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Factors associated with allergic rhinitis and combined allergic rhinitis and asthma syndrome (CARAS) in children aged 5-18 years undergoing immunotherapy in a tropical low- or middle-income country

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Abstract

Background: Tropics have some particularities that can impact the natural history and factors associated with allergic diseases. However, few studies described the characteristics of patients with allergic rhinitis (AR) and combined AR and asthma syndrome (CARAS) in Latin American tropical countries.

Objective: This study aimed to determine the medical, social, and environmental factors associated with AR and CARAS in children aged 5-18 years treated with immunotherapy in two allergy referral centers in Bogotá (Colombia).

Material and methods: An observational, cross-sectional study was conducted between January 2018 and January 2019. International Study Asthma Allergies Childhood-III and socio-demographic questionnaires were applied to adolescents and parents of children undergoing immunotherapy at the allergy consult in the Hospital Universitario Fundación Santa Fe de Bogotá and UNIMEQ-ORL.

Results: Among 830 children aged 5-18 years, 38.1% (n = 316) were women. Up to 63.25% of the population had a positive skin prick test for house dust mites: 63.25% for *Dermatophagoides pteronyssinus*, 61.81% for *Dermatophagoides farinae*, and 31.57% for *Blomia tropicalis*. The factors associated with AR were male sex (PR: 1.31, 95% CI: 1.08-1.57), antibiotic consumption during the first year of life (PR: 0.80; 95% CI: 0.63-0.99), and exposure to dogs (PR: 1.32; 95%

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CI: 1.06-2.66). The factors associated with CARAS were older age (PR=0.95; 95% CI: 0.95-0.99), acetaminophen consumption over four times a year (PR: 1.31; 95% CI: 1.03-1.55), and antibiotic consumption during the first year of life (PR: 1.21; 95% CI: 1.06-1.34).

Conclusion: A high prevalence of *B. tropicalis* was found in this study. The factors associated with AR and CARAS are like those described in high-income tropical countries. Further studies are needed in low- or middle-income tropical countries to identify modifiable factors associated with allergic diseases.

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Introduction

Allergic rhinitis (AR), asthma, and atopic dermatitis (AD) are inflammatory diseases mediated by immunoglobulin E (IgE)-dependent reactions.¹ An innocuous environmental antigen (allergen) triggers these immunological reactions in previously sensitized patients.¹ Prior studies described a high prevalence of allergic diseases in tropical countries from Africa and Latin America due to geographical or environmental characteristics that prompt the predominance of allergens such as house dust mites.²⁻⁴ However, these diseases are poorly understood in low- or middle-income tropical countries, and their management guidelines are based on European and North American populations.³

Colombia is one of the tropical Latin American countries with the highest prevalence of allergic diseases.^{5,6} In Bogotá, the capital city of Colombia, the factors associated with AR in children using the International Study of Asthma and Allergies in Childhood phase III (ISAAC-III) methodology include asthma, AD, frequent acetaminophen consumption, antibiotic use during the first year of life, higher maternal education, and passive exposure to cigarette smoke.⁷ Nevertheless, the ISAAC-III strategy is based on self-reported symptoms, and the clinical suspicion is not enough for diagnostic confirmation of allergic diseases.⁸

Research studies with diagnostic confirmation by specific allergen testing such as the skin prick test (SPT) are needed. The SPT allows the identification of allergens, as well as the targeting through specific immunotherapy.^{8,9} To date, there are no studies in Latin America assessing the factors associated with allergic diseases confirmed by SPT in patients undergoing allergy immunotherapy. This study aimed to describe the medical, sociodemographic, and environmental factors associated with AR and combined AR and asthma syndrome (CARAS)¹⁰ in children aged 5-18 years undergoing specific immunotherapy in two reference centers of allergy in Bogotá, Colombia: the Hospital Universitario Fundación Santa Fe de Bogotá (FSFB) and UNIMEQ-ORL. The factors associated with AR and CARAS were determined by applying the ISAAC-III questionnaire.¹¹

Materials and Methods

Study design

This is an observational, analytical, cross-sectional study conducted at the FSFB and UNIMEQ-ORL between January 2018 and January 2019. This study assessed the factors

associated with AR and CARAS by applying the ISAAC-III questionnaire to parents or legal tutors and adolescents aged 5-18 years who had a clinical diagnosis of AR or asthma confirmed with SPT and treated with specific immunotherapy. The written questionnaires were applied to parents or legal tutors of children aged 5-12 years, while the adolescents aged 13-18 years received self-administered written questionnaires. The diagnosis of AR and prescription of immunotherapy were performed by allergists based on the European Academy of Allergy and Clinical Immunology (EAACI) guidelines.⁸ Sociodemographic and clinical data were collected from the clinical records of the FSFB.

