

Inverse Association between Skin Response to Aeroallergens and *Schistosoma mansoni* Infection

Maria Ilma Araujo^a Antônio Alberto Lopes^a Manoel Medeiros^a
Álvaro A. Cruz^a Luiza Sousa-Atta^a Dirceu Solé^b Edgar M. Carvalho^a

^aServiço de Imunologia do Hospital Universitário Prof. Edgard Santos, Universidade Federal da Bahia, Salvador,

^bUniversidade Federal de São Paulo, São Paulo, Brasil

Key Words

Schistosoma mansoni · Schistosomiasis · Atopy in schistosomiasis · Immediate hypersensitivity test in schistosomiasis · Immunology of schistosomiasis

Abstract

Background: Helminthic infections and allergic disease are highly prevalent in many areas of the world. It is known that IgE antibodies are involved in the pathogenesis of both helminthiasis and atopy. However, the consequences of the presence of helminthic infections in atopic patients are still not completely understood. **Methods:** Subjects infected by *Schistosoma mansoni* with more than 200 eggs/g of feces (n = 42) and uninfected subjects (n = 133) were selected from an endemic area of schistosomiasis. The history of allergy and results of the immediate hypersensitivity prick tests with inhalant allergen extracts were registered. Total IgE and IgE specific to *S. mansoni* and aeroallergens were measured in serum by ELISA. **Results:** The proportion of individuals with a positive skin test to allergens was higher in the uninfected group (24.3%) than in the group with more than 200

eggs/g of feces (4.8%). The odds of atopy (defined as a positive test for at least one of the antigens) were 5 times higher (odds ratio = 7.0; 95% confidence interval = 1.6–31.1%; p = 0.01) in the uninfected group, after taking into account the potential influence of gender and age. While there was a tendency for higher total and *S. mansoni*-specific IgE levels in infected patients, an opposite trend, that is higher aeroallergen-specific IgE, was observed in uninfected subjects. **Conclusions:** There was a strong and statistically significant inverse association between the immediate skin test response to common aeroallergens and infection by *S. mansoni*. The results indicate that immediate hypersensitivity reactions may be suppressed in *S. mansoni*-infected individuals.

Copyright © 2000 S. Karger AG, Basel

Introduction

Atopic diseases, similar to helminthic infections, are related to increased secretion of Th2-type cytokines, which results in eosinophilia and increased production of IgE [1–4]. However, the relationship between helminthic

infection and immunological responses in atopic conditions is still not well understood [5, 6]. Considering the high frequency of both helminthic diseases and atopic manifestations, it is important to explore whether aeroallergen specific IgE levels and immediate hypersensitivity reactions are influenced by the presence of helminthic infection. The present investigation was conducted in a hyperendemic area of schistosomiasis in Brazil (more than 90% of the population is or had been infected by *Schistosoma mansoni*) where our research team has been working for more than 20 years [7]. The study was developed to assess evidence of a relationship between positive skin tests to environmental allergens and schistosomiasis, taking into account the potential influences of age and gender on this association.

