

Relationship between helminthic infection and IgE response in atopic and nonatopic children in a tropical environment

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Background: Although IgE antibody is clearly involved in allergic reactions to environmental allergens, this immunoglobulin is an important component of host-protective immune responses against the helminthic parasites that are endemic in the majority of the world population. However, these infections not only stimulate the production of anti-parasite IgE antibody but can nonspecifically induce polyclonal IgE synthesis that results in highly elevated total serum IgE levels. Such polyclonal stimulation can diminish specific IgE antibody responses and cause saturation of mast cell Fcε receptors, thus inhibiting allergic reactivity. This may represent a mechanism of immune evasion by the parasite.

Objective: Because an atopic disposition is generally recognized to be associated with elevated IgE synthesis against environmental allergens, the aim of this study was to evaluate the influence of atopy on the antiparasite response. To this end, we examined two groups of Venezuelan children in whom the intestinal helminth *Ascaris lumbricoides* is endemic but that differ greatly in their level of atopy. One group was from an island population (Coche Island) that has a very strong atopic background and in which the prevalence of allergic disease is extremely high. The other was a group of nonatopic children belonging to a mainland population (Barrio Los Erasos) that is of comparable socioeconomic level and has an exposure to helminthic infection similar to that of the island group but a relatively low expression of allergic diseases.

Results: Although the living conditions and the prevalence of *Ascaris* infection of the two groups were comparable, the intensity of the parasitic infection was considerably higher in the nonatopic mainland children (geometric mean values of eggs per gram of feces: Barrio Los Erasos, 7621;

Coche Island, 1435; $p < 0.001$). In addition, their total serum IgE levels were significantly more elevated than in the atopic island group (geometric mean: Barrio Los Erasos, 2172; Coche Island, 941 IU/ml; $p < 0.001$). In contrast, the specific anti-*Ascaris* response was much stronger in the atopic children (geometric mean: Barrio Los Erasos, 0.30; Coche Island, 0.91 PRU/ml; $p < 0.001$), which resulted in the ratio of specific to total IgE being nine times higher than in the nonatopic mainland subjects. These differences were maintained even when the children were matched on the basis of infection intensity, thus indicating that the atopic children have an intrinsic propensity to favor specific over polyclonal IgE responses to the parasite.

Conclusions: The children with a strong atopic background demonstrated IgE responses concordant with an enhanced protective response against helminthic parasites and had significantly lower intensities of infection than their nonatopic counterparts. These observations support the concept that the atopic state has conferred a selective evolutionary advantage that could compensate for its involvement in allergic disease. (*J Allergy Clin Immunol* 1998;101:217-21.)

Key words: Atopy, allergic disease, IgE, helminthic parasites, *Ascaris lumbricoides*

The capacity of common environmental allergens to stimulate IgE responses and thus to produce allergic disease has tended to overshadow the fact that helminthic parasites are possibly the most potent inducers of this immunoglobulin that exist in nature.^{1, 2} Although there is some debate regarding the relationship between helminthic infection and the IgE response,^{3, 4} there is considerable evidence that IgE antibody is an important component of immune protection against these parasites.⁵⁻⁹ In fact, it can be argued that this is the primary function of the allergic response and that allergic diseases represent undesirable reactions toward normally inoffensive environmental materials,¹⁰ particularly in situations in which parasitic infections occur only rarely.¹¹⁻¹³ This concept is complementary to that in which the increasing prevalence of allergic disease in developed countries is attributed to a T_H1/T_H2 imbalance caused by diminishing exposure to common infections.^{14, 15}

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Abbreviations used

epg:	Eggs per gram
MSAS:	Venezuelan Ministry for Health and Social Assistance

It has been well established that helminthic infections not only stimulate IgE responses against their own antigens but also induce a strong nonspecific T_H2 /IL-4-dependent polyclonal synthesis of this immunoglobulin.¹⁶⁻¹⁸ The nonspecific nature of this polyclonal stimulus can suppress allergic responses by reducing the production of specific IgE antibody against any given antigen¹⁸⁻²⁰ and by causing mast cell blockade by Fcε receptor saturation.^{12, 13, 18, 20, 21} One consequence of this is a reduction of the allergic reactivity against environmental allergens, which results in lower prevalences of allergic diseases in populations in which helminthic infections are endemic.²²⁻²⁴ Perhaps of even greater importance is the possibility that the inhibitory effect of excess IgE represents a means of evasion of the parasites from the immune response.²⁵ In this respect, we have previously shown that in endemic areas, persons with the highest total IgE levels are preferentially reinfected after antihelminthic treatment.²⁶

Assuming that IgE antibody participates in antihelminthic mechanisms, it can be hypothesized that atopic individuals, who are predisposed to the production of this immunoglobulin,²⁷ should have higher responses against such parasites²⁸ and that in evolutionary terms this might compensate for the adverse effects of allergic disease.

