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Detection of Parasitic Infections in Children with Allergic Rhinitis Compared to Healthy Control in Upper Egypt

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Abstract

Objectives: This study aimed to evaluate parasitic infections in children with allergic rhinitis (AR) referring to a tertiary center in Egypt.
Methods: A case-control study was conducted on 139 children (78 males) with allergic rhinitis aged from 6 to 14 years attending Assiut University Hospitals, as well as 70 healthy children as controls. All participants underwent stool analysis, serology for IgG antibodies to *Toxocara canis*, IgE antibodies to *Ascaris lumbricoides*, serum IL-5 levels, and urinary leukotriene E_4.
Results: AR patients showed significantly higher values of absolute eosinophilic count (AEC), IL-5, urinary leukotriene E_4, and total IgE than controls. Anti-*Ascaris* IgE and IgG anti-*Toxocara canis* were positive in 18.7% and 18% of patients respectively. Giardia infection was detected in stools of 20.1% of patients. Patients with parasitic infections showed significantly higher AEC, serum IL-5, and urinary leukotriene E_4 values than those with negative infection and controls.
Conclusions: Our study revealed that infections with *Ascaris*, *Toxocara*, and *Giardia* were more common among AR children compared to healthy children and they were significantly associated with disease severity so the infection with these parasites may be a risk factor for AR among Upper Egyptian children.

Keywords: Allergic Rhinitis, *Ascaris lumbricoides*, *Giardia lamblia*, Toxocara Species, Egypt

1. Background

Parasitic infections have been reported in about 25% of the world's population. These infections are more prevalent in developing countries, especially in rural areas of tropical and subtropical regions (1, 2). In Egypt, parasitic diseases represent a serious public health problem in both immunocompetent and immunocompromised patients with clinical and economic impacts. The prevalence of parasitic infections among children is high, with levels reaching up to 50%. This high prevalence is mainly due to overcrowding and poor hygiene patterns that significantly contributed to the spread of parasitic infections (1-3).

Allergic rhinitis (AR) is the most common airway allergic disease. Nowadays, AR is a significant health problem affecting up to forty percent of children worldwide, which have a significant influence on children's quality of life, costs involved, and load on national health care services. AR is an allergic inflammation of the nasal mucous membranes. It is a type I hypersensitivity reaction mediated by allergen-specific IgE antibodies, presented by repetitive paroxysmal sneezing, watery rhinorrhea, and nasal blockage. AR often shares the common risk factors for bronchial asthma, especially atopy (4). Genetic and environmental risk factors are involved in the pathogenesis of AR; however, the exact etiology remains to be identified (5, 6). Epidemiological studies conducted in many countries have reported that helminthic infections are, associated with a reduced or increased prevalence of atopy and allergic diseases (7, 8). Total IgE, IL-5 and leukotriene E_4 may be involved in the pathogenesis of atopic and allergic disorders, and patients with allergy may have enhanced levels of both compared with normal individuals (8, 9). Although there

have been many recent studies, the association between helminthic infections and childhood atopy remains controversial (5).

2. Objectives

Because of the conflicting results in the literature on parasitic infections in pediatric allergic disorders, especially AR and the number of the studies are very few; the present study aimed to evaluate parasitic infections in children with AR referring to a tertiary care center in Upper Egypt.

3. Methods

3.1. Study Design

This was a case-control study undertaken in Assiut Children University Hospital, Assiut, Upper Egypt.

3.2. Participants

This study included 139 children with AR attending Assiut University Children's Hospitals, Egypt from January 2014 to May 2016. The diagnosis of AR was established by a senior ENT consultant before recruitment of patients into the study. Diagnosis of AR was confirmed according to Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines (10). Severity grading and classification of AR patients were performed based on ARIA criteria as follows: Intermittent AR (mild or moderate-severe) or persistent AR (mild or moderate-severe) (10). All manifestations of AR including sneezing, rhinorrhea, nasal obstruction, and itching, and facial features (allergic salute, shiners, nasal crease, mouth breathing, conjunctivitis, and infraorbital fold) were assessed in all patients. Seventy age- and sex-matched non-atopic, non-asthmatic healthy children were recruited as healthy controls. The controls were enrolled after exclusion of chronic systemic diseases or family history of atopy. Treatment with systemic antihistamines and corticosteroids was stopped at least two weeks before the study. Children were excluded from the study if they had any of the following: 1) manifestations of allergic symptom exacerbation, 2) associated other diseases, e.g., sinusitis, asthma, acute respiratory tract infections, and nasal septum deformities, and 3) recent history of antiparasitic medications or immunotherapy six months before the study.

