

The relationship among markers of allergy, asthma, allergic rhinitis, and eczema in Costa Rica

Celedón JC, Soto-Quiros ME, Hanson LÅ, Weiss ST. The relationship among markers of allergy, asthma, allergic rhinitis, and eczema in Costa Rica.

Pediatr Allergy Immunol 2002; 13: 91–97. © 2002 Blackwell Munksgaard

The association between allergy markers and asthma and allergic rhinitis is stronger in countries with a Western lifestyle than in rural areas of Africa and Asia. We examined the relationship among allergy markers, asthma, rhinitis, and eczema in a case-control study of 198 schoolchildren, 10–13 years of age, living in Costa Rica, a Latin American country. The geometric mean total serum immunoglobulin E (IgE) level in subjects with and without asthma was 465.0 and 143.0 IU/ml, respectively (difference=322 IU/ml, 95% CI=141.8–616.1 IU/ml, $p<0.001$), and that in subjects with and without allergic rhinitis was 442.5 and 144.3 IU/ml, respectively (difference=298.2 IU/ml, 95% CI=125.7–581.0 IU/ml, $p<0.001$). After adjusting for age, gender, and skin test reactivity to allergens, we found a linear relationship between serum total IgE level and the log odds ratio (OR) of having asthma. In a multivariate analysis, there was a linear relationship between skin test reactivity to allergens and the log OR of having allergic rhinitis. The odds of having allergic rhinitis were almost three times higher in children who had four positive skin tests than in non-reactors. Skin test reactivity to greater than five aeroallergens was an independent predictor of eczema in a multivariate analysis (OR=3.1, 95% CI=1.1–8.4). Although the geometric mean total serum IgE levels of Costa Rican children with either asthma or allergic rhinitis are higher than those of children with asthma or allergic rhinitis in most industrialized countries, the relationship among markers of allergy, asthma, rhinitis, and eczema in Costa Rica is similar to that found in countries with a Western lifestyle and different from that found in rural areas of Asia and Africa.

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Key words: asthma; rhinitis; eczema in Costa Rica

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Accepted 20 April 2001

Asthma is a major public health problem, affecting over 17 million people in the United States (1). The prevalence of asthma has been increasing in the United States and world-wide (2–7), and parallel increases in allergic rhinoconjunctivitis and eczema have been reported in some industrialized countries (4–6,8). In Costa Rica, a Latin American country, the prevalence of childhood asthma is one of the highest in the world (9). A recent estimate based on written questionnaires from the International Study of Asthma and Allergies in Childhood (ISAAC), indicated that parents reported current wheezing in 32.1% of 6–7-year-old children and in

23.7% of 13–14-year-old children in Costa Rica (10).

In population-based studies conducted in countries with a Western lifestyle, the total serum immunoglobulin E (IgE) level was found to be a strong predictor of asthma, whereas skin test reactivity to aeroallergens was closely correlated with allergic rhinitis and eczema (11–15). To date, no population-based studies have examined the relationship among allergy markers and asthma, allergic rhinitis, and eczema in a Latin American country. We were therefore interested in examining the relationship among total serum IgE level, skin test reactivity to aeroallergens,

asthma, allergic rhinitis, and eczema in 198 Costa Rican schoolchildren.

Subjects and methods

Study population

In 1998, 75 of 5,000 educational centers registered in Costa Rica were selected for inclusion in the study by randomly stratifying for geographical location, including urban and rural areas. Core questionnaires from phase I of the ISAAC (16) were sent to the parents of 1,500 10-year-old children enrolled in these schools; 1,105 (73.7%) of these questionnaires were completed and returned. Of these 1,105 schoolchildren, 299 had a parental report of wheezing in the previous 12 months, and a random sample of 174 of these children and a random sample of 132 of the remaining 806 children were included in this study.

Procedures

Data were collected between November 1998 and November 1999. After written informed consent was obtained from the parents of participating children, the following procedures were carried out in accordance with protocols from phase II of the ISAAC (17):

- 1 Completion of a standardized questionnaire that included questions on respiratory and nasal symptoms; respiratory health status; management of asthma, rhinitis, and eczema; home environment; and family history of respiratory and allergic illnesses.

