

High prevalence of house dust mite sensitization in children with severe asthma living at high altitude in a tropical country

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Abstract

Background: Some studies, mainly in Europe, have shown a low level of sensitization to house dust mite (HDM) allergens at high altitude (HA). Differently, some others in tropical countries have shown a higher level. The aim of this study was to evaluate allergens sensitization, including HDM, in children with severe asthma (SA), residents at HA in a tropical middle-income developing country.

Methods: Observational, analytical, cross-sectional study in children aged 6–15 years old with SA at HA (2640 m). Skin prick tests (SPT), serum IgE, exhaled fraction of nitric oxide (FE_{NO}), spirometry, and asthma questionnaire (ACT) were performed. Associations were explored by Pearson or Spearman coefficients.

Results: We included 61 children. Most patients were male (61.3%), median age: 10 years (Interquartile range [IQR]: 8–12), median BMI: 17 kg/m² (IQR: 16–20); Median of positive SPT: 2 (IQR: 2–3). At least one SPT was positive in 88.7% of patients and 87.9% were positive for at least one HDM. Serum IgE: 348 UI/mL (IQR: 154–760) and FE_{NO}: 22 ppb (IQR: 9–41). Prebronchodilator values were (% predicted): FVC: 109.7% (±15.5%), FEV₁: 98.4% (±16.3); FEV₁/FVC: 82% (±8%). SPT were inversely correlated with the FEV₁/FVC (Rho: −0.34; 95% CI: −0.55 a −0.09; P = 0.008).

Conclusions: These children with SA living at HA in a tropical middle-income developing country have a high prevalence of HDM sensitization. One explanation for this might be that tropical conditions, such as temperature and humidity, could modify the effect of the altitude on asthma.

KEYWORDS

altitude, asthma & early wheeze, children, mites, severity of illness index

1 | INTRODUCTION

The joint guidelines from the European Respiratory Society (ERS) and the American Thoracic Society (ATS)¹ define severe asthma (SA) in children over 6 years of age as one that has required treatment in the

past year with high doses of inhaled corticosteroids (IC) in combination with one or more additional controller medications (GINA steps 4 and 5)² or the use of systemic corticosteroids (SC) ≥50% of the previous year to maintain asthma controlled or one that remains uncontrolled despite this level of treatment.^{1,2} These children have worse clinical

outcomes and quality of life³ and generate high costs for healthcare systems, particularly due to hospitalizations, visits to emergency departments and unscheduled doctor visits.⁴

High altitude (HA) has been proposed as a therapeutic option for SA based on some studies, mainly done in Europe, that have shown clinical and functional improvement of asthma in patients moving to HA.^{5,6} The mechanisms explaining this improvement are not clear.⁷ Although low house dust mite (HDM) concentration and sensitization at HA have been suggested,^{5,8} atopic and non-atopic adult patients with SA benefit from HA irrespective allergic sensitization.⁹

There are differences between HA areas in Europe and South America in terms of HDM concentration and sensitization probably due to climate differences like humidity.^{10,11} There is scarce information about the characteristics of children with SA residents at HA in tropical countries. Bogota, at an altitude of 2640 m, is the capital of Colombia, a tropical middle-income developing country of South America where the prevalence of asthma in children from 5 to 17 years of age is 16.8%¹² but the proportion and characteristics of children with SA are unknown. Defining HA as that between 2500 and 3500 meters above sea level,¹³ Bogota is the most highly populated (8 million) city in the world located at HA. The aim of this study was to evaluate allergen sensitization, including HDM, in children with severe asthma (SA) who reside at HA in a tropical middle-income developing country.

2 | MATERIALS AND METHODS

2.1 | Design and study population

Analytical, observational, cross-sectional study, nested in a historical cohort of children with SA aged between 6 and 15 years old, which included consecutive patients from the Pediatric Pulmonology consultation of the Fundación Neumológica Colombiana (FNC) between October, 2014 and October, 2015. FNC is a referral institution in respiratory health located in Bogotá, a city located at HA (2640 meters). SA was defined according to the joint ERS/ATS criteria.¹ We used the dose chart of the ERS/ATS consensus that separates children from 6 to 12 years of age from those >12 years of age for defining high doses of IC.¹ HA was defined as that between 2500 and 3500 meters above sea level.¹³ Children with wheezing respiratory diseases other than asthma were excluded.