Patients and Methods

In a cross-sectional study, individuals (n = 175) from Caatinga do Moura, an endemic area of schistosomiasis in Bahia, northeastern Brazil, were consecutively recruited according to *S. mansoni* infection status: subjects infected with more than 200 eggs per gram of feces (n = 42) or uninfected subjects (n = 133). The stool examination was performed by the Kato-Katz method, considered the most suitable one for the estimation of parasitic load in patients with *S. mansoni* infection [8, 9]. It is important to note, however, that the parasitism is only reliably detected by this method if there are 24 or more eggs per gram of stool. Therefore, uninfected subjects are those with less than 24 eggs of *S. mansoni* per gram of feces. Considering that more than 90% of the population is or had been infected by *S. mansoni*, subjects with less than 24 eggs/g of stool may have a low degree of infection or may have had *S. mansoni* infection in the past. Intestinal protozoa such as *Giardia lamblia* and *Entamoeba histolytica* were found in 40% of the subjects, while 5% were infected with helminths such as *Ascaris lumbricoides* and *Ancilostoma duodenali*. There was no difference in the rate of parasite infections between the two groups studied, except for schistosomiasis. The immediate hypersensitivity prick test with inhalant allergen extracts (IFIDES, Aristegui, Spain) was performed in the forearm. The antigens used were *D. pteronyssinus*, *B. tropicalis*, a mixture of fungi, epithelium of dog, epithelium of cat, *B. germanica* and *P. americana*. The wheal diameters were measured after 15 min and the result was considered positive when the diameter was greater than or equal to 3 mm, in the absence of significant reactivity of the diluent negative control. A positive control prick test was also performed with histamine. Total and *S. mansoni* antigen-specific IgE were determined by ELISA as previously described [10]. IgE against a mixture of dust antigens (*D. pteronyssinus*, *D. farinae*, *D. microceras*, *L. destructor*, *T. putrescentia*, *G. domesticus*, *E. maynei*, *B. tropicalis*) and against a mixture of mold antigens (*P. notatum*, *C. herbarum*, *A. fumigatus*, *A. alternata*) were performed by ELISA with reagents from DPC (Los Angeles, Calif., USA), and the results are presented as kU/l. These tests were performed in 43 out of 175 subjects evaluated; 29 of them were uninfected by *S. mansoni* and 14 were infected with more than 200 eggs/g of stool.

Subjects with more than 200 *S. mansoni* eggs per gram of stool and uninfected subjects were compared regarding the odds of presenting a positive skin response to at least one of the antigens and the odds of an episode suggestive of allergic rhinitis or asthma during the previous 12 months. The statistical analysis was performed using the software Statistical Package for Social Science (SPSS), version 6 for Windows [11, 12]. The Yates' continuity corrected χ^2 test and the Fisher's exact test were used to compare proportions. The difference in mean age was assessed by the Student's t test for independent samples after natural logarithmic transformation of the variable. The Mann-Whitney U test was used to compare the means of IgE. Multivariate logistic regression was used to estimate the association between parasitic load and skin test response to aeroallergens, adjusted for age and gender. In the logistic model, age was treated as a dichotomous variable (≤ 15 and > 15 years). This study was approved by the Ethical Committee of the Hospital Universitário Prof. Edgard Santos, and informed consent was obtained from patients or from their guardians.

Results

Table 1 shows that the uninfected group was, on average, older (mean $\pm$ SD: 20.18 $\pm$ 11.89 versus 17.95 $\pm$ 9.71 years) and had a smaller percentage of males than the group with more than 200 *S. mansoni* eggs per gram of feces. The uninfected group also had a higher proportion of persons who reported at least one episode suggestive of respiratory allergy in the past 12 months. None of these differences, however, was statistically significant ($p > 0.1$). On the other hand, the presence of a positive skin test for at least one of the antigens was significantly ($p = 0.01$) associated with *S. mansoni* infection status. The proportion of patients with a positive skin test for at least one of the antigens was approximately 5 times greater in the uninfected group (24.3%) than in the group with more than 200 eggs of *S. mansoni* per gram of feces (4.8%). Patients with a parasitic load > 200 eggs/g of stool had higher total and *S. mansoni*-specific IgE and lower values of aeroallergen-specific IgE than the uninfected group. These differences, however, were not statistically significant.

Table 2 shows the estimates of the association between *S. mansoni* infection and atopy by logistic regression. In the unadjusted analysis of the odds of atopy (defined as a positive test for at least one of the antigens), the odds were 6.3 (95% confidence interval = 1.4–27.6; $p = 0.01$) times greater for the uninfected group compared to the group with a parasitic load > 200 eggs/g of feces. This association was not significantly changed after adjusting for the potential effects of age and gender (odds ratio = 7.0; 95% confidence interval = 1.6–31.1; $p = 0.01$).