To evaluate the influence of an atopic state on the antiparasite IgE response, in this study we evaluated children on an island (Isla de Coche, or Coche Island) close to the coast of Venezuela, South America (latitude 10 degrees north), where not only is infection by the intestinal helminth *Ascaris lumbricoides* endemic, but also it has been reported²⁹ that the prevalence of asthma (>30%) is far higher than in comparable children^{12, 13, 22-24} on the mainland (< 10%). Further investigation of this population (M. Palenque, personal communication, 1994) revealed that the prevalence of allergic diseases in general is extremely high and accompanied by immediate hypersensitive skin test reactivity to environmental allergens, including extracts of *Ascaris*, thus indicating the high level of atopy of this group. The reason for this heightened atopic state has not been established but may be related to the fact that the population originated from a small group who were shipwrecked in 1526 and evolved as a relatively closed community. If there was an excess of individuals with allergies among the founders, this could have resulted in an enrichment of the genes that determine atopy, similar to what seems to have occurred on the island of Tristan da Cunha.³⁰

As a comparison group, we chose nonatopic children

from a slum area of Caracas, Venezuela (Barrio Los Erasos), which we have evaluated over a number of years^{12, 13} and in which the living conditions and prevalence of *Ascaris* infection are similar to the island group but the prevalence of allergic disease is relatively low.

METHODS

Study populations

Coche Island has a total population of approximately 7000 people, and the study group was selected at random with the use of census information from the four consolidated villages on the island. Informed parental consent to participate in the study was obtained for 626 children (56% female) between the ages of 2 and 12 years (mean $\pm$ standard deviation: 6.8 ± 2.9 years).

All of the approximately 300 family groups established in Barrio Los Erasos, a clearly delimited slum area of Caracas, were invited to participate in the study. A total of 187 children (54% female, 7.1 ± 3.0 years of age) who had no history of allergic disease and fulfilled the criteria of informed parental consent were evaluated.

The socioeconomic level of these two populations was determined with the method developed by the Center for Biological Studies of Growth and Development of the Venezuelan population (FUNDACREDESA), and that was adapted from the Graffar scale by H. Mendez-Castellano.³¹ This method takes into account a wide variety of variables that include the type of dwelling, construction materials, piped water, sanitary facilities, family size, level of education of the mother, and, independently, total family income. A score is calculated from these data, and the families are classified on a scale from I to V, with level V corresponding to extreme poverty. Apart from differences inherent to different geographical areas, the socioeconomic level and living conditions of the two study groups were closely comparable. Thus 58% of the families on the island were in Graffar level IV and 42% in level V. The percentages for the mainland group were 52% and 48%, respectively.

Ethical considerations

Because asthma is a major public health problem on Coche Island, an asthma clinic has been established in the Rural Medical Dispensary of the Venezuelan Ministry for Health and Social Assistance (MSAS), and the tests performed in this study were offered as part of the routine screening program that has been implemented at a population level. We obtained the approval of the Ethical Committee of the Institute of Biomedicine, Faculty of Medicine, Central University of Venezuela, the Regional Coordination of Tuberculosis and Pulmonary Diseases (MSAS), and the Medical Board of the rural dispensary for this study.

The urban slum area of Barrio Los Erasos has a medical dispensary that is run jointly by the MSAS and the J.M. de Los Ríos Childrens Hospital. Blood samples were obtained from the children, and as a service to the slum community, routine hematologic studies and feces examinations were performed. We obtained the collaboration of the community leaders for this study and received ethical permission from the Institute of Biomedicine and the Childrens Hospital.

The principles of these studies were ratified by the Venezuelan National Council for Scientific and Technological Investigation (CONICIT) and the Council for Scientific and Humanistic Development (CDCH) of the Central University of Venezuela. The informed consent of the legal representatives of the children was obtained for both the service and research

components of this study, and antiparasite treatment was administered to all children found to be infected after the blood sample had been collected.

Clinical evaluation

The children were examined by a group of physicians who were under the direct supervision of a pediatric allergist, a chest specialist, or both. A clinical history of allergic disease was established by questioning of the parents, and a comprehensive physical examination, including nasopharyngeal exploration, was performed. These data were also complemented by information provided by the permanent staff of the medical dispensaries and from the medical records of these. The presence of asthma was defined according to the guidelines of the World Health Organization/National Institutes of Health Global Initiative for Asthma (NIH publication 95-3659). In appropriate cases, the diagnosis was also supported by the determination of eosinophilia in nasal mucus and by skin testing with a variety of common environmental allergens that included house dust mites, molds, insects, animal epithelia, and *Ascaris* extract. In the children of Coche Island, the diagnosis of asthma was routinely confirmed by tests of pulmonary function before and after bronchodilator inhalation ($2 \times 100 \mu\text{g}$ salbutamol) and in some cases by histamine challenge.

