Schistosoma mansoni infection is associated with a reduced course of asthma

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Background: Helminthic infections decrease skin reactivity to indoor allergens, but data on whether they influence asthma severity are lacking.
Objective: This study evaluated the course of asthma in patients with and without *Schistosoma mansoni* infection.
Methods: Asthmatic subjects were enrolled from 3 low-socioeconomic areas: a rural area endemic for schistosomiasis (group 1) in addition to a rural area (group 2) and a slum area (group 3), both of which were not endemic for schistosomiasis. A questionnaire on the basis of the International Study of Asthma and Allergies in Childhood study was applied in these 3 areas, and from each area, 21 age- and sex-matched asthmatic subjects were selected for a prospective 1-year study. Pulmonary function tests, skin prick tests with indoor allergens, stool examinations, and serum evaluations were performed in these subjects. Every 3 months, the subjects were evaluated for asthma exacerbation through physical examination, and a questionnaire regarding asthma symptoms and use of antiasthma medicine was administered.
Results: The prevalence of *S mansoni* infection was greater in group 1 compared with in groups 2 and 3 ($P < .0001$), whereas the frequency of other helminth and protozoa infections was similar among the 3 groups. The frequency of positive skin test responses to indoor allergens was less (19.0%) in group 1 subjects relative to those in group 2 (76.2%) and group 3 (57.1%; $P < .001$). The frequencies of symptoms, use of antiasthma drugs, and pulmonary abnormal findings at physical examination were less in group 1 subjects than in group 2 and 3 subjects ($P = .0001$).
Conclusion: Our results suggest that *S mansoni* infection is associated with a milder course of asthma. (J Allergy Clin Immunol 2003;111:947-51.)

Key words: *Asthma, skin prick test, dust mites, helminths, Schistosoma mansoni, IL-10, IgE*

A striking variation in the prevalence of asthma has been documented among countries throughout the world. In Brazil, a developing country, the prevalence of self-reported asthma symptoms among teenagers is similar to the prevalence observed in the United States and several European countries.[1] Evidence for a role of childhood infection in the development of asthma has accumulated in recent years, and an inverse association between a variety of infections and atopy has been documented.[2-6] Additionally, it has been speculated that the improvement in sanitation and the reduction in childhood infections through vaccinations in developed countries could shift the balance of the immune response toward a T_H2 type, increasing the expression of T_H2 cytokines generally associated with allergies.[7,8]

Helminth infections are highly prevalent in tropical countries, and the influence of worm infection in allergic response needs to be clarified. Lynch et al[9] showed that although subjects infected with *Ascaris lumbricoides* had a decrease in the frequency of positive skin prick test (SPT) responses to house dust mite (HDM) allergens, treatment of this parasitic infection increased the frequency of positive SPT responses to HDM. Similarly, we have previously shown that there is an inverse association between the positive SPT response to HDM and the parasitic load of *Schistosoma mansoni*,[10] suggesting that this parasite could modulate the allergen reactivity in atopic subjects. However, it is still unclear why helminthic infections reduce the allergic response.

Although a negative association has been well demonstrated between patients infected with *A lumbricoides*, *S mansoni*, or *Schistosoma haematobium* and SPT responses,[9-11] there is no direct evidence that helminth infection reduces the prevalence of atopy.[12] The aim of this study was to evaluate, in a prospective manner, the clinical course of asthma in subjects with *S mansoni* infection.

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Abbreviations used
HDM: House dust mite
PEF: Peak expiratory flow
SPT: Skin prick test
SWAP: *Schistosoma mansoni* worm antigen

METHODS

Subjects and endemic areas

Subjects were selected from 2 villages (Caatinga do Moura and Lages do Batata) belonging to the city of Jacobina, state of Bahia, and from a slum located in Salvador, the capital of Bahia, Brazil. Caatinga do Moura has been known for more than 30 years to be an endemic area for schistosomiasis. No exposure to *S mansoni* occurs in Lages do Batata or Salvador. The prevalence of bronchial asthma in these areas was determined through a directed questionnaire on the basis of the International Study of Asthma and Allergies in Childhood.[13] In this study all residents of Caatinga do Moura (n = 443) and Lages do Batata (n = 498) were interviewed regarding asthma symptoms. Otherwise, in the slum area 488 subjects were randomly enrolled and interviewed regarding asthma symptoms.