- 2 Spirometry.

- 3 Measurement of airway responsiveness to hypertonic saline.

- 4 Skin testing for reactivity to eight aeroallergens along with a positive and a negative control.

- 5 Collection of a blood sample for measurement of total serum IgE.

In addition, the height and weight of the subjects were measured by standard methods after they had removed their shoes and outerwear. Height was measured on a portable stadiometer and the value was rounded up to the next 0.1 cm. Weight was measured with the subject standing motionless on the scale and was rounded up to the next 0.1 kg. The study was approved by the Institutional Review Board of the Hospital Nacional de Niños in San José, Costa Rica.

Spirometry

A Vitalograph Compact II Spirometer (Vitalograph Ltd, Maids Moreton, Bucks., UK) was

used to perform spirometry in a standardized manner, with subjects seated and wearing a noseclip. As many as eight attempts were performed by each participant in order to obtain three acceptable measures. Spirometry was performed in accordance with the specifications of the American Thoracic Society (18): the highest forced expiratory volume in 1 second (FEV_1) value from two reproducible measures (within 5%) was recorded as the baseline FEV_1 .

Measurement of airway responsiveness to hypertonic saline

Challenge testing with hypertonic saline was performed in all subjects whose baseline FEV_1 was $\geq 65\%$ of predicted, in accordance with the ISAAC phase II protocol (17). Subjects were classified as having increased airway responsiveness to hypertonic saline if their FEV_1 fell by $\geq 15\%$ from their baseline value at any time during challenge testing.

Study participants were asked to withhold use of short-acting inhaled bronchodilators, inhaled sodium cromoglycate, and inhaled nedocromil sodium for at least 6 h before testing, unless significant respiratory symptoms required treatment.

Allergy skin testing

Skin testing was performed according to the ISAAC phase II protocol (17). In addition to positive (histamine, 10 mg/ml) and negative (diluent) controls, the following antigens were applied to the skin of the volar aspect of the left forearm: *Periplanetaria americana* (cockroach), *Dermatophagoides pteronyssinus* (Der p 1), *Dermatophagoides farinae* (Der f 1), dog dander, cat dander, mixed tree pollen, mixed grass pollen, and *Alternaria tenuis*. All of the allergen extracts and the controls were purchased from ALK Laboratories (Wallingford, CT, USA). A test was considered positive if the maximum diameter of the wheal was >3 mm after subtraction of the wheal diameter of the negative control.

Measurement of total serum IgE

Total serum IgE levels were determined by using the Abbott IMx system (Abbott Diagnostics, North Chicago, IL, USA). All values were transformed to a $\log_{10}$ scale for analysis, in accordance with the recognized logarithmic distribution of total serum IgE levels in the general population (19).

Table 1. Predictors of asthma on bivariate analyses

Predictor	Asthma=No	Asthma=Yes	Odds ratio (95% CI)
Age			
≤11 years	16	13	
>11 years	75	94	1.5 (0.7–3.4)
Gender			
Female	48	43	
Male	43	64	1.7 (0.9–2.9)
STR to ≥ 1 aeroallergen			
No	30	16	
Yes	61	91	2.8 (1.4–5.6)
Serum total IgE (IU/ml)			
≤75	28	18	1.0
75.1–279.9	30	17	0.9 (0.4–2.0)
280.0–948.0	21	31	2.3 (1.0–5.2)
>948	12	41	5.3 (2.2–12.7)
Serum total IgE (IU/ml)			
<100	32	21	
≥100	59	86	2.2 (1.2–4.2)
Allergic rhinitis			
No	56	27	
Yes	35	78	4.6 (2.5–8.5)
Airway hyper-responsiveness*			
No	55	29	
Yes	36	78	4.1 (2.3–7.5)

*A fall in the forced expiratory volume in 1 second (FEV_1) of $\geq 15\%$ from the baseline value during challenge testing with hypertonic saline.
IgE, immunoglobulin E; STR, skin test reactivity.