3.3. Laboratory Investigations

All patients and controls underwent laboratory tests, which included stool examination, total IgE, absolute eosinophilic count (AEC), serology for IgE antibodies to *Ascaris lumbricoides*, ELISA for IgG antibodies to *Toxocara canis*, serum IL-5 levels, and leukotriene E_4 in urine.

3.3.1. Stool Examination

Stool samples from all participants were collected in sterile clean stool plastic disposable cups with lids labeled with the patient's serial number, name, age, sex, group of AR and date of collection. The parasitological examinations were immediately processed within half an hour. A direct wet smear was performed using iodine and lactophenol cotton blue. Afterward, fomol-ether sedimentation was done to the stool samples and examined by direct wet smear (as previous) and Kinyoun acid-fast staining procedure.

3.3.2. Urinary Leukotriene E4

LTE_4 levels were measured using the commercially available enzyme immunoassay (Cayman Chemical; Ann Arbor, MI, USA).

3.3.3. Blood Samples

Blood samples were collected from the subjects by venepuncture. Cellular assay (AEC) was performed (Eosinophilia corresponded to levels above 400/mm^3), and the serum samples collected were stored at -70°C until the serological analysis.

3.3.4. Levels of Total IgE

The levels of the total IgE were measured by ELISA where levels above 200 IU/mL were considered high. All samples were measured in duplicate.

3.3.5. Human IL-5 Level Assay

IL-5 levels were measured using the commercially available human enzyme-linked immunosorbent assay kit (Biosource International, Inc., Camarillo, California, USA), according to the manufacturer's instructions. The lowest level of detection of IL-5 was 2 pg/mL. The intra-assay coefficient of variation was 7.4%, and the inter-assay coefficient of variation was 10%.

3.3.6. Serological Detection of Ascaris lumbricoides Infection

Specific IgE levels against Ascaris were measured by the CAP-FEIA fluoro enzyme immunoassay method (Phadia AB, Uppsala, Sweden).

3.3.7. Serological Detection of Toxocara canis Infection

Excretory/secretory antigens were prepared from laboratory cultivated second stage larvae of *T. canis*. The antigen was stored at -70°C until used as a crude antigen. IgG against *T. canis* was detected by ELISA technique. ELISA plates (Flow Lab. Cat. No., 76-321-05) were coated by the prepared antigen. Anti-human IgG peroxidase (Sigma-A 602g) conjugate and orthophenylene diamine substrate buffer citrate (OPD Sigma Cat. No. P-4512) were used.

3.4. Statistical Analysis

Data were analyzed using SPSS statistics version 22 (IBM Corporation, NY, USA). Values were expressed as means and standard deviation (SD). Qualitative variables were presented as number (n) and percentage (%). Chi-square test was used to compare qualitative variables between groups. Unpaired *t*-test and Mann-Whitney "U" tests were used to compare quantitative variables. Anti-*Ascaris* IgE was classified into quartiles based on the distribution of the study participants.

4. Results

Table 1 shows the demographic and laboratory data for patients and controls. The mean age of the patient group was 6.8 ± 3.6 years, and their age range was 6 - 14 years, with insignificant differences with the control group. AR patients showed significantly higher values of AEC, IL-5 and total IgE than controls. Furthermore, AR children showed significantly higher urinary LTE_4 levels than controls (Table 1). In the patient group, 86.3% of the AR children resided in urban districts, while the remaining (13.7%) lived in rural regions. In the control group, 85.7% of children lived in urban areas, while 14.3% lived in rural regions.

Table 1. Demographic and Laboratory Data for Patients and Controls[a,b]

Variables	AR Patients (N = 139)	Controls (N = 70)	P Value
Age, y	6.8 ± 3.6	7.1 ± 2.9	0.85
Weight, kg	24.8 ± 16.6	26.1 ± 15.4	0.35
Height, cm	121.0 ± 15.7	122.0 ± 14.2	0.28
BMI	16.9 ± 5.7	17.2 ± 4.8	0.30
Gender			0.28
Males	78 (56.1)	40 (57.1)	
Females	61 (43.9)	30 (42.9)	
IL-5, pg/mL	45.2 ± 32.5	6.7 ± 3.9	0.0001
AEC	731.9 ± 244.3	121.9 ± 51.6	0.0001
LTE_4, pg/mL	395.0 ± 286.2	35.2 ± 5.0	0.001
Total IgE, IU/mL	426.4 ± 51.2	32.9 ± 14.2	0.0001

Abbreviations: AEC, absolute eosinophilic count; IL-5, interleukin-5; LTE_4, leukotriene E_4.
[a] Values are expressed as mean ± SD or No. (%).
[b] No significant (P > 0.05).