In Caatinga do Moura only 21 subjects with a history of wheezing in the last 12 months fit the inclusion criteria (group 1). Age- and sex-matched individuals with a history of wheezing in the last 12 months were enrolled in Lages do Batata (group 2, n = 21) and in Salvador (group 3, n = 21). In addition, 21 individuals with negative personal or familial histories of atopy or wheezing who were age- and-sex matched with group 1 subjects were enrolled in Caatinga do Moura (group 4, n = 21) to control group 1 laboratory evaluations. Children less than 6 years of age were excluded because of difficulties in performing pulmonary function tests, as were subjects older than 35 years, active smokers, and those with signs and symptoms of pulmonary and systemic infection. All subjects had a similar low socioeconomic status, as evaluated on the basis of indicators such as familial income and material used for house construction. Their houses were evaluated for the presence of pets and indoor pollutants, such as smoke from tobacco, kerosene, and fuel used for cooking. None of the participants were taking antiallergic drugs that could interfere with the SPT or had never been treated with specific immunotherapy. Previously, we demonstrated that the subjects enrolled in this study were exposed to levels of Der p 1 from *Dermatophagoides pteronyssinus* of greater than 2 □g/g of house dust.[14]

The Ethical Committee of the Hospital Universitario Prof Edgar Santos approved the present study, and informed consent was obtained from subjects or their legal guardians.

Considering that asthmatic subjects in all areas tend to have mild asthma and a single true-point cross-sectional analysis to show a difference would require large numbers of patients, a prospective study was conducted to evaluate the course of asthma.

Subjects were evaluated every 3 months for 1 year (ie, 4 evaluations per subject). At each evaluation, they had physical examinations performed by the same 2 physicians (blind to schistosomiasis status) to check for abnormal findings, such as cough, dyspnea, and wheezing. In addition, a questionnaire elicited information on asthma (ie, asthma attacks and the treatment location [at home, emergency department, or hospital]) and the use of prophylactic or symptomatic antiasthma drugs (eg, antihistamine, inhaled or oral $\square_2$-agonist, and inhaled, oral, or parenteral corticosteroid) since the last evaluation. These parameters were scored as follows: physical examination as 0 (normal examination result) and 1 (at least one abnormal finding); asthma exacerbations as 0 (no), 1 (yes, if treated at home), and 2 (yes, if treated at an emergency department or at a hospital); and use of antiasthma drugs as 0 (no), 1 (yes, except for oral or parenteral corticosteroid use), and 2 (yes, if oral or parenteral corticosteroid had been used). For each individual, the scores were summed for each period. The scores for each individual within a group were totaled for the year observation and transformed as a percentage of the total year evaluations. All enrolled subjects were given a Mini Wright Peak Flow Meter (Clement Clark International Ltd) to monitor daily peak expiratory flow (PEF).

Pulmonary function tests and SPTs

Pulmonary function tests were performed on all subjects at enrollment. During the follow-up period, subjects measured PEF values over a 30-day period using the provided device, and recorded these values in a diary. SPTs were performed on the right forearms of all individuals with *D pteronyssinus*, *D farinae*, *Blomia tropicalis*, *Periplaneta americana*, and *Blattella germanica* glycerinated allergen extracts (IPI-ASAC). We also used histamine (1:1000) and glycerinated saline as positive and negative controls, respectively. A positive skin reaction was defined as a wheal with a mean diameter of greater than 3 mm. The SPT results were read 20 minutes after application, and a positive SPT response was considered as a positive skin reaction induced by at least one of the 5 tested allergens.

Laboratory evaluation

Three stool samples from each individual were examined by using the Hoffman sedimentation method to identify helminths and enteric protozoa and by using the Kato-Katz method, which is considered the most suitable assay for the estimation of parasitic load in patients with *S mansoni* infection.[15,16] Because treatment for *S mansoni* infection is performed regularly in the population of Caatinga do Moura, serologic tests for evidence of previous *S mansoni* infection were performed in subjects living in the endemic area, as well as in the other 2 nonendemic areas. IgG_4 anti-*S mansoni* antibodies were measured in the sera of subjects from all groups through indirect ELISA by using polystyrene wells covered with crude *S mansoni* worm antigen (SWAP).