Table 1. Characteristics of the samples according to parasitic load

Subjects	Uninfected (n = 133)	>200 eggs/g of stool (n = 42)	p value
Age, years, mean ± SD	20.2 ± 11.9	18.0 ± 9.7	0.60
Gender, % male	46.6	52.4	0.64
Symptoms of asthma or rhinitis, % positive	44.4	38.1	0.59
Skin test, % positive	24.1	4.8	0.01
Total IgE, IU ¹			
Mean ± SD	964 ± 1,392	1,252 ± 1,318	0.34
Median	265	699	
<i>S. mansoni</i> -specific IgE (OD) ¹			
Mean ± SD	0.198 ± 0.429	0.329 ± 0.545	0.11
Median	0.064	0.103	
Aeroallergen-specific IgE, % positive ¹	41.4	14.3	0.10

¹ Only 43 patients were evaluated for total IgE, *S. mansoni*- and aeroallergen-specific IgE.

Discussion

This study showed a strong and inverse association between skin response to allergens and infection by *S. mansoni* among persons living in an area with a high rate of *S. mansoni* transmission. A reduction in the allergic reactivity against aeroantigens has been previously documented in an area endemic for the intestinal helminth *A. lumbricoides* [13]. Antihelminthic therapy was followed by an increase in immediate hypersensitivity skin test reactivity and an increase in the serum level of specific IgE antibodies against environmental allergens [13]. The inverse association between *S. mansoni* infection and skin test positivity in the present study could not be explained by age or gender. It is also unlikely that differences in environmental exposure to allergens may fully explain this association, given the similarities in housing conditions, socioeconomic status and level of education among families living in the subject village of this study.

In the present study, a history suggestive of respiratory allergy in the previous year was weakly and not statistically significantly associated with schistosoma infection. The direction of this association, however, was the same as that observed for the relationship between skin response to antigens and parasitic load. The role of random (or nondifferential) misclassification in increasing the similarities regarding past history of respiratory allergy between the group infected with more than 200 eggs per gram of stool and the uninfected group cannot be completely ruled out. It is important to note that past history alone may not reliably discriminate allergic from nonallergic diseases, particularly in populations with a low edu-

Table 2. Unadjusted and adjusted (by logistic regression) associations between *S. mansoni* infection and skin test positivity to aeroallergens

	OR (95% CI)	p value
Unadjusted	6.3 (1.5–27.6)	0.01
Adjusted	7.0 (1.6–31.1)	0.01

OR = Odds ratio; CI = confidence interval.

cational level, such as the one in the study village. Another study in Brazil failed to show statistically significant differences in allergic symptoms between patients with chronic schistosomiasis and persons without evidence of *S. mansoni* infection [14].

The strong inverse association between skin response to aeroallergens and infection by *S. mansoni* in the absence of correlation with allergic disease is consistent with the hypothesis that helminthic infection decreases immediate hypersensitivity reactions but does not influence clinical manifestations to the same extent. These findings are equally compatible with the hypothesis that anti-*S. mansoni* IgE competes for the same high-affinity IgE receptors targeted by allergen-specific IgE. An increase in IgE production and saturation of mast cell receptors are plausible mechanisms to explain the inverse association between the parasitic load of *S. mansoni* and skin reactions to allergens [14]. The higher levels of total and *S. mansoni*-specific IgE in the infected group support this hypothesis. An alternative explanation to our findings

could be the hypothesis of Lynch et al. [6] that atopy is a marker of an enhanced protective response against helminthic parasites. In such a case, atopy would be envisaged as helping the host to kill *S. mansoni*, thus resulting in low parasitism. Our findings presented here indicate that helminthic infections may indeed suppress immediate hypersensitivity reactions. The observation that patients infected with *S. mansoni* had lower specific IgE to allergen in spite of having high total levels of IgE indicates that studies should be designed to evaluate whether, in addition to inducing a negative skin test, the immunological response against helminths may also downregulate IgE production to unrelated antigens.