As regards the severity of AR, patients were classified into two groups; mild and moderate/severe AR. Group I included 78 patients with mild AR (45 males and 33 females) and group II included 61 patients with moderate/severe AR (33 males and 28 females).

As regards the frequencies of parasitic infections among the examined patients and controls; stool examination for *Ascaris* ova and larvae and anti-*Ascaris* IgE were positive in 26 (18.7%) patients and seven controls (10%). IgG anti-*Toxocara canis* was detected in 25 (18 %) patients and five controls (7.1%), whereas Giardia infection was detected in stools of 28 (20.1%) patients and four controls (5.7%). Among 26 patients infected with Ascaris 24 patients had moderate/severe AR, and only two patients had mild AR. Among AR patients infected with Toxocara 21 patients had moderate/severe AR and only four patients had mild AR. Of 28 AR patients infected with Giardia 20 patients had moderate/severe AR, and eight patients had mild AR. AEC, serum IL-5 and urinary LTE_4 levels were significantly higher in patients with moderate/severe AR when compared to children with mild AR (Table 2). Patients with positive parasitic infections showed significantly higher values for AEC, serum IL-5, and urinary LTE_4 than those with negative infection. We found that AR patients with Giardia infection, anti-*Ascaris* IgE, and anti-*Toxocara* IgG were significantly associated with AEC, total IgE, IL5 and Leukotriene E_4. No association was found with age, sex, and residence, but a definite association with disease severity.

5. Discussion

The incidence of allergic diseases in children, e.g., allergic rhinitis, asthma, and atopic eczema has been continuously rising, especially over the last two decades (11). Given the influence on children's quality of life, financial impact, and considerable load on the national health care services, there have been numerous clinical studies to recognize the predisposing factors and treatment modalities of allergic diseases. The link between helminthic infections and childhood atopy remains controversial. In this study, we investigated the prevalence and relation of parasitic infections with *Ascaris lumbricoides*, *Toxocara canis*, *Giardia lamblia* and the severity of AR in children compared to healthy children. As regards the association of parasitic infections (ascariasis, toxocariasis, and giardiasis) and AR, anti-*Ascaris* IgE and IgG anti-*Toxocara canis* were detected in 18.7% and 18% of patients, respectively, whereas Giardia infection was detected in 20.1% of our cohort. All the three types of parasitic infections were significantly higher in AR patients when compared to control group (P = 0.01 for each). Moreover, parasitic infections with *Ascaris*, *Toxocara*, and *Giardia* were more common among moderate/severe AR children than mild AR. This was supported by the detected significantly higher AEC, urinary LTE_4 and IL-5 in *Ascaris* (Table 3), *Toxocara* and *Giardia* positive AR than negative cases.

Table 2. AEC, Serum IL-5 and Urinary LTE_4 of Studied Patients Versus Controls[a]

	Group I Mild AR (N:78)	Group II Moderate/Severe AR (N:61)	Group III Controls (N:70)	P1-Valuei Versus III	P2-Value II Versus III	P3-Value Versus II
AEC	332.6 ± 100.6	953.5 ± 122.0	121.9 ± 51.6	0.001	< 0.0001	0.0001
IL-5, pg/mL	13.3 ± 3.6	74.3 ± 30.3	6.7 ± 3.9	0.001	< 0.0001	0.0001
LTE_4, pg/mL	110.1 ± 49.4	656.3 ± 259.7	35.2 ± 5.0	0.001	< 0.0001	0.0001

Abbreviations: AEC, absolute eosinophilic count; IL-5, interleukin-5; LTE_4, leukotriene E_4.
[a] Values are expressed as mean ± SD.