Total and specific IgE anti-*D pteronyssinus*, anti-*D farinae*, and anti-*B tropicalis* antibodies were determined by means of enzyme-linked fluorescent assay in the CAP System (Pharmacia) in randomized individuals from the 4 groups (16 subjects in each group). The results were expressed in kilo–international units per liter.

The amount of histamine released from blood basophils (in nanomoles per liter) from subjects of groups 1, 2, and 4 (16 randomized individuals in each group) after in vitro stimulation with *D pteronyssinus* and SWAP was determined by means of a competitive ELISA (Immunotech).[17]

Statistical analyses

Statistical analyses were performed with the SPSS and EPI Info software packages. The frequencies of positive SPT results, pollutant and allergen exposure, presence of intestinal parasites, physical examination abnormalities, asthma exacerbations, and antiasthma drug consumption were expressed as percentages. The Yates' continuity corrected $\square^2$ test and the Fisher exact test were used to compare proportions. Nonparametric tests were used to compare the levels of total and specific IgE, IgG_4 anti-*S mansoni* antibodies, and histamine released from basophils between the groups. The mean values of pulmonary function tests and PEF measurements were analyzed by using ANOVA. Statistical significance was established at the 95% CI.

RESULTS

The prevalence of bronchial asthma, evaluated by using the International Study of Asthma and Allergies in Child-

TABLE I. Demographic data from asthmatic and nonasthmatic subjects from 3 low-socioeconomic-status areas in Bahia, Brazil, and comparative data for pollutants, pet exposure, pulmonary function tests, and positive SPT responses with indoor allergens

	Group 1 (n = 21)	Group 2 (n = 21)	Group 3 (n = 21)	Group 4 (n = 21)
Median age (y)	15.2	14.7	14.7	15.2
Sex (male/female)	9/12	9/12	9/12	9/12
Wood as cooking fuel (%)	52.4	47.6	14.3*	42.8
Pollutants: kerosene, tobacco, other smoke (%)	66.7	71.4	57.1	57.1
Pets at home (%)	38.0	57.1	42.8	47.6
Mean FEV_1 (L)	83.94 ± 17.80	80.27 ± 18.67	88.06 ± 18.91	ND
Mean PEF (L/s)	62.59 ± 24.21	55.93 ± 24.21	66.67 ± 19.81	ND
Positive SPT response (n/%)	4/9.0†	16/76.2	12/57.1	1/4.8‡
D pteronyssinus (n/%)	3/14.3†	9/42.9	8/38.1	1/4.8
D farinae (n/%)	0†	8/38.1	4/19.0	0
B tropicalis (n/%)	1/4.8†	10/47.5	9/42.9	0
B germanica (n/%)	0	2/9.5	2/9.5	0
P americana (n/%)	0	3/14.3	2/9.5	0

Group 1, Asthmatic subjects from a rural *S mansoni*–endemic area; *group 2,* asthmatic subjects from a rural non-*S mansoni*–endemic area; *group 3,* asthmatic subjects from a slum non-*S mansoni*–endemic area; *group 4,* nonasthmatic subjects from a rural *S mansoni*–endemic area; *ND,* not done.
*Group 3 differs from groups 1, 2, and 4 ($P = .03$).
†Group 1 differs from groups 2 and 3 ($P = .001$).
‡Group 4 differs from group 1 ($P = .001$) and from groups 2 and 3 ($P = .0001$).

hood written questionnaire, was similar among the 3 areas: 11.1% (49/443) in Caatinga do Moura, 10.4% (52/498) in Lages do Batata, and 14.5% (71/488) in Salvador.

Although evidence of *S mansoni* infection determined by means of stool examination and detection of IgG_4 anti-*S mansoni* antibodies was observed in 87.5% of subjects from groups 1 and 4, only 6.3% and 12.5% of subjects from groups 2 and 3, respectively, were infected with *S mansoni* ($P < .0001$). Intestinal protozoa, such as *Giardia lamblia* and *Entamoeba histolytica*, were found in 14.2%, 23.8%, and 14.2% of subjects from groups 1, 2, and 3, respectively. Regarding helminths, 14.2%, 23.8%, and 19.0% of subjects from groups 1, 2, and 3, respectively, were infected with *A lumbricoides*, *Ancilostoma duodenalis*, and others.