Acknowledgement

We thank Edward Pearce for suggestions and review of the text, Elbe Myrtes Silva for preparing the manuscript, and the medical students who helped with the fieldwork, namely Ana Cecilia Travassos, Ana Paula Laranjeiras, Andrea Pimentel, Antonio Ralf Jr., Fabio F. José and Sidney Lima. This work was supported by NIH grant AI-30639, Programa de Núcleos de Excelência (PRONEX) and FINEP. E.M.C. is senior investigator of the Brazilian Research Council (CNPq).

References

- 1 Aalberse RC: The IgE response and atopy. *Eur Respir J* 1991;4:78–84.
- 2 Bradding P, Roberts JA, Britten KM, Montforts S, Djukanovic R, Mueller R, Heusser CH, Howarth PH, Holgate ST: Interleukin-4, -5 and -6 and tumor necrosis factor- α in normal and asthmatic airways: Evidence for the human mast cell as a source of these cytokines. *Am J Respir Cell Mol Biol* 1994;10:471–480.
- 3 Sabin E, Araújo MI, Carvalho EM, Pearce EJ: Impairment of tetanus toxoid-specific Th1-like immune responses in humans infected with *Schistosoma mansoni*. *J Infect Dis* 1996;173:2269–2272.
- 4 Butterworth AE, Dunne DW, Fulford AG, Ouma JH, Starrock RF: Immunity and morbidity in *Schistosoma mansoni* infections: Quantitative aspects. *Am J Trop Med Hyg* 1996;55:109–115.
- 5 Larrick JW, Buckley CE III, Machamer CE, Schlager GD, Yost JA, Blessing-Moore J, Levy D: Does hyperimmunoglobulinemia-E protect tropical populations from allergic disease? *J Allergy Clin Immunol* 1983;71:184–188.
- 6 Lynch NR, Hagel IA, Palenque ME, Di Prisco MC, Escudero JE, Corao LA, Sandia JA, Ferreira LJ, Botto C: Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment. *J Allergy Clin Immunol* 1998;101:217–221.
- 7 Jesus AR, Almeida RP, Bacellar O, Araújo MI, Demeure C, Bina JC, Dessein A, Carvalho EM: Correlation between cell-mediated immunity and degree of infection in subjects living in an endemic area of schistosomiasis. *Eur J Immunol* 1993;23:152–158.
- 8 Katz N, Coelho MZ, Pellegrino J: Evaluation of Kato's quantitative method through the recovery of *Schistosoma mansoni* eggs added to human feces. *J Parasitol* 1970;56:1032–1033.
- 9 Katz N, Chaia G: Coprological diagnosis of schistosomiasis. I. Evaluation of quantitative techniques. *Rev Inst Med Trop São Paulo* 1968;10:295–298.
- 10 Sousa-Atta MLB, Araújo MI, D'Oliveira Junior A, Ribeiro-de-Jesus A, Almeida RP, Atta AM, Carvalho EM: Detection of specific IgE antibodies in parasite diseases. *Braz J Med Biol Res* 1999;32:1101–1105.
- 11 Norusis MJ: SPSS for Windows: Base system user's guide, release 6.0. Chicago, SPSS Inc, 1993.
- 12 Norusis MJ: SPSS for Windows: Advanced Statistics, release 6.0. Chicago, SPSS Inc, 1993.
- 13 Lynch NR, Hagel IA, Perez M, Di Prisco MC, Lopez R, Alvarez N: Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. *J Allergy Clin Immunol* 1993;92:404–408.
- 14 Catapani WR, Pinto PLS, Amato-Netto V, Mendes E: Prevalence of allergic diseases in patients with schistosomiasis mansoni. *J Allergy Clin Immunol* 1997;100:142.

Copyright: S. Karger AG, Basel 2000. Reproduced with the permission of S. Karger AG, Basel. Further reproduction or distribution (electronic or otherwise) is prohibited without permission from the copyright holder.