Table 3. AEC, Serum IL-5 and Urinary LTE_4 in Patients with Positive and Negative Ascaris Infection Versus Controls[a]

	I Patients with Positive Ascaris Infection (N: 26)	II Patients with Negative Ascaris Infection (N: 113)	III Controls (N: 70)	P Values		
				I Versus III	II Versus III	I Versus II
AEC	888.0 ± 249.7	696.3 ± 230.8	121.9 ± 51.6	0.0001	0.0001	0.010
IL-5, pg/mL	62.7 ± 37.4	41.2 ± 30.3	6.7 ± 3.9	0.0001	0.0001	0.031
LTE_4, pg/mL	665.8 ± 308.5	340.9 ± 253.5	35.2 ± 5.0	0.0001	0.001	0.009

Abbreviations: AEC, absolute eosinophilic count; IL-5, interleukin-5; LTE_4, leukotriene E_4.
[a] Values are expressed as mean ± SD.

In line with our results; Dold et al. (12), studied Ascaris-specific IgE and allergic sensitization in a large cohort of atopic children in East Germany (2300 children) in two surveys. They reported that seropositive *Ascaris*-IgE had tenfold higher levels of total IgE than negative patients. Furthermore, these patients had higher prevalence rates of seropositive allergen-specific IgE. Also, they had a higher prevalence of allergic rhinitis ($P < 0.001$) and asthma ($P < 0.05$). After adjustment for age, sex and other variables, a positive result of Ascaris IgE was a stronger risk factor for allergic sensitization to inhalant allergens. The study reported that low doses of parasitic antigens are accompanied with an increase of IgE production, and parasitic infestations were not causative factors for the low prevalence of allergies in East Germany (12). The observations about Ascariasis and allergy were reported by many epidemiological studies, using numerous approaches. These reports have shown that Ascariasis is a risk factor for atopic diseases (13-16). Not all studies, however, have shown an association between Ascariasis and allergy, some reports have indicated inverse associations between allergen skin test reactivity and infections with Ascariasis (17, 18).

As regards *Toxocara* infection, the pieces of evidence from the previous epidemiological studies were also conflicting. In agreement with our research, most of the studies (19-21) suggested that *Toxocara* infection contributed to the development of atopy and allergic disorders. Chan et al. (19) reported that *Toxocara* infection might increase the predisposition to atopy and allergic diseases, especially in children. Furthermore, toxocariasis was associated with higher levels of total serum IgE, allergen-specific IgE, eosinophil counts, atopic asthma, increased skin sensitivity to aeroallergens, and reduced lung functions in the *Toxocara* seropositive patients than in the seronegative group (19-21). On the other hand, not all studies supported the previous findings. Few studies were unable to show any positive association between *Toxocara* seropositivity and allergen skin test reactivity and atopic diseases (22, 23).

Few studies investigated the association between giardiasis infection and allergic diseases. In line with our study, Di Prisco et al. (24) reported that 70% of the patients infected with *G. lamblia* presented with allergies, such as allergic rhinitis, asthma, atopic dermatitis, angioedema, acute urticaria, and chronic urticaria, compared to only 43% of non-parasitized patients. The authors attributed the increase of these allergic diseases to changes in intestinal mucosal cells of the infected host, which may favor the absorption of non-adequately metabolized protein antigens with the following development of allergic disorders (24). Also, other studies found that patients infected with *G. lamblia* had high titers of total and specific IgE, as well as cutaneous hyperreactivity for environmental antigens (25, 26). On the other hand, studies found no association between *G. lamblia* infection and the respiratory tract allergies (27).

5.1. Conclusions

Our study revealed that infections with *Ascaris*, *Toxocara*, and *Giardia* were more common among AR children compared to healthy children and they were significantly associated with the disease severity so the infection with

these parasites may be a risk factor for allergic rhinitis among Upper Egyptian children.

5.2. Limitations to the Present Study

There were some limitations to our study. Firstly, it was a case-control study; so, our data did not deliver direct information as to whether parasitic infections are a cause of the development of AR. In addition, we could not do skin prick tests, which helps in the diagnosis of AR.

Footnotes

Authors' Contribution: Khaled Saad, Alam-eldin Mohammed Abdalla, Mohamed Diab Aboul-Khair, and Abobakr Abdelmoghny conceptualized and designed the study protocol development, assessment of the patients, and writing manuscript. Doaa Yones, and Asmaa Mohammed Zahran, performed all lab investigations. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflict of Interests: All authors declare no potential conflict of interest concerning the research, authorship, and/or publication of this article.

Ethical Approval: The protocol of this study was in accordance with the regulations of the relevant clinical research ethics committee and with those of the code of ethics of the world medical association Declaration of Helsinki. Written informed consents of caregivers of all children were taken according to the Ethical Committee of Faculty of Medicine, Assiut University, Egypt, the date of approval 2-Jan-2014 (number 126-1-2014).

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