Definitions of asthma, allergic rhinitis, and eczema

Our definition of asthma was based on an affirmative answer to the question ‘Has your child ever been diagnosed by a doctor as having asthma?’, as well as by the presence of greater than one of three respiratory symptoms (current or usual cough without a cold, wheezing, nocturnal wheezing/cough) or a history of asthma attacks during the 12 months preceding completion of the questionnaire. The presence of allergic rhinitis was determined by affirmative answers to the questions ‘Has your child ever had hay fever or a runny or blocked nose with sneezing and itching when he/she did not have a cold?’ and ‘Does your child still have these symptoms?’. Children were classified as having eczema if their parents reported that they had visited a health care provider, had been hospitalized, or had missed at least one school day because of eczema in the 12 months preceding the interview.

Statistical methods

Bivariate relationships between predictor and outcome variables were analyzed using the chi-squared test for pairs of categorical variables or with the two-tailed *t*-test for a categorical and a continuous variable. Logistic regression was used to study the relationship between allergy markers (total serum IgE and skin test reactivity to allergens) and the outcomes of interest (asthma,

allergic rhinitis, and eczema), while adjusting for potential confounders and examining interactions. All of the analyses were performed using the SAS statistical software package (SAS Institute, Inc., Cary, NC, USA).

Results

Subject characteristics

The study originally included 306 Costa Rican schoolchildren. The present analyses were limited to 198 subjects on whom complete information was available regarding total serum IgE and skin test reactivity to allergens. The age-range of 197 of these subjects was 10–12 years; one subject was 13 years of age.

No statistically significant differences in age, gender, current wheezing, total serum IgE level, or skin test reactivity to allergens was found between subjects included in the current analysis ($n=198$) and those excluded from the analysis ($n=108$). Whereas allergic rhinitis was present in 113 (57%) of the 198 subjects included in the analysis, it was reported in only 35 (32.4%) of the 108 subjects excluded from the analysis ($p=0.009$).

Among the 198 study participants, 99 (50%) had a parental report of usual or current cough without a cold, 98 (49.5%) had a parental report of wheezing in the preceding 12 months, 77 (38.9%)

Table 2. Predictors of allergic rhinitis on bivariate analysis

Predictor	Rhinitis=No	Rhinitis=Yes	Odds ratio (95% CI)
Age			
≤11 yr	10	19	
>11 yr	73	94	0.7 (0.3–1.5)
Gender			
Female	46	44	
Male	37	69	1.9 (1.1–3.5)
STR to ≥ 1 aeroallergen			
No	28	17	
Yes	55	96	2.9 (1.4–5.7)
Serum total IgE (IU/ml)			
≤75	31	14	1.0
75.1–279.9	21	26	2.7 (1.2–6.4)
280.0–948.0	17	34	4.4 (1.9–10.5)
>948	14	39	6.2 (2.6–14.8)
Serum total IgE (IU/ml)			
<100	33	19	
≥100	50	94	3.3 (1.7–6.3)

IgE, immunoglobulin E; STR; skin test reactivity.

had a parental report of nocturnal cough or wheezing in the preceding 12 months, 47 (23.7%) had a history of asthma attacks in the preceding 12 months, and 114 (57.6%) had increased airway responsiveness to hypertonic saline.

Bivariate analyses of the relationship among total serum IgE, asthma, allergic rhinitis, and eczema

The geometric mean serum total IgE level in subjects with and without asthma was 465.0 and 143.0 IU/ml, respectively (difference=322 IU/ml, 95% CI=141.8–616.1 IU/ml, $p<0.001$); that in subjects with and without allergic rhinitis was 442.5 and 144.3 IU/ml, respectively (difference=298.2 IU/ml, 95% CI=125.7–581.0 IU/ml, $p<0.001$). Data on the relationship of asthma and allergic rhinitis to total serum IgE level is presented in Tables 1 and 2. We found no significant association between total serum IgE level and eczema in our study population. There was a strong association between allergic rhinitis and asthma among participating children (Table 1). Of 107 children with asthma, 78 (72.9%) had allergic rhinitis.

Bivariate analyses of the relationship among skin test reactivity to aeroallergens, asthma, rhinitis, and eczema

Tables 1 and 2 summarize the predictors of asthma and allergic rhinitis in the bivariate analyses. The median number of positive skin tests was higher in subjects with asthma than in those without asthma (three vs. one, $p<0.001$) and in subjects with allergic rhinitis than in those without allergic rhinitis (three vs. one, $p<0.001$).

