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Human Toxocariasis among Asthmatic Patients in Basrah Province/ Iraq

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Abstract: *Objective: To study seroprevalence of Toxocara antibody immunoglobulin G , epidemiological risk factors and assess the immunological pattern including cytokines interleukin-6 and interleukin-10 and immunoglobulin E among bronchial asthmatic patients in Basra. Subjects and Methods: 113 asthmatic patients with ages range from 2-80 years (51 females and 62 males) and 109 apparently healthy persons(control) (59 females and 50 males) were enrolled in the study. It was done during the period from December 2017 to November 2018 at Pediatric and Respiratory Consulting Clinic of Basrah Teaching Hospital. The risk and epidemiologic factors were assessed by a questionnaire which was completed by the patients themselves or relative. immunoglobulin and cytokines were assessed by using ELISA while IgE by immunoturbidometric assay for every asthmatic patients and healthy group. Results: Thirty (26.55%) asthmatic patients were seropositive for Toxocara antibody (IgG) in comparation with 2 (1.83%) of control with significant difference between them (p=0.0001). There wasn't significant difference between seropositive and seronegative asthmatic patients in regard to characteristic features of population and risk factors . The immunological assessments revealed an elevation in the level of IgE and IL-10 in seropositive group as compared with Seronegative while IL-6 concentration was elevated in seronegative group. Conclusion: Toxocariasis may play role as a risk factor for asthma. Thumb sucking and family history may increase risk of infection. Toxocariasis may lead to elevated levels of IgE and IL-10 in these patients but it appears has weak influence on concentration of IL-6.*

Keywords: Toxocariasis ,Asthma ,IL-10 ,IL-6, IgE

1. INTRODUCTION

Migrating larvae of roundworm *Toxocara canis* or *Toxocara cati* that reside in the tissue of dogs or cats respectively can also infect other animals and human beings. The infection route is well-known for humans including accidental swallowing of embryonated eggs either from soil or contaminated food, or may by ingestion of encapsulated larvae of *Toxocara. spp* that present in the tissue of a paratenic hosts (1). After ingestion by human, the larvae penetrate the mucosa of intestine and migrate to many organs like liver, lungs, skeletal muscle, eyes, brain and heart (2). These larvae do not multiply within the paratenic host, like man, but remain in host tissues at arrested for development state (3). The symptomatic toxocariasis gives 3 clinical features including ocular larva migrans (OLM), visceral larva migrans (VLM) and neurological Toxocariasis (NT) (4). While covert or common toxocariasis is a subclinical form of *Toxocara* infection and accordance with (5), this form of toxocarasis may associate with asthma and atopic disease. However the type of clinical manifestations resulting from human infection with *Toxocara spp* are determined by factors associated with parasite itself like the pathway of the larvae migration and the parasite load in addition to the host's immune response to the parasite (6).

It has been suggested through epidemiological and experimental studies that human infection with *Toxocara spp* lead to increase the development of allergic manifestations such as asthma (7) as a result of allergic inflammation in the lungs with bronchial hyperreactivity (8). Therefore, *Toxocara* infection can be considered as a possible etiologic agent of asthma (9) and participate in asthma symptoms mainly among young children who exposed to high doses or repeated infection in regions where the infection is endemic. Thus, the toxocarasis can be considered as a risk factor for asthma (10). Infection with this parasite may result in asthmatic like symptoms such as airflow obstruction, coughing and wheezing which have been associated with hypereosinophilic syndrome (11).

Toxocara larvae invasion to various tissues, such as brain, muscles and eyes, demand an exceptional ability to evade or block or host immune attack in order to survive for years in tissues. This ability is related to deployment of molecules that are secreted or excreted by the parasite or released from its surface (12,13). These molecules or antigens secreted by *Toxocara spp* larvae have allergenic properties, suggesting that this parasite may generate high levels of total IgE (14). However, the Immune responses are mediated by (Th2) via the induction of cytokines e.g. IL–4, IL-5, IL-13, and IL-10, that can result in an increasing in the level of eosinophilia and specific antibodies (13,15).

