
Skin test reactivity and Der p–induced interleukin 10 production in patients with asthma or rhinitis infected with *Ascaris*

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Background: Helminth infections have been associated with reduced reactivity to aeroallergens, which could be related to interleukin 10 (IL-10) production, as reported in schistosomiasis.

Objective: To compare skin responses to aeroallergens with Der p specific IL-10 production in patients with asthma or rhinitis according to *Ascaris* infection status.

Methods: Cross-sectional study of 113 patients with asthma or rhinitis from a region endemic for geohelminths. Stool examinations and skin prick tests to aeroallergens were performed in all the patients. Der p specific IL-10 production was measured in the supernatant of peripheral blood mononuclear cell (PBMC) cultures of a subsample of 53 patients.

Results: Forty-seven patients had *Ascaris* in their stool samples. Skin test results were positive in 77% of *Ascaris*-infected patients and in 71% of uninfected individuals. Median levels of Der p specific IL-10 in PBMC cultures of infected and uninfected patients were similar (7.8 and 8.4 pg/mL, respectively). The lack of association remained when parasite load was taken into account and when patients with evidence of previous infection were removed from the uninfected group.

Conclusions: In patients with asthma or rhinitis living in an urban area endemic for geohelminths, we found no association between *Ascaris* infection and skin reactivity to aeroallergens. Furthermore, there was no difference in Der p specific IL-10 production by PBMCs. These negative findings indicate that different from what is observed in *Schistosoma* infection, *Ascaris lumbricoides* infection in individuals living in an urban area does not induce strong regulatory responses.

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INTRODUCTION

The prevalence of allergic diseases is increasing around the world. Studies¹ have shown a higher prevalence of asthma in Western industrialized countries compared with developing countries. To explain these differences, factors such as childhood infections have been studied, and there is some evidence that exposure to infections protects against allergic diseases.^{2,3} The mechanisms of such protection are not well established.

Although helminth infections and allergic diseases lead to a T_H2 immune response, a negative association among the prevalence of these diseases has been demonstrated.^{1,4} Furthermore, *Schistosoma* (blood fluke) infection is associated with reduced skin prick test reactivity to common aeroallergens^{5,6} and with an attenuated course of asthma.⁷ Geohelminths such as *Ascaris lumbricoides* (roundworm), *Trichuris trichuria* (whipworm), and Ancylostomidae (hookworm) might also interfere with skin test reactivity. Some large

cross-sectional studies^{8,9} have demonstrated less atopy and fewer asthma symptoms in patients infected with geohelminths. However, cross-sectional surveys are not sufficient to establish a causal relationship between helminth infection and course of allergy. Recently, van den Biggelaar et al¹⁰ demonstrated, in a randomized controlled trial, that antihelminthic treatment of infected children results in increased atopic reactivity, which indicates that helminth infections suppress allergic reactions.

One hypothesis to explain the inhibition of atopy by helminths is related to the regulatory effect of some cytokines produced during helminth infections, such as interleukin 10 (IL-10). High levels of IL-10 produced in response to parasite antigens have been documented in patients infected with *Onchocerca volvulus*¹¹ and *Schistosoma mansoni*.^{12–14} Interleukin 10 is a cytokine produced by monocytes, T_H2 or T_H3 cells, which may inhibit the T_H1 and T_H2 immune response.¹⁵ Recently, it was demonstrated that IL-10 is capable of inhibiting the release of histamine by mast cells.¹⁶ Van den Biggelaar et al⁵ demonstrated an association between high levels of helminth-specific IL-10 production and the lack of skin prick test reactivity to common aeroallergens in children infected with *Schistosoma hematobium*.

We conducted a cross-sectional study to investigate whether *A lumbricoides* infection is associated with attenuation of skin prick test response to allergens in patients with asthma or rhinitis living in an urban area of high risk of

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geohelminth infection. Furthermore, we evaluated *Dermatophagoides pteronyssinus* specific IL-10 production by peripheral blood mononuclear cells (PBMCs) to evaluate immune regulatory activity in this group of individuals.