The FSFB is a high complexity academic hospital that provides access to all medical specialties. The FSFB and UNIMEQ-ORL are allergy and immunotherapy referral centers located in Bogotá, Colombia. Both institutions treat populations affiliated to Health-promoting Entities, which provide health insurance packages to populations of all socioeconomic status. Colombia is a low- or middle-income country with tropical climate characteristics. The ethics committee of the FSFB approved the protocol of this study (CCEI-10248-2019) according to the Helsinki Declaration. No incentives were offered for study participation.

Study population

The study population met the following inclusion criteria for immunotherapy according to the EAACI guidelines:⁸ (a) Patients aged 5-18 years; (b) had evidence of positive SPT to one or more clinically relevant allergens; (c) reported moderate or severe symptoms of the disease that interfered with their daily activities or sleep, despite pharmacotherapy and/or allergen avoidance; and (d) were treated with immunotherapy between 2018 and 2019 at the FSFB and/or UNIMEQ-ORL. The ISAAC-III questionnaire was applied during the immunotherapy appointments.

ISAAC-III questionnaire

The ISAAC-III questionnaire was applied to all patients who met the inclusion criteria to determine the frequency and factors associated with allergic diseases. This questionnaire has been previously adapted and validated in the Spanish language.¹¹ For this study, determination of AR, asthma, and AD symptoms were based on a positive response to the following questions: "In the last 12 months, have you had a problem with sneezing, snoring, or mouth blockage when you did not have a cold/flu"; "Have you had wheezing or

whistling in your chest in the past 12 months”; “Have you ever had an itching or rash that came and went for at least 6 months or at any time in the last 12 months?”.¹¹

Statistical analysis

Stata16MP was used for the statistical analysis, and the “a priori” significance level for the comparisons was 5%. Regarding the descriptive analysis, absolute and relative frequencies were calculated for qualitative variables. Measures of central tendency (average/median) were estimated for the quantitative variables, and standard deviation and interquartile range for the dispersion measures. A multivariable analysis based on logistic regression was performed to identify the factors associated with AR and CARAS. The variables were included considering the biological plausibility and the statistical associations with a $P < 0.2$ found in a Fisher or Chi-square test or t- or Mann-Whitney test. A transformation of the odd ratio (OR) to prevalence ratio (PR) was carried out considering the overestimation of the strength of the associations related to OR compared to PR when the frequency of the condition of interest is greater than 10%.¹² Moreover, a diagnostic analysis of the models was performed based on linearity and goodness-of-fit tests, as well as an assessment of collinearity problems and evaluation of deviance residuals and leverage points.¹³

Results

A total of 830 children aged 5-18 years were included, of which 38.1% were females and 57.9% were aged between 5 and 12 years. Up to 22.3% of the population remained in immunotherapy treatment during 24-36 months. The baseline demographic characteristics of the study population are described in Table 1.

Regarding the sensitization results obtained by SPT, the most frequent allergens were house dust mites (80.24%): 63.25% of the SPT were positive for *Dermatophagoides pteronyssinus*, 61.81% for *Dermatophagoides farinae*, and

Table 1 Baseline demographic and clinical characteristics of the study population.

Variables	n = 830	
	n	%
Sex, Female/Male	316/514	38.07/61.93
Age in years*	11.2 (3.5)	11.1 (8.5-14)
Age group		
5-12 years old	481	57.9
13-18 years old	349	42.0
Socioeconomic status		
Low-income levels	348	41.9
Middle-income levels	461	55.5
High-income levels	20	2.4
No data	1	0.2
Mother's educational level		
Primary education	36	4.3
Secondary education	202	24.3
Technical education	213	25.7