Parasitologic evaluation

Serially collected feces samples were examined by the method of Kato,³² and the number of helminth eggs were calculated per gram of feces (epg). In both the island population and the mainland slum area, virtually the only helminths detected were *A. lumbricoides* and *Trichuris trichiura*. Possibly because *T. trichiura* does not have a systemic migratory phase,³² this parasite does not seem to be a major factor in modifying the IgE response, and thus only *Ascaris* infection was considered in this study.

We should note here that this study represented the first comprehensive parasitologic evaluation that these communities had received for many years and that antihelminthic treatment had not been administered to either of the study groups at a population level over the previous 5 years. Such treatment was occasionally applied on an individual basis when medically indicated, but this was not a routine practice in either of the dispensaries because of a lack of material. The low socioeconomic level generally precluded the purchase of antihelminthics by the families in these underprivileged areas.

IgE measurement

Serum levels of total IgE were measured by the Phadebas Paper-Radioimmunosorbant Test (PRIST; Pharmacia Diagnostics, Uppsala, Sweden) and the results expressed as international units per milliliter.

The levels of specific anti-*Ascaris* IgE were measured by the Phadebas RAST (Pharmacia) and the results expressed as Phadebas RAST units per milliliter (PRU/ml), with the use of the Phadebas reference kit. As suggested by the manufacturer and confirmed by our experience in previous studies, RAST values greater than 0.7 PRU/ml (RAST level 2) were considered positive.

Statistical analysis

As values of epg and total and specific IgE are not normally distributed, these were logarithmically transformed and the means and standard deviations calculated. These were com-

TABLE I. Infection by *Ascaris* and IgE response in island and mainland children

	Coche Island (n = 626)	p Values	Barrio Los Erasos (n = 187)
<i>Ascaris</i> infection			
Prevalence (%)	51	> 0.05	57
Intensity (epg)*	1435	< 0.001	7621
Total IgE† (IU/ml)	941	< 0.001	2172
Anti- <i>Ascaris</i> IgE			
% Positive‡	61	< 0.001	37
Concentration‡ (PRU/ml)	0.91	< 0.001	0.30

*Geometric mean epg of feces in infected children.

†Geometric mean.

‡Percentage of group with RAST levels ≥ 2 (0.7 PRU/ml).

pared between different groups by Student's *t* test. The antilogarithms of the means (geometric mean) were presented. Differences in the proportions of discrete variables between groups were compared by chi-square analysis.

RESULTS

Allergic disease in Coche Island children

Of the 626 children randomly selected from the island population, 380 (61%) were found to have a recent clinical history of asthma and/or rhinitis. Asthma was the predominant pathologic condition, with 92% of the symptomatic subjects reporting this compared with 35% with rhinitis. Although the establishment of a history of dermatologic allergy by questioning was somewhat difficult in this population, and conditions such as atopic dermatitis, urticaria, and angioedema were reported less frequently than the respiratory symptoms, the experience of the asthma clinic indicates that these also have a high prevalence. When all of the manifestations of allergic disease were taken into account, approximately 80% of the island children reported a history of allergy. This contrasts with less than 20% in the mainland slum area.^{12, 13}

Infection by *Ascaris* and IgE response in the study groups

In Table I it can be seen that although the prevalence of *Ascaris* infection was little different between the island and mainland groups, the intensity of infection in the children who were positive for this parasite in feces examination was far higher in the mainland children. The total serum IgE levels were also considerably higher in the mainland group. In contrast, the specific IgE antibody levels against the parasite were significantly higher in the island children. When the anti-*Ascaris* IgE antibody levels were expressed as percentages of the total IgE levels for each child, the geometric mean value was 0.09% for the island children and 0.01% for the mainland group ($p < 0.001$).

TABLE II. IgE response in island and mainland children selected for equivalent intensity of *Ascaris* infection

	Coche Island (n = 79)	p Values	Barrio Los Erasos (n = 76)
Total IgE*	1169	< 0.005	2570
Anti- <i>Ascaris</i> IgE			
% Positive†	73	< 0.001	36
Concentration* (PRU/ml)	1.30	< 0.001	0.32

*Geometric mean.

†Percentage of group with RAST levels ≥ 2 (0.7 PRU/ml).**IgE response in children selected for equivalent infection intensity**

In Table II, the total and specific IgE levels are presented for 79 *Ascaris*-infected island children who were selected to have fecal egg counts (geometric mean of group: 7656 epg) similar to that of the infected children of the mainland population (geometric mean: 7621 epg). It can be seen that despite the equivalent intensity of *Ascaris* infection, the total IgE levels were significantly higher and the anti-*Ascaris* levels considerably lower in the mainland children compared with the island children.