METHODS

Study Population

Patients were recruited from 4 slum areas with the same low socioeconomic status in Salvador, Bahia, Brazil. Patients were included in the study according to the following criteria: aged 12 to 30 years, current clinical diagnosis of asthma or rhinitis for at least 2 years, and high risk of parasite infection characterized by the presence, in the past year, of a documented geohelminth infection in the patient or in a family member living in the same household. Patients with systemic diseases, those with *S. mansoni* infection, and pregnant women were excluded. The diagnosis of asthma was based on the presence of dyspnea, wheeze, or cough, reversible spontaneously or with short-acting β_2 -agonist bronchodilators. The diagnosis of rhinitis was based on the presence of nasal obstruction, sneezing, rhinorrhea, and pruritus. This study was nested in a clinical trial of the safety of anti-IgE therapy conducted in the University Hospital of Federal University of Bahia after approval by the institutional review board. Written informed consent was obtained from the patients or their guardians.

Study Design

This was an exploratory study, and the sample size was chosen by convenience. The selected patients were submitted to clinical and laboratory evaluations, including 2 stool examinations using the method of Kato-Katz for quantitative helminth parasite load. In addition, the Baermann technique was performed to identify *Strongyloides stercoralis* infection. Patients were classified as *A. lumbricoides* infected or noninfected (24 eggs per gram of feces is the lower limit of detection). For parasite load analysis, patients were divided into those uninfected with *A. lumbricoides*, those with 24 to 1,000 eggs per gram of feces, and those with more than 1,000 eggs per gram of feces. We considered positive specific IgE to *A. lumbricoides* as a marker of previous infection in those whose parasite examination results were negative for the parasite,¹⁷ whereas the presence of eggs in the stool samples was an indicator of active infection. Thus, we divided the patients into 3 groups according to the presence of previous or active infection: no *A. lumbricoides* infection (no ova in feces sample and no specific IgE to *A. lumbricoides*), no active infection but evidence of previous infection (no ova in feces sample but specific IgE to *A. lumbricoides*), and active infection (*A. lumbricoides* identified in the feces sample independent of specific IgE to *A. lumbricoides*). The end points of this study were skin reactivity to aeroallergens, determined by the proportion of individuals positive to at least 1 of the antigens tested, and levels of Der p specific IL-10 in PBMC cultures.

Skin Tests, Specific IgE, and IL-10

The immediate-type hypersensitivity skin prick test with aeroallergen extracts was performed in the forearm. We used antigens from the following house dust mites: *D. pteronyssinus*, *Dermatophagoides farinae* (Hollister-Stier, Spokane, WA), and *Blomia tropicalis* (IPI ASAC Brazil, São Paulo, Brazil), which are the most common aeroallergens in Bahia. The wheal diameters were measured 15 minutes after puncture, and the results were considered positive when the greater diameter was at least 3 mm larger than the negative control with saline solution. We also took the sum of the greater diameters of cutaneous reactions for analysis.

Total and specific IgE to *D. pteronyssinus*, *D. farinae*, and *B. tropicalis* were performed using immunofluorimetry. The allergen of interest linked to Immucap reacts with total or specific IgE, forming a complex. After incubation, the enzyme not linked was washed, and the complex was incubated in a solution for color development. After incubation, the fluorescence of the eluate was measured in the fluorocount. All the equipment and reagents were from Pharmacia AB (Uppsala, Sweden). Specific IgE tests to aeroallergens were performed in patients with negative skin prick test results, and specific IgE tests to *A. lumbricoides* were performed in all the patients. Patients were considered atopic if they had positive specific IgE test results to aeroallergens and positive skin prick test results and nonatopic if they had negative specific IgE test results to aeroallergens and negative skin prick test results.

Der p specific IL-10 was measured in the supernatant of PBMC cultures of a subset of 53 patients. The PBMCs were obtained by the Ficoll-Hypaque gradient and were adjusted to the concentration of 3×10^6 cells/mL in the RPMI medium. Cells were stimulated with *D. pteronyssinus* antigen at a concentration of 25 μ g/mL (Der-P₁; IPI-ASAC, Madrid, Spain). Cultures were incubated at 37°C in 5% carbon dioxide for 72 hours. After incubation, the supernatants were collected and maintained at -20°C for further cytokine assays. Levels of IL-10 were measured using the enzyme-linked immunosorbent assay sandwich technique (R&D Systems, Minneapolis, MN). The standard curve was used to express the results, and the minimal detectable value was 7.8 pg/mL. All the patients performed an automated complete blood cell count, and eosinophils in peripheral blood were quantified.