Since no work has been done on the interaction of toxocariasis with asthma, this work has been studied and covered this aspect in Basrah province

SUBJECTS AND METHODS:

Study site and population:

This study was carried out at Basrah Teaching Hospital from December 2017 to November 2018. One hundred thirteen (113) asthmatic patients (62 males, 51 females) who attend Pediatric and Respiratory Consulting Clinic of Basrah Teaching Hospital. were included in the study. The patients ages ranges between 2-80 years. Exclusion criteria were history of diabetic mellitus, rheumatic diseases, diarrhea and abdominal pain. In addition 109 apparently healthy persons (volunteers) were enrolled in this study as a control group. Both groups are sex and age matched. A full history were taken from patients or their parents and full clinical examination was done for each patient. Pulmonary function tests (spirometry reversibility test and peak expiratory flow arte) were done to each patient more than 5 years of age in order to confirm diagnosis. Children younger than 5 years of age, the diagnosis depends on special criteria.

A questionnaire was applied to each patient and child parents or guardians to obtain socioeconomic and epidemiological information e.g. sex, age, animal ownership, presence of garden at home, exposure to soil, onychophagia or geophagia habit, thumb sucking, medicine intake, family history of the disease, residence, occupation and duration of disease.

A five milliliter of venous blood sample was collected from each patients and control group under strict aseptic conditions by plane tube with gel and clot activator without EDTA Sera were later separated from clotted blood by centrifugation and immediately frozen at -80^{o}C until used.

Measurement of seropositivity for toxocariasis:

Toxocara antibodies were detected by the commercial human IgG *Toxocara* microwell serum and plasma ELISA Kits (T8072, usbiological life science, united states) with sensitivity 87.5% and specificity 93.3%. According to the protocol, the result is positive when the absorbance reading ≥ 0.3 OD units while the negative < 0.3 OD unites.

Measurement of total IgE in serum:

Serum IgE levels were evaluated in all seropositive group(30) against 30 of seronegative group and 30 of control taken by using kits QUANTIA IgE Reagent Kit (6k42-01), (biokit S.A.Can Male,s/n08186 Llica d Amunt Barcelona Spain distributed by Abbott). This kit intended for quantitative determination of IgE (IU/mL) in plasma or serum by immunoturbidometric assay by using the Abbott Architect c System using standard protocol as mentioned in the kit through using Architect c4000 system apparture (Japan)

Measurement of IL-10 and IL-6 concentration:

The same groups and method of preparation of serum sample as measurement of total IgE have been used to detect concentration of IL-10 and IL-6 but by using Human IL-10 ELISA kit (E-EL-H0103) and Human IL-6 ELISA kit (E-EL-H0102) from Elbscience (USA). However, after followed, each one procedure, the optical density was determined (OD value) by micro–plate reader set to 450 nm and then calculate the concentration according to kite procedure.

Data analysis:

Data for characteristics features of population and risk factors was analyzed by chi square .

Data for (IL-10,IL-6,IgE)were analyzed by using one way analysis of variance (ANOVA) which is supported by Turkey's spost. Risk ratio was evaluated by odd ratio (95% CI). The significant p-value is at $p < 0.05$. Data analysis was performed by Graph Pad Prism software for windows (version 7, Graph Pad Soft ware, Inc).

RESULT

Thirty out of 113 (26.55%) asthmatic patients were found to be positive for *Toxocara* antibodies in comparison to only 2 (1.83%) were positive in the control group (both were 40 years old). This difference is statistically (p-value is 0.0001) as shown in table-1.

Tabe-2 shows the relation between seropositive and seronegative asthmatic patients with age and sex, and the difference is statistically not significant (p-value 0.834 and 0.07 respectively).