DISCUSSION

We have previously reported that the prevalence of allergic diseases, particularly asthma and rhinitis, in Venezuelan children from urban slum areas, such as the Barrio Los Erasos, is substantially lower than in children of higher socioeconomic levels, in which the prevalence is comparable to other areas of the world.^{11-13, 24} Evidence has been obtained to suggest that this is due at least in part to suppressive effects of the helminthic parasites that are endemic in such underprivileged groups.¹⁸⁻²¹ Thus such infections can nonspecifically stimulate a polyclonal IgE response that results in highly elevated total serum IgE levels and causes mast cell Fcε receptor saturation and lower specific IgE antibody responses against any given allergen.¹⁸⁻²¹ The population of Coche Island is very unusual in this respect because despite a prevalence of helminthic infection similar to that of the mainland group, there is an extremely high expression of atopy. Of particular significance is the finding that even though the living conditions on the island are closely comparable to the mainland group, the intensity of infection by the most common helminth, *A. lumbricoides*, in infected individuals was considerably lower in the island population. This could be due to differences between the environments of the two groups, but it is also possible that the highly atopic state of the island population is an important contributing factor. For example, the intensity of hookworm infection in atopic individuals has been found to be significantly lower than in their nonatopic counterparts in the same geographic area of Papua, New Guinea, despite similar

prevalences of infection in the two groups.³³ Although the dynamics of helminthic infection in an endemic situation are complex,^{34, 35} it may be that the similar prevalences result from comparable risk factors for infection but that the differences in intensities reflect a more effective immune control in atopics. This could be due to the fact that allergic reactions are important components of the protective immune response against helminths¹⁻¹⁰ and that the capacity for IgE synthesis is elevated in atopy.²⁷ Indeed, in the current study we found that the specific-IgE anti-*Ascaris* antibody levels were far higher in the island population than in the mainland group. In this respect it is interesting that although the atopic state favors IgE synthesis,²⁷ the total serum IgE levels were considerably higher in the nonatopic mainland group, indicating that the polyclonal response was stronger in these children. The fact that the ratio of anti-*Ascaris* IgE antibody to total serum IgE levels was ninefold higher in the island children compared with the mainland group allows us to suggest that the atopic state favors the specific antiparasite response over the nonspecific polyclonal IgE stimulus induced by the infection. As there is evidence that the excess polyclonal IgE represents a mechanism of immune evasion by the parasite,^{25, 26} the enhanced specific response conferred by the atopic state could be expected to increase the effectiveness of host-protective mechanisms.

We should note here that mild helminthic infections, in contrast to more intense infections, can augment allergic reactivity¹¹⁻¹³ and that we have found clinical improvement of Coche Island children with asthma after anthelmintic treatment.³⁶ It could therefore be suggested that in the island group it is not the elevated atopic state that is responsible for the low parasite load, but the inverse. This, however, seems unlikely to explain the pattern of IgE response we observed, because even when we selected a subgroup of island children whose infection intensities matched those of the mainland group, the total IgE levels were lower and the specific antibody levels higher in the atopic group. It appears therefore that the higher specificity of the antiparasite response is indeed intrinsic to the atopic state.

Our results possibly resolve some doubts about the influence of atopy on infection intensity that have arisen from a report³⁷ that contradicts the above-mentioned finding³³ of lower hookworm loads in atopic individuals in Papua, New Guinea. Thus the level of allergic reactivity in the population of New Guinea is very low, and relatively few atopic individuals can be identified.³⁸⁻⁴⁰ In contrast, in Coche Island, the vast majority of the persons have an atopic background. This did, however, require that the nonatopic control group for our study be chosen off-island. Despite this, the relative homogeneity of the mixed-race ("Creole") Venezuelan population permits valid comparisons between different areas.^{12, 13} Apart from the inevitable differences in climate between Coche Island and the mainland, we have identified no evident environmental factors that could be responsible

for the high prevalence of allergy in the former, particularly given that elevated atopy is not necessarily characteristic of coastal populations in Venezuela (G. Isturiz, personal communication, 1995). The allergic disease on Coche Island does not appear to present any unique characteristics (apart from the high prevalence) that would cause us to suspect that the findings of the present study are due to some unusual attribute restricted to this population. On the other hand, the demographic characteristics of the island community permit speculation that the operation of a "founder effect" has resulted in the enrichment of genes determining atopy.^{30, 41} If this were the case, our results support the concept that such genes provide an evolutionary advantage by enhancing the resistance to helminthic infection and that allergic disease represents an inappropriate response toward inherently inoffensive environmental allergens.

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