Table I shows demographic data, pulmonary function values, and positive SPT responses in the 3 groups at the first evaluation. The number of houses that used wood as a cooking fuel was lower in group 3 (slum) relative to that in the other 2 groups ($P = .03$). Regarding the presence of domestic pollutants and pets at home, there were no differences among the groups. The mean values of FEV_1 and PEF were similar among the 3 groups, likely because of the subjects with mild asthma in each group. The overall frequency of positive SPT reactions in group 1 (19.0%) was significantly lower than that observed in groups 2 (76.2%) and 3 (57.1%; $P < .001$).

Table II shows the levels of total and specific IgE and histamine released from blood basophils in the 4 groups. There was no statistically significant difference in the total IgE levels among the groups. IgE anti-*D pteronyssinus* antibodies were detected in 8, 9, 4, and 1 subjects, respectively in groups 1, 2, 3, and 4. IgE anti-*D farinae* antibodies were detected in 9 subjects from groups 1 and 2 and 5 and 2 subjects, respectively, from groups 3 and 4. Finally, IgE anti-*B tropicalis* antibodies were detected in 7 subjects from groups 1 and 2 and 6 and 3 subjects, respectively, in groups 3 and 4. Group 4 differed statistically from groups 1, 2, and 3 ($P = .01$) when the levels of these 3 specific IgE antibodies were compared. Histamine levels released after challenge with Der p 1 were lower in nonasthmatic subjects from the *S mansoni*–endemic area (group 4) relative to those of subjects from groups 1 and 2 ($P < .05$). Furthermore, the in vitro levels of histamine released from blood basophils after stimulus with SWAP was lower in group 2 relative to those in groups 1 and 4 ($P < .05$).

The course of asthma in groups 1, 2, and 3 determined by the score obtained with questionnaire data and abnormal findings on physical examination is shown in Table III. Subjects from group 1 had a significantly lower frequency of asthma attacks, antiasthma medicine consumption, and abnormal findings on physical examination relative to subjects from groups 2 and 3 ($P = .0001$).

DISCUSSION

This study demonstrates that asthmatic subjects infected with *S mansoni* from a rural area had a milder course of asthma when compared with asthmatic subjects without shistosomiasis living in rural or urban areas. This conclusion is strengthened by the fact that the studied populations had mild asthma according to pulmonary function test results and PEF measurements. In addition, many other possible confounding variables were also controlled, such as age, sex, socioeconomic level, indoor pollutant level, sensitizing mite exposure, and climate conditions.

Atopy is characterized by increased levels of total and specific IgE for common environmental allergens and evidence of in vivo IgE-mediated immediate hypersensitivity, as determined by means of SPTs with the same allergen.[18] It has been proposed that exposure to indoor allergens is related to sensitization but not to an increased

TABLE II. Laboratory data from 64 asthmatic and nonasthmatic subjects in the 4 groups (16 subjects in each group): Total IgE and specific IgE levels against HDM and in vitro histamine released by basophils after challenge with Der p 1 and SWAP

	Minimum	25th Percentile	Median	75th Percentile	Maximum
Total IgE (kIU/L)					
Group 1	20.00	71.50	426.00	825.50	1648.00
Group 2	65.00	159.50	390.50	762.00	2677.00
Group 3	93.00	415.00	565.50	1054.50	5000.00
Group 4	14.00	43.00	286.00	661.00	3764.00
Specific IgE (kAU/L)					
Anti-*D pteronyssinus*					
Group 1	0.00	0.00	0.29	2.93	100.00
Group 2	0.00	0.00	0.83	28.87	100.00
Group 3	0.00	0.00	0.00	0.37	100.00
Group 4	0.00	0.00	0.00	0.00	3.60
Anti-*D farinae*					
Group 1	0.00	0.00	0.97	3.28	45.50
Group 2	0.00	0.00	0.45	30.80	100.00
Group 3	0.00	0.00	0.00	0.75	100.00
Group 4*	0.00	0.00	0.00	0.00	1.73
Anti-*B tropicalis*					
Group 1	0.00	0.00	0.00	1.81	25.40
Group 2	0.00	0.00	0.00	25.84	101.00
Group 3	0.00	0.00	0.00	0.53	6.10
Group 4*	0.00	0.00	0.00	0.00	1.36
Histamine delivered					
Challenge with SWAP					
Group 1	0.00	11.25	54.00	450.00	756.00
Group 2†	0.00	0.00	9.00	445.00	693.00
Group 4	0.00	9.00	171.00	735.70	819.00
Challenge with Der p 1					
Group 1	0.00	3.25	49.50	234.00	891.00
Group 2	0.00	36.00	234.00	234.00	873.00
Group 4‡	0.00	11.25	27.00	139.50	783.00