Table (3) shows no significant association between *Toxocara* prevalence and various risk factors in asthmatic patients (residence, exposure to soil, geophagia, animal ownership, presence of home garden, onychophagia, thumb sucking, medicine intake, family history, duration of asthma disease and occupation). It also it shows (according to value of Odd Ratio) an elevation in risk ratio of five variable risk factors, (onychophagia, thumb sucking, geophagia, medication intake and family history (risk factor is 1.133, 5.587, 2.4 , 2.063and 16.193 respectively) in contrast to other variable factors regarding their influence onseroprevalence of *Toxocara* antibody in asthmatic patients.

Table(1): Seroprevalence of Toxocariasis

Groups	Asthmatic *Toxocara* Positive Total no. = 30	Asthmatic *Toxocara* Negative Total no. = 83	Control Group Total no. = 109	P-value
Seropositive	30 (26.55%)	-----	2 (1.83%)	0.0001
Seronegative	-----	38 (73.45%)	107 (98.17%)	

Table(2): Seroprevalence of *Toxocara* in relation to age and sex in asthmatic patients

Variable		Asthmatic *Toxocara* Positive Total no. = 30	Asthmatic *Toxocara* Negative Total no. = 83	P-value
Sex	Male	17	45	0.834
	Female	13	38	
Age (Years)	2-18	12	21	0.07
	19-39	10	32	
	40-59	5	28	
	60-80	3	2	

Table (3): Seroprevalence of *Toxocara* in relation to different risk factors in asthmatic patients

Variable		Asthmatic *Toxocara* Positive Total no. = 30	Asthmatic *Toxocara* Negative Total no. = 83	P-value	Odd ratio (95% CI)
Residence	City center	24	72	0.38	0.611 (0.204-1.830)
	Uptown	6	11		
Exposure to soil	High	14	45	0.527	0.739 (0.320-1.707)
	Low	16	38		
Geophagia	Yes	4	5	0.234	2.4 (0.599-9.613)
	No	26	78		
Animal ownership (dogs, cats)	Yes	5	16	0.99	0.838 (0.278-2.527)
	No	25	67		
Garden in house	Yes	10	33	0.662	0.758 (0.315-1.821)
	No	20	50		
Onychophagia	Yes	6	15	0.79	1.133 (0.395-3.255)
	No	24	68		
Thumb sucking	Yes	2	1	0.17	5.587 (0.511-67.098)
	No	28	82		
Medication intake	Yes	26	63	0.3	2.063 (0.643-6.627)
	No	4	20		
Family history for asthma	Yes	19	8	0.294	16.193 (5.72-45.84)
	No	11	75		
Duration of asthma	< 1 year	13	23	0.409	x
	1-3 years	7	30		
	4-5 years	2	7		
	> 5 years	8	23		
Occupation	Pupils	15	30	0.224	x
	Housewife	7	23		
	Employed	2	19		
	Unemployed	6	10		
	Child	0	1		

The levels of total IgE concentration (IU/mL) in the serum of asthmatic patients who are seropositive to *Toxocara* antibody (Asth.T.posative)was higher in comparison with both seronegative asthmatic patients (Asth.T.Negative) and control group. The difference between seropositive and control groups is statistically significant (p-value is 0.0032) as shown in Fig. 1

Fig.2, we can see that the asthmatic patients who are seropositive to *Toxocara* antibody (Asth.Tok .posative)have increased levels of IL-10 concentration than in those who are Seronegative(Asth.Tok.Negative) and control group. The relation between IL-10 levels and *Toxocara* seropositivty (Asth.Tok.posative)is statistically significant (p=0.006). While the difference is statistically not significant between these groups in relation to the levels of IL-6 as shown in Fig.3.