Pulmonary Function and Asthma Severity

Forty-four of 63 patients with a history of asthma underwent pulmonary function testing using a spirometer (Microlab 3300; Micro Medical Ltd, Chatham, England) for evaluation of forced expiratory volume in 1 second (FEV₁). The FEV₁ was taken as an objective marker of asthma severity, and patients were divided into 3 categories: those with severe asthma (FEV₁ <60% of predicted), moderate asthma (FEV₁ 60%–80% of predicted), and mild asthma (FEV₁ >80% of predicted).

Statistical Analysis

The statistical analysis was performed using a software program (SPSS for Windows; SPSS Inc, Chicago, IL). The distributions of the continuous variables are expressed as medians and 25th to 75th percentiles. The Mann-Whitney test, the χ^2 test, and the Fisher exact test were used to compare the continuous and categorical variables between the *Ascaris*-infected and noninfected groups. To compare more than 2 different groups, the Kruskal-Wallis test was used. $P < .05$ was considered statistically significant, and all the tests were 2-tailed.

RESULTS

We screened 282 individuals who visited the community centers and volunteered to participate in this study. Twenty-five percent of these patients were infected with at least 1 species of helminth. One hundred thirteen of the screened patients fulfilled the inclusion criteria; 35% of them were male, and the mean age was 18 years (range, 15–25 years). Fifty-nine percent of the patients had asthma, and 98% had rhinitis. Skin prick test reactions to aeroallergens were positive to at least 1 tested antigen in 74% of the patients. Stool samples were positive to at least 1 helminth in 55% of the selected patients: 42% had *A lumbricoides* infection, with a median parasite load of 1,992 eggs per gram of feces (range, 288–7,320 eggs per gram of feces). *Trichuris* infection oc-

curred in 37% of the patients and Ancylostomidae in 6%. *Strongyloides stercoralis* was identified in only 2 patients. Pulmonary function tests were performed in 44 asthmatic patients: 31 (70%) had mild asthma, 12 (27%) had moderate asthma, and only 1 (2%) had severe asthma.

Table 1 gives demographic data, results of stool examinations, skin prick test results, total and specific IgE to *A lumbricoides*, and asthma severity for all the participants according to the presence or absence of *A lumbricoides* infection based in parasite examinations. There were no statistically significant differences in age, frequency or severity of asthma, proportion of any positive skin prick test results, or the presence of Ancylostomidae in feces samples between these 2 groups. However, a trend for greater frequency of asthma in patients infected with *A lumbricoides* was observed. As expected, *Trichuris* eggs were more frequent in the stool samples of *A lumbricoides*-infected patients. Also, total and specific IgE to *A lumbricoides* were found in higher levels in the *A lumbricoides*-infected group. The sum of the greater diameters of cutaneous reactions and the levels of Der p specific IL-10 were comparable in *A lumbricoides*-infected and noninfected individuals.

Table 2 reinforces the negative findings in Table 1 by demonstrating that there were no significant differences in the proportion of positive skin prick test results, the sum of the greater diameters of cutaneous reactions, and the frequency

Table 1. Characteristics of 113 Patients With Asthma or Rhinitis by *Ascaris lumbricoides* Infection Status Based on Parasite Examinations

Characteristics	<i>Ascaris</i> negative (n = 66)	<i>Ascaris</i> positive (n = 47)	P value
Sex, No. (%)			.03
M	18 (27)	22 (47)	
F	48 (73)	25 (54)	
Age, median (25th–75th percentile), y	20 (16–25)	17 (15–22)	.07
Asthma diagnosis, No. (%)	33 (50)	30 (64)	.10
Atopy diagnosis, No. (%)	54 (82)	37 (79)	.88
<i>Trichuris</i> positive, No. (%)	14 (21)	28 (60)	<.01
Ancylostoma positive, No. (%)	2 (3)	5 (11)	.1
Total IgE, median (25th–75th percentile), IU/mL	604 (268–1,572)	1,090 (545–3,078)	.02
Specific IgE to <i>Ascaris</i> , median (25th–75th percentile), IU/mL	0.8 (0–3.8)	4.6 (1.1–13.8)	<.01
Eosinophils in blood, median (25th–75th percentile), %	4.6 (2.0–9.5)	8.1 (4.8–13.8)	<.01
Positive skin prick test results, No. (%)	46 (70)	34 (72)	.45
Sum of greater diameters of skin reactions to mite allergens, median (25th–75th percentile), mm	6 (4–13)	9 (4–13)	.3
Asthma severity, No. (%)*			.4
Mild	18 (75)	13 (65)	
Moderate	5 (21)	7 (35)	
Severe	1 (4)	0	
Der p specific IL-10, median (25th–75th percentile), pg/mL†	8.4 (7.8–76)	7.8 (7.8–115)	.89