Variables	n = 830	
	n	%
Higher education	366	44.1
No data	13	1.6
Father's educational level		
None	4	0.5
Primary education	48	5.8
Secondary education	240	28.9
Technical education	180	21.7
Higher education	316	38.1
No data	42	5.1
Z score of BMI*	0.17 (1.3)	0.21 (-0.6;1.11)
Classification of Weight Status by BMI score**		
Underweight, Grade 3	18	2.2
Underweight, Grade 2	27	3.3
Underweight, Grade 1	66	8.0
Normal weight	558	67.2
Overweight	135	16.3
Obesity	25	3.0
Exercise frequency per week		
Occasionally or none	126	15.2
1 to 2 times per week	455	54.8
3 or more times per week	249	30.0
Passive exposure to cigarette smoke		
Yes	90	10.8
Parents or siblings with		
Allergic rhinitis	535	64.5
Atopic dermatitis	288	34.7
Current exposure to pets		
Dog	216	26.0
Cat	93	11.2
Antibiotic consumption during the first year of life		
Yes	425	51.2
Acetaminophen consumption during the last year		
Never	66	8.0
Less than 4 times per year	392	47.2
More than 4 times per year	372	44.8
Length of immunotherapy		
Less than 6 months	257	31.0
6-12 months	127	15.3
12-18 months	104	12.5
18-24 months	81	9.8
24-36 months	185	22.3
36-48 months	44	5.3
More than 48 months	32	3.9

*Values are expressed in mean (SD) and median (P = 25-75).

**WHO categories. BMI: Body mass index

31.57% for *Blomia tropicalis*. Up to 18.43% (n = 153) of the population obtained a positive SPT for these three house dust mites. Excluding house dust mites, the most frequent allergens were dog hair (13.13%), cat hair (12.5%), grasses (11.45%), and food (4.22%).

Frequency of allergic diseases

Overall, 35.18% of the population presented exclusive AR. AR was frequently found in comorbidity with asthma (CARAS, 27.83%) and AD (18.43%). The combination of the

Table 2 Prevalence of allergic diseases in the study population.

Allergic disease	n = 830		
	n	%	95% CI
Allergic rhinitis	292	35.18	(32–38.5)
Asthma	1	0.12	(0.02–0.68)
Atopic dermatitis	2	0.24	(0.07–0.87)
Allergic rhinitis in combination with:			
Asthma	231	27.83	(24.8–31.01)
Atopic dermatitis	153	18.43	(15.8–21.2)
Asthma in combination with:			
Atopic dermatitis	0	0	0
Presence of allergic rhinitis, asthma, and atopic dermatitis	151	18.19	(15.7–20.9)

three allergic diseases was found in 18.19% of the children. These results are shown in [Table 2](#).

Factors associated with AR and CARAS

The factors associated with AR and CARAS are described in [Tables 3](#) and [4](#). Factors associated with AR included: male sex (PR: 1.31, 95% CI: 1.08–1.57), presence of dogs in the house (PR: 1.32; 95% CI: 1.06–2.66), and antibiotic consumption during the first year of life (PR: 0.80; 95% CI: 0.63–0.99). Meanwhile, the factors associated with CARAS were older age (PR: 0.95; 95% CI: 0.95–0.99), acetaminophen consumption over four times a year (PR: 1.31; 95% CI: 1.03–1.55), and antibiotic consumption during the first year of life (PR: 1.21; 95% CI: 1.06–1.34). About the diagnosis of these regression models, linearity tests and goodness-of-fit tests were carried out and no collinearity problems were found. During the evaluation of deviance residuals and leverage points, no extreme or influential values that could affect the model were found.

Discussion

This study describes the factors associated with AR and CARAS in children treated with specific immunotherapy in a low-income tropical country. Most of these patients have moderate to severe symptoms of AR confirmed by SPT according to the ECAA guidelines.⁸ About the socio-demographic characteristics of the study population, the atopic peaks ranged between the ages of 6–7 and 13–14 years which were consistent with prior ISAAC-III studies including pediatric population from high-income temperate countries.¹⁴

The SPT findings in our population are consistent with the previously described distribution of allergens in patients undergoing immunotherapy in tropical countries.³ The most frequent allergens in tropical countries are house dust mites (*B. tropicalis*, *D. pteronyssinus*, and *D. farinae*), animal hair, and pollen.³ Up to 31.57% of our study population tested positive for *B. tropicalis*, while prior studies in Mexico City described a frequency that remains around

Table 3 Model of factors associated with AR.