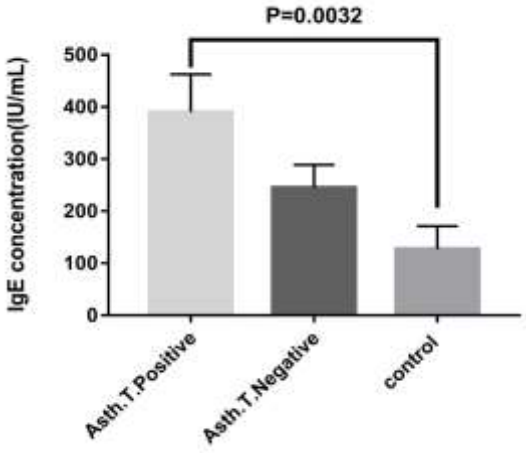

Fig.1**: Total IgE levels in relation to *Toxocara* seroprevalence in asthmatic patients and the control groups.**

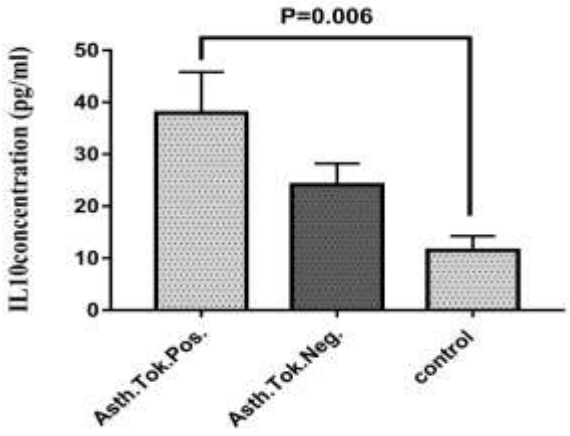

Fig.**2: Correlation between IL-10 levels and *Toxocara* seroprevalence in asthmatic patients and control groups.**

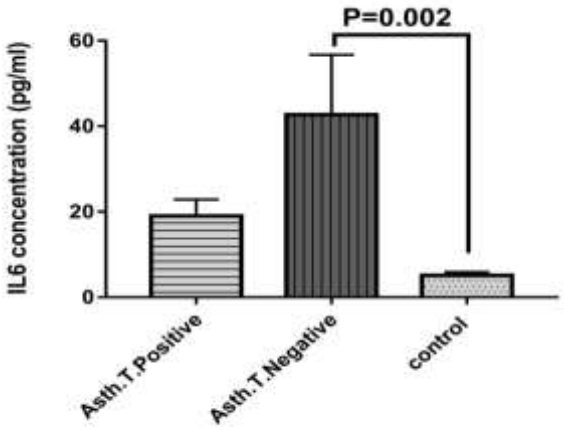

Fig.3: Correlation between IL-6 levels and *Toxocara* seroprevalence in asthmatic patients and control groups.

Discussion

Toxocara infection is prevalent among stray dog in Basrah province. 26.5% of stray dogs in different regions of Basrah were infected with *Toxocara canis* (16). The present study on asthmatic patients has revealed elevation in titer of *Toxocara spp* antibody with significant difference between them and control group, and this is in agreement with previous studies in Egypt(17,18) as well as in Iran(19). These findings support the suggestion that toxocariasis could represent as a risk factor for asthma (7). Larvae of *Toxocara* can migrate to the host lungs causing irritation, strong inflammatory reaction and lesions and these consider predisposing factor in the onset of asthma (20). However, other didn't find significant correlation between asthma and *Toxocara* seropositivty as in Turkey(21).

In the present study, there was no significant relationship regarding characteristic feature of population (sex and age) and the risk of toxocariasis which is in agreement with previous findings (21,19), but two fold increase in risk of toxocariasis in boys as compared with girls in Brazil(22).

The present study has shown lack of significant difference between urban and uptown residency regarding *Toxocara* seropositivty that can be explained by exposure of patients in the two regions to the same predisposing factors for infection in accordance with findings of (17).

There wasn't any association between positive seroprevalence of *Toxocara spp* with keeping animals (dogs or cats) in present study. Similar result has been reported in Iran(19). Also animals ownership don't consider a risk factor for infection in this study that may be explained by small number of patients were having pets in their houses.

