially in urban areas. Serological investigations for *Toxocara* IgG by ELISA and clinical factors are so reasonable and effective in detection, diagnosis and treatment of toxocariasis. we recommended for a large population based study survey to assess the magnitude of this disease and to identify more details about risk factors.

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