Variable*	Bivariate analysis		Multivariable analysis	
	PR	95% CI	PR	95% CI
Age in years	1.02	(0.99–1.05)	1.02	(0.98–1.05)
Sex				
Male	1.29	(1.07–1.54)	1.31	(1.08–1.57)
Socioeconomic status				
Middle-income levels (3–4)	1.05	(0.86–1.25)	1.07	(0.85–1.31)
High-income levels (5–6)	0.72	(0.30–1.41)	0.69	(0.27–1.45)
Cesarean delivery				
Yes	0.88	(0.71–1.05)	0.85	(0.67–1.06)
Mother's educational level				
Secondary education	1.14	(0.69–1.55)	1.11	(0.67–1.66)
Higher education	1.12	(0.70–1.51)	1.12	(0.70–1.65)
Acetaminophen consumption				
Less than 4 times a year	1.51	(0.96–2.10)	1.24	(0.84–1.70)
More than 4 times a year	0.92	(0.51–1.47)	0.98	(0.54–1.56)
Dog ownership at home				
Yes	1.85	(1.02–2.58)	1.32	(1.06–1.59)
Cat ownership at home				
Yes	0.91	(0.65–1.21)	0.83	(0.57–1.16)
Fast food consumption				
Yes	1.08	(0.87–1.30)	1.11	(0.88–1.37)
Wheat consumption				
Yes	0.92	(0.63–1.48)	0.91	(0.59–1.32)
Antibiotic consumption during the first year of life				
Yes	0.82	(0.67–0.98)	0.80	(0.63–0.99)
Overweight or obesity				
Yes	0.89	(0.68–1.12)	0.89	(0.66–1.16)

Bold numbers highlight the significant associations with adequate 95% CI.

*Log-likelihood of the model: –593.358; AIC: 1070.716; BIC: 1146.201. CI: Confidence intervals; PR: Prevalence ratio

12.1% in patients with RA or asthma.¹⁵ The frequency of *B. tropicalis* was also high compared to the previous reports of atopic populations from temperate environments in developed countries.¹⁶ The diverse environmental conditions in the tropical countries in Latin America could account for these differences. Earlier studies described that mites species have geographical fluctuations depending on the humidity and proximity to the Equatorial zone.³ Therefore, studies about the geographical distribution of allergen sensitization are needed in tropical Latin American populations.

AR was most frequent in male sex (PR: 1.31; 95% CI: 1.08–1.57). Similarly, previous studies reported gender-specific differences in the prevalence of AR, displaying a higher prevalence of AR in male children aged 6–11 years, followed by a homogeneous distribution during adolescence.^{17,18} This phenomenon could be explained by hormonal factors such

Table 4 Model of factors associated with CARAS.

Variables*	Bivariate analysis		Multivariable analysis	
	PR	95% IC	PR	95% CI
Age in years	0.97	(0.95–0.99)	0.95	(0.95–0.99)
Sex				
Male	0.89	(0.75–1.03)	0.77	(0.73–1.02)
Socioeconomic status				
Middle-income levels (3–4)	0.88	(0.74–1.01)	0.90	(0.75–1.05)
High-income levels (5–6)	1.12	(0.67–1.52)	1.15	(0.69–1.57)
Cesarean delivery				
Yes	1.16	(1.00–1.32)	1.15	(1.00–1.29)
Mother's educational level				
Secondary education	0.95	(0.63–1.29)	0.94	(0.63–1.26)
Higher education	0.86	(0.58–1.18)	0.85	(0.57–1.16)
Acetaminophen consumption				
Less than 4 times a year	1.39	(1.08–1.65)	1.29	(1.00–1.53)
More than 4 times a year	1.41	(1.10–1.66)	1.31	(1.03–1.55)
Dog ownership at home				
Yes	0.81	(0.73–1.05)	0.89	(0.73–1.05)
Cat ownership at home				
Yes	1.11	(0.83–1.29)	1.13	(0.90–1.34)
Fast food consumption				
Yes	0.87	(0.71–1.03)	0.87	(0.84–1.83)
Wheat consumption				
Yes	1.23	(0.89–1.56)	1.16	(0.88–1.42)
Antibiotic consumption during the first year of life				
Yes	1.26	(1.09–1.43)	1.21	(1.06–1.34)
Overweight or obesity				
Yes	1.02	(0.83–1.21)	1.02	(0.84–1.20)

Bold numbers highlight the significant associated factors with adequate 95% CI.

*Log-likelihood of the model: –550.192; AIC: 1132.384; BIC: 1207.869

CI: Confidence intervals; PR: Prevalence ratio

as hypothalamic-pituitary and sex hormones that modulate the immune system and protect women during childhood and adolescence.¹⁹ These differences between sexes may also fluctuate between different geographical conditions. Further studies addressing epidemiological issues of allergic diseases in tropical populations and environments are needed.