Multivariate analysis of the relationship between asthma and total serum IgE

After adjusting for age, gender, and skin test reactivity to allergens, we observed a linear relationship between total serum IgE level and the log odds ratio (OR) of having asthma. The multivariate model in which the total serum IgE level was treated as a linear variable (Model 1, Table 3) was the best-fitting model compared with those in which total serum IgE level was treated as a categorical variable or as a 'score' variable. Furthermore, the linear relationship between total serum IgE level and asthma was not appreciably changed if an alternative definition of asthma (increased airway responsiveness and history of more than one respiratory symptom or asthma attacks in the previous 12 months) was employed. When the analysis was restricted to the 83 subjects who did not have rhinitis, the association between total serum IgE level and asthma became slightly stronger (Model 2, Table 3). We found no significant modification of the effect of total serum IgE level by skin test reactivity to allergens, age, or gender.

Multivariate analyses of the relationship among allergic rhinitis, eczema, skin test reactivity to aeroallergens, and total serum IgE

After adjustment for age, gender, and total serum IgE level, a linear relationship was observed between the number of positive skin tests to aeroallergens and the log OR of having allergic rhinitis in our study population ($p=0.008$); the best-fitting multivariate model was the one in which the skin test reactivity to allergens was expressed as a linear variable (Model 1, Table 4). A linear

Table 3. Multivariate analysis of the relationship of asthma to serum total immunoglobulin E (IgE) and skin test reactivity (STR) to aeroallergens

Model	Odds ratio (95% CI)	p-value
Model 1*		
Serum total IgE (IU/ml)		
10	1.0	
100	2.0 (1.3–3.2)	
1000	4.1 (1.7–10.2)	0.002
STR to aeroallergens		
0	1.0	
1–4	1.5 (0.7–3.4)	0.28
5–8	2.7 (0.9–8.6)	0.08
Model 2*		
Serum total IgE (IU/ml)		
10	1.0	
100	2.3 (1.1–4.9)	
1000	5.4 (1.2–24.4)	0.02
STR to aeroallergens		
0	1.0	
1–4	1.6 (0.5–5.2)	0.41
5–8	3.5 (0.5–25.2)	0.21

*Adjusting for age and gender.

relationship was also noted between total serum IgE level and the log OR of having allergic rhinitis ($p=0.02$) (Model 1, Table 4); this linear relationship persisted after exclusion of the 107 asthmatic subjects from the analysis. Neither the effect of skin test reactivity to allergens nor the effect of total serum IgE level on allergic rhinitis was significantly modified by any of the other variables in the model.

After adjustment for age, gender, and total serum IgE level, subjects who had greater than five positive skin tests to aeroallergens had an OR of having eczema that was 3.1 times higher than those who had fewer than five positive skin tests (Model 2, Table 4). No significant association between total serum IgE level and eczema was found, and the effect of skin test reactivity to

allergens on eczema was not modified by age, gender, or total serum IgE level.

Discussion

To our knowledge, this is the first population-based study in the English language literature to examine the relationship among allergy markers, asthma, allergic rhinitis, and eczema in a Latin American country. Among 198 schoolchildren living in Costa Rica, we found that the relationship among serum total IgE level, skin test reactivity to aeroallergens, asthma, rhinitis, and eczema was similar to that found in countries with a Western lifestyle.

Costa Rica is notable among Latin American countries for its long-standing democratic form of government. The implementation of compul-

Table 4. Multivariate analysis of the relationship among allergic rhinitis, eczema, skin test reactivity (STR) to aeroallergens, and serum total immunoglobulin E (IgE) level

Model	Odds ratio (95% CI)	p-value
Model 1 (allergic rhinitis)*		
Serum total IgE (IU/ml)		
10	1.0	
100	1.7 (1.1–2.7)	
1000	2.9 (1.2–7.2)	0.02
Number of positive skin tests		
0	1.0	
2	1.7 (1.1–2.4)	
4	2.7 (1.3–5.7)	
8	7.4 (1.7–32.8)	0.008
Model 2 (eczema)†		
STR to >4 aeroallergens		
No	1.0	
Yes	3.1 (1.1–8.4)	0.03

*Adjusting for age and gender.