*Group 4 differs from groups 1, 2, and 3 ($P = .01$).
†Group 2 differs from groups 1 and 4 ($P = .05$).
‡Group 4 differs from group 2 ($P = .05$).

TABLE III. Asthma severity scores in 63* asthmatic subjects in 3 groups

	Total of evaluations per group		
Indices for asthma (totaled scores/%)	**Group 1 (n = 75)**	**Group 2 (n = 84)**	**Group 3 (n = 80)**
Asthma symptoms	14/18.6	35/41.6	47/58.7
Antiasthma drug consumption†	12/16.0	38/45.2	58/72.5
Physical examination, abnormal findings‡	8/10.6	27/32.2	31/38.8

*Twenty-one subjects in each group (maximum of 4 evaluations for each subject per year).
†Antihistamines, β_2-agonists, corticosteroids, or xanthines (for asthma attacks or prophylactic use).
‡Cough, dyspnea, and wheezing.
Group 1 differs from groups 2 and 3 in all 3 indices for asthma ($P = .001$).

prevalence of asthma.[19] Although it is not clear how helminths decrease SPT response to aeroallergens, it has been speculated that the high levels of IgE, mast cell FcεRI blockage by polyclonal IgE, high concentrations of antigen-specific IgG_4, or downregulation of mite-specific IgE production might participate in this phenomenon.[20-24] Our findings argue against the hypothesis that high levels of polyclonal IgE antibodies reduce SPT reactivity in helminth-infected subjects[9] because we did not find a difference in the levels of total IgE antibodies among the groups. Previous studies have shown that infection with *S mansoni*, *S haematobium*, and *A lumbricoides* decreases the skin test response to indoor allergens.[9-11] In this study we demonstrated that subjects living in an *S mansoni*–endemic area had significantly less skin reactivity to HDMs, despite the fact that previously we showed that all enrolled subjects were exposed to sensitizing levels of HDMs, particularly Der p 1. Interestingly, although worms induce a type 2 immune response, it has been shown that oligosaccharides play an important role in this phenomenon by inducing IL-10 production and that they are found more frequently in *S mansoni* than in other

helminths.[25,26] Because shistosomiasis is associated with high IL-10 production, which might modulate hypersensitivity reaction by decreasing release of histamine and other mediators released by mast cells,[26] it is possible that this mechanism could explain why the frequency of positive SPT responses to indoor allergens, as well as the course of asthma, are reduced in *S mansoni*–infected subjects. Although no difference was observed in the histamine release test results, this cannot be ruled out because the test was performed in vitro, the cytokine environment was not the same, and, consequently, no reduction in the histamine release could be observed.

Although this and other studies have shown that helminthic infection does not decrease the prevalence of asthma,[12] we showed that despite equal exposure to sensitizing levels of HDM allergens, home pollutants, socioeconomic status, and climate conditions, subjects with mild asthma from an *S mansoni*–endemic area had fewer positive SPTs to indoor allergens and a milder course of asthma in a 1-year follow-up when compared with individuals with mild asthma not living in an *S mansoni*–endemic area. The occurrence of asthma is dependent on genetic, immunologic, and environmental factors.[27] Such environmental factors might include exposure to high levels of allergens, air pollution, and farm animals and diet.[28] Therefore it is possible that although helminth infections could modulate the immune response and subsequently change the course of asthma, they do not sufficiently alter the prevalence of the disease. The documentation that individuals infected with *S mansoni* had a milder asthma course is of 2-fold importance. First, the availability of treatment and support therapy for these patients is reduced in those areas. Second, it could lead to studies that could identify helminth antigens that might be involved in modulation of allergic responses and could be used to reduce morbidity for asthmatic patients here and elsewhere.

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