Abbreviation: IL-10, interleukin 10.

* Includes only 44 patients.

† Includes only 53 patients: 28 in the negative group and 25 in the positive group.

Table 2. Frequency of Asthma, Positive Skin Prick Test Results, and IL-10 Production by *Ascaris lumbricoides* Parasite Load

	Not infected (n = 66)	<1,000 eggs per grams of feces (n = 22)	≥1,000 eggs per gram of feces (n = 25)	P value
Positive skin prick test results, No. (%)	46 (70)	15 (68)	19 (76)	.72
Asthma diagnosis, No. (%)	33 (50)	14 (64)	16 (64)	.35
Sum of greater diameters of skin reactions to mite allergens, median (25th–75th percentile), mm	6 (4–13)	10.5 (4–13)	8.5 (5–13)	.84
Der p specific IL-10, median (25th–75th percentile), pg/mL*	8.4 (7.8–76)	7.8 (7.8–241)	22 (7.8–65)	.98

Abbreviation: IL-10, interleukin 10.

* Includes only 53 patients: 28 uninfected, 10 with a low parasite load, and 15 with a high parasite load.

of asthma or Der p specific IL-10 production between individuals with different levels of *A lumbricoides* infection. Table 3 adds new information for the comparison among groups, which are now classified according to the result of feces sample examination and IgE to *A lumbricoides*. The lack of association between positive skin test results and current infection with *A lumbricoides* was not modified by the result of a serologic marker of previous contact with the helminth. Neither were Der p specific IL-10 levels associated with *A lumbricoides* specific IgE.

DISCUSSION

The present study found no association between current *A lumbricoides* infection and skin prick test reactivity to common aeroallergens in patients with asthma or rhinitis. Furthermore, analysis of subgroups according to the intensity of infection and evidence of past infection reinforce the results. Large cross-sectional studies^{8,9} have explored the interrelationship between atopy and parasite infections and have observed an inverse association between helminth infection and atopy or asthma symptoms. The protective effect of helminth infections on allergic diseases is suggested by clinical trials^{10,18} that observed an increase in the frequency of atopy in children treated with antihelminthic drugs. There are studies,^{17,19} however, demonstrating a positive association between helminth infections and atopy, and 1 clinical trial²⁰ of asthmatic patients living in a low socioeconomic area dem-

onstrated a reduction in asthma symptoms in patients treated with albendazol. Possible explanations for these conflicting results could be related to the age of the population, the age of infection, the intensity of infection, whether it is acute or chronic, and also the living environment (rural vs urban areas). Furthermore, several helminths have a pulmonary cycle during acute infection, and it would be possible that during this phase helminths worsen symptoms of asthma, whereas in chronic infection there is a reduction in the symptoms of asthma.

One hypothesis to explain the mechanism of atopy inhibition by helminth infections is the induction of immune regulatory mechanisms, such as the production of IL-10. In patients infected with *Schistosoma*^{5,12} or *O volvulus*,¹¹ there is a high induction of helminth specific IL-10 production.²¹ In *Schistosoma* infection, this cytokine seems to have a central role in suppressing atopy⁵ and the T_H2 inflammatory response.¹² In the present study, there was no association between Der p specific IL-10 production and *A lumbricoides* infection. Previously published data^{22,23} have demonstrated that *A lumbricoides* infection does not induce helminth specific IL-10 production.