†Adjusting for age, gender, and total serum IgE level.

sory health insurance and primary education in Costa Rica in the first half of the 20th century led to a very high literacy rate ($\approx 95\%$) and a low infant mortality rate (12.6 per 1000 live births) in 1998 (20). In addition, the progressive industrialization of the country's economy has also resulted in profound changes in the lifestyle of Costa Ricans.

Even though the geometric mean total serum IgE levels among asthmatic (465 IU/ml) and non-asthmatic (143 IU/ml) subjects in our study population were markedly higher than the geometric mean total serum IgE levels of 89 asthmatic (224 IU/ml) and 994 non-asthmatic (43 IU/ml) subjects who were 6–34 years old and were included in a population-based study of the relationship between allergy markers and asthma in the United States (11), our findings regarding the relationship of asthma with total serum IgE level and the number of positive skin tests to allergens are similar to those of Burrows and colleagues (11). In contrast to our findings, Sunyer and co-workers recently found no significant difference in the geometric mean total serum IgE level between pregnant women with and without asthma who lived in a semi-rural area of Tanzania (21).

The prevalence of current symptoms related to allergic rhinoconjunctivitis among 13–14-year-old Costa Rican children participating in the ISAAC was $\approx 15\%$, a value lower than identified in other Latin American countries (Paraguay, Argentina, Peru, and Brazil) but higher than in non-industrialized societies (e.g. Ethiopia, rural China) (10). Whereas a linear relationship between the number of positive skin tests to allergens and allergic rhinitis has been described in children and adults living in industrialized countries (11,22), the prevalence of allergic rhinitis in children living in rural China is very low despite a high prevalence of atopy (23). In a study of Chinese children living in the rural province of San Bu, no significant association was found between skin test reactivity to any of five aeroallergens and allergic rhinitis (23).

A subset of patients with atopic eczema were found to have exacerbations of their skin lesions after contact with certain aeroallergens (24,25). A recent nested case-control study of German schoolchildren, 5–14 years of age, found a direct association between the degree of sensitization to aeroallergens and the severity of atopic eczema, as assessed by complete skin examinations conducted by senior dermatologists (15).

We recognize several limitations to our study. First, it is a cross-sectional study, and one cannot conclude that the 'Westernization' of the Costa

Rican lifestyle over the last 50 years has resulted in the current close correlation between atopy and asthma and allergic rhinitis. Second, we ascertained the presence of eczema on the basis of a parental report by questionnaire, a method that probably resulted in an under-estimation of the prevalence of eczema in our study population. Third, we did not examine stool samples for ova and parasites. However, the prevalence of parasitism among Costa Rican children is low and therefore unlikely to explain the high serum total IgE levels of children participating in our study. In a recent study of 268 Costa Rican schoolchildren, intestinal parasites (*Ascaris lumbricoides*, *Necator americanus*, *Trichuris trichiura*, *Hymenolepis nana*) were found in only 5.4% of the stool samples examined, and only 1% of the children in the study were infected with two or more parasites (26). Fourth, there were a greater number of subjects with allergic rhinitis among those included in the analysis than among those excluded, partly explaining the relatively high geometric mean total serum IgE levels and high prevalence of atopy among subjects without asthma or eczema. This led to a slight under-estimation of the measure of association between total serum IgE level and asthma (Table 3, Models 1 and 2) and probably reduced our statistical power to examine the relationship between skin test reactivity to aeroallergens and eczema.

In summary, we found a strong association among markers of allergy and asthma, allergic rhinitis, and eczema in Costa Rica, which was similar to the association found in developed countries with a Western lifestyle and different from findings in rural societies in Asia and Africa. The high prevalence of asthma in contemporary Costa Rica may be related, at least in part, to lifestyle changes resulting from this nation's social development over the last 50 years.

Acknowledgments

Dr Celedón is supported by NRSA Grant HL-07427 and by a Charles A. King Trust Fellowship Award.

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