There was no significant association between socioeconomic categories in the present results as findings of previous study results (9) . Some have shown a positive significant with socioeconomic status in Brazil(23).

Significant association was appeared between toxocariasis and exposure to soil (9) in contrast with findings of present study which shows exposure to soil don't represent a risk factor for infection. This may be due to a small number of patients have been exposed to soils in our study.

In the present study, there was no correlation between seropositivity and geophagia and onychophagia, this is may be explained by that the patients didn't tell an accurate information about their habits in agreement with study in Brazil (24). In contrast other studies had found significant relationship between seropositivity and geophagia (17) and onychophagia (23). While in present study, geophagia and onychophagia show elevation of risk ratio. However the main role for these habits are to facilitate ingestion of infective eggs from contaminated soil which is represent the main route for infection (25).

In the present study, patients with thumb sucking were at a higher risk of developing toxocariasis. However, thumb sucking doesn't appear to have a significant correlation with seropositivity of *Toxocara* and the same results were reported in Iran(26). This higher risk for infection is explained by that this habit facilitates transferring the infective eggs to mouth.

Medication intake and different types of asthma medicines appeared to have a high risk factor ratio on their influence on *Toxocara* infection, as indicated in the present study, and this may be due to that most cases in this study were under treatment and such treatments may an immune-modulation on the patients.

Patients who have family history of asthma are at sixteen times greater risk of being *Toxocara* seropositive as compared to others with no family history of asthma. The reason may be due to genetics of the host that determine resistance or susceptibility to parasitic infection via innate or acquired immunity (27).

The elevation in the level of total IgE in serum of seropositive asthmatic patients group with significant difference between them and control group has been confirmed in this study as previous study in Egypt (17). This may confirms the fact that toxocariasis is associated with increasing levels of serum total IgE (28).

The present study showed higher level of IL-10 concentration in seropositive asthmatic patients than in seronegative asthmatic patients or control group with a significant difference between them and control group, similarly the study of on *T. canis* monoinfected children(29) which has confirmed significant increase in the plasma values of IL‑10 and TNFα as compared with control . This is because Inflammatory response including release of large amount of pro-inflammatory agents like TNFα which can, in turn, induce the synthesis and release of anti-inflammatory cytokines to inhibit production of pro-inflammatory cytokines e.g. IL-10 and hence their raised plasma levels of TNFα and IL-10 (30,31). In addition, It has been found in asthmatic patients an increasing levels of IL-10 than in control group and this increment occurs only after exposure to allergens which act as mitogens(32). The present study results have confirmed the role of *Toxocara* infection in increasing levels of IL-10 in asthmatic patients.

Also the present study result shows that patients who are seropositive to *Toxocara* with high levels of IL-10 have low IL-6 concentration which agrees with the fact that IL-10 may have a role in decreasing the synthesis of nonspecific pro-inflammatory cytokines such as IL -6 (33).Also through result of previous experiment on splenocytes from infected mice with *Toxocara* produce less amounts of IL-6 compared to control group (34). In contrast with other study which was found through a linear regression analysis, that the higher the index of sreopositivity of *Toxocara* leads to higher levels of IL-6(35). The present study has shown an elevation in the level of IL-6 in the serum of seronegative group as compared to the control group with a significant difference which is in agreement with study which was illustrated that an elevation in the level of circulating IL-6 concentration in asthmatic patients and even in asymptomatic asthmatic one(36).

Conclusion: In asthmatic patients in Basra province infection with *Toxocara spp* may play role as a risk factor for asthma. Risk factors such as onychophagia, thumb sucking, medication intake and family history may increase risk infection with *Toxocara spp* in asthmatic patients. Also toxocariasis may lead to elevated concentration level of IgE and IL-10 in these patients but it appears has weak influence on concentration of IL-6.

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