This study and others found consistent inhibition of skin reactivity to allergens associated with *Schistosoma* infection, and data about the association between *A lumbricoides* infection and atopy are controversial. A possible explanation for differences in atopy inhibition between *Schistosoma* and *A*

Table 3. Subgroup Analysis of Patients With No Current Infection With *Ascaris lumbricoides*

	<i>Ascaris</i> in stools (n = 43)	No <i>Ascaris</i> in stools		P value
		Positive IgE to <i>Ascaris</i> (n = 45)	Negative IgE to <i>Ascaris</i> (n = 18)	
Positive skin prick test result, No. (%)	34 (79)	33 (73)	12 (67)	.65
Asthma diagnosis, No. (%)	30 (70)	25 (56)	8 (44)	.32
Sum of greater diameters of skin reactions to mite allergens, median (25th–75th percentile), mm	9 (4–13)	6 (3.5–14.5)	5 (4–9.5)	.53
Der p specific IL-10, median (25th–75th percentile), pg/mL*	7.8 (7.8–115)	8.4 (7.8–78)	20 (7.8–105)	.99

Abbreviation: IL-10, interleukin 10.

* Includes only 53 patients: 25 with *Ascaris* in stools, 18 without *Ascaris*/positive IgE to *Ascaris*, and 10 without *Ascaris*/negative IgE to *Ascaris*.

lumbricoides is the life cycle of these helminths. Whereas *Schistosoma* is a parasite that lives in the venules and lymphatic vessels, which requires the development of evasion mechanisms from the host immune system for survival, *A lumbricoides* is a parasite that lives in the gastrointestinal tract lumen and might lead to a less intense systemic immunomodulation. Thus, our findings indicate that helminth infections might not be equally protective against allergy in humans.

The main design difference in this and other studies is that most other studies enrolled individuals independent of the history of asthma or rhinitis symptoms, whereas we studied only patients with a diagnosis of asthma or rhinitis. This approach focused our observations in a rather unusual group that combines a high risk of helminth infection and a history of asthma or rhinitis.

A positive aspect of the sample we studied is that the helminth-infected and noninfected patients have the same socioeconomic level, live in the same conditions, and have the same educational status. A factor that could have confounded our analysis was co-infection with other helminths. However, these infections were more frequent in patients infected with *Ascaris*, and it is, therefore, unlikely to be a cause of confusion because we found no association. Another possible confounding factor is related to the fact that 68% of the patients without *A lumbricoides* in their stool samples had positive IgE to *A lumbricoides*, indicating a high frequency of previous contact with helminths in the group without *A lumbricoides* in their stool samples. We controlled this factor by analyzing the subgroup of patients with negative *A lumbricoides* in stool samples and negative IgE to *A lumbricoides* separately, which provided confirmatory results.

Because we did not survey the entire population, we cannot ensure the external validity of the findings. On the other hand, by selecting patients with a high risk of atopy and helminth infection living in similar conditions and belonging to the same ethnic origin, we enhanced the power of this study. A post hoc calculation estimates that a power of 80% would be achieved by a sample of 44 individuals (in each group) for an $\alpha = .05$ to demonstrate as significant a difference of 20% in a proportion of 70%. This means that the proportion of patients with any positive skin test reaction would be significantly different if the difference between groups was greater than 20%. On the other hand, it also means that there is a 20% chance of not detecting as significant a true existing difference (β error).

A trend toward a greater frequency of history of asthma symptoms was seen among patients currently infected with *A lumbricoides* or with evidence of past infection. We think we should not build any conclusions on these observations, first because the difference is not statistically significant and second because the study was not population based and there could have been selection bias influencing this observation (asthma diagnosis was one of the inclusion criteria). Although the available severity classifications for asthma and rhinitis are not accurate and objective, they allow a qualita-

tive comparison between patients of different status regarding *A lumbricoides* infections. It would have been interesting to look at serum levels of IL-10 and other cytokines to expand our stimulated ex vivo observations to measurements of live circulating levels, which would provide information on the systemic repercussions of the processes. However, the lower limit of detection of the available assays would not allow accurate serum measurements of IL-10.

We conclude that there is no association between skin prick test reactivity to common aeroallergens and current *A lumbricoides* infection in this sample of patients with asthma or rhinitis with high risk of helminth infection. Furthermore, we demonstrated no effect of *A lumbricoides* infection in Der p specific IL-10 production. Because the present findings in patients infected with *A lumbricoides* differ from observations in *Schistosoma*-infected patients, different helminth infections might not be equally protective against allergy in humans.

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