The presence of dogs in the house was also associated with AR (PR: 1.32; 95% CI: 1.06–2.66). There is still controversy in the literature regarding this association. A study in pediatric Colombian populations reported that no association was found between AR and the presence of pets at home.²⁰ Conversely, a study in Ecuador reported an association between the presence of pets (cats/dogs) in the house as a risk factor for AR (OR: 1.34; 95% CI: 1.09–1.63).²¹ The International AR consensus stated that due to conflicting

evidence and insufficient studies on this association, it could not be established whether this is an actual risk factor for AR.²² Studies following standardized methodologies are needed to assess this association. Finally, antibiotic consumption during the first year of life (PR: 0.80; 95% CI: 0.63–0.99) was associated with AR. Conversely, this variable has been previously reported as a risk factor associated with AR (OR: 1.7; 95% CI: 1.3–2.3) in children in Colombia.⁷ However, this study highlights that this variable could be strongly influenced by recall bias. The association between antibiotic consumption during the first year of life and AR requires study designs that can attenuate these biases.

Overall, 27.8% of the population presented CARAS diagnosis. A prior study described the coexistence of AR with asthma in 10–40% of patients with allergic diseases.²² CARAS requires special attention, as an increased risk of asthma attacks has been described in patients with uncontrolled AR symptoms.²³ In our study population, older age was found to be an associated factor for CARAS (PR: 0.95; 95% CI: 0.95–0.99). As the patient's age increases, the frequency of AR and asthma decreases. The immature immune system of children that begins the process of sensitization and exposure to allergens during the first years of life could explain this association.²⁴ Furthermore, the genetic predisposition to produce specific IgE triggered by an allergen exposure could be essential in the development of AR and asthma.^{24,25}

Frequent acetaminophen consumption over four times per year was found as an associated factor for CARAS (PR: 1.31; 95% CI: 1.03–1.55). Prior studies in Bogotá reported an association between AR and the frequent consumption of acetaminophen (OR: 2.6; 95% CI: 1.4–4.9).⁷ Moreover, several studies reported that regular use of acetaminophen led to a dose-dependent risk of developing allergic respiratory diseases, as well as worsening multiple respiratory diseases and lung function.²⁶ Besides, the association between acetaminophen and allergic diseases may mirror reverse causality likelihood (i.e., children with a genetic predisposition to allergic diseases are more susceptible to febrile respiratory tract infections, and use more acetaminophen).

Antibiotic consumption during the first years of life was also associated with CARAS (PR: 1.21; 95% CI: 1.06–1.34). This was also associated with the development of asthma and AR in children as reported by Ni et al.²⁷ Changes in the microbiome induced by the use of antibiotics in this early stage of life would lead to immune fluctuations that would ease the development of atopic respiratory diseases.²⁷ Reverse causality cannot be ruled out, because an individual with a significant atopic burden at birth can have a higher probability of frequent respiratory infections, and therefore require antibiotics.²⁷ Finally, this study highlights that this variable can be affected by recall bias as it is a self-reported information that depends on the data communicated by the patients' parents.

Regarding the strengths of the study, the diagnosis of RA, asthma, and DA was performed by allergists following the EAACI guidelines.⁸ The diagnosis of these diseases was confirmed by SPT and therefore avoided biases related to heterogeneity in the medical practice. Data collection was carried out by trained medical professionals with

wide experience in the application of the ISAAC-III questionnaire.¹⁴ Finally, regarding the limitations of the study, we stand out that only moderate or severe patients were included. Population with mild AR may have different associated factors, and our results should be interpreted considering this limitation. Moreover, the epidemiologic design of this study cannot prove causality because this study design is useful for establishing preliminary evidence for a causal relationship. We highlight that the intensity of symptoms was assessed through self-reported questionnaires, and no objective tests were performed. Self-reported data can be strongly affected by reporter bias and overestimation of the true frequencies of the symptoms.²⁸ Reporter biases could be significant in this study. Besides, no environmental controls were applied in the study population, which might have had a significant effect on AR and CARAS symptoms, and this is a major limitation of the study.

Conclusion

An association was found between AR, asthma, and AD in the pediatric population with moderate to severe allergy symptoms confirmed by SPT and treated with immunotherapy. The frequency of *B. tropicalis* allergy was higher compared to studies in tropical developed countries. The factors associated with AR and CARAS are consistent with previous reports from developed temperate countries. Further research assessing the factors associated with AR and CARAS in young populations of Latin America who are treated with immunotherapy is needed.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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