A sample size of 60 patients was calculated based on an estimated prevalence of SA among the general population of asthmatic children of 5-15%¹⁴ and that an average of 500 children with asthma attend to the FNC per year.

2.2 | Questionnaires and measurements

We applied the following questionnaires and tests in all the included children: Asthma Control Test questionnaire (ACT) questionnaire, pre- and post-bronchodilator spirometry, skin prick test (SPT), immunoglobulin E (IgE), and fractional exhaled nitric oxide (FE_{NO}).

2.2.1 | Asthma control test (ACT)

As previously described in children,¹⁵ we used the following interpretation of control status: totally controlled: ≥ 20 ; partially (not well) controlled: 13-19; insufficiently (poorly) controlled: ≤ 12 .

2.2.2 | Pulmonary function tests

A pre- and post-bronchodilator spirometry was performed according to ERS/ATS recommendations.¹⁶ Obstruction was defined by a ratio of forced expiratory volume in 1 s over the forced vital capacity (FEV₁/FVC) < 80% as established by the Third Expert Panel of National Asthma Education and Prevention Program of United States (NAEPP) for children from 6 to 11 years of age.¹⁷ We used the same cutoff for children from 12 to 15 years of age. The degree of obstruction was established according to the percentage value of the FEV₁ in relation to the predicted value (%FEV₁).¹⁸

Response to bronchodilator

The post-bronchodilator spirometry was performed 20 min after administering 400 μ g of salbutamol. According to the NAEPP, a positive response (reversibility) was considered when there was an improvement of the FEV₁ and/or the FVC > 12%.¹⁹ The test was interpreted by one of the researchers who was blinded to the child's clinical condition.

2.2.3 | Skin prick tests (SPT) and atopic phenotype definition

SPT were performed with aeroallergens in accordance with international recommendations.²⁰ The test was performed in the anterior surface of the forearm by a trained allergist physician or nurse, using the following standardized allergens: *Aspergillus fumigatus*, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, *Lepidoglyphus destructor*, cat (epithelium), horse and dog epithelium, *Cupressus arizonica* (cypress), *Ambrosia* (herbs), nut, egg, lentils, and wheat flour. Single-head metal lancets were used for skin punctures with a tip of 1 mm; 10 mg/mL of histamine was used as positive control and saline solution as negative control. Those weals with a diameter ≥ 3 mm larger than the negative control were considered positive responses. Atopy or atopic phenotype was defined as the presence of at least one positive SPT to an aeroallergen or food.

2.2.4 | Total serum immunoglobulin E (IgE)

Levels of IgE were determined by the ELISA technique. We used <100 IU/mL as a normal reference value, which was used in the asthma prevalence study in Colombia.¹²

2.2.5 | Exhaled nitric oxide (FE_{NO})

We used the single-breath technique with direct exhalation in the measuring device, with the child sitting and breathing calmly, which has a high reproducibility and is free of intra- and inter-daily variations.¹⁹

Two reproducible exhalations were obtained for at least two plateau values of nitric oxide, with less than 10% of variability. We used the reference values recommended by Buchvald et al²¹ in healthy children from 4 to 17 years of age. According to the 2011 ATS consensus,¹⁹ we define a value ≥ 20 ppb as a cutoff for determining the presence or absence of eosinophilic inflammation.

2.2.6 | Statistical analysis

The categorical variables were described by absolute and relative frequencies. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied for defining the normality of the distribution of the quantitative variables; based on these results, averages and the standard deviation (SD) were used if normal distribution was found, and interquartile range (IQR) if otherwise. The correlation between quantitative variables was explored by the correlation coefficients of Pearson or Spearman-Rho according to parametric or non-parametric distribution of the corresponding variables.

2.2.7 | Financial and approval

The study was sponsored by Novartis Colombia S.A. Novartis did not participate in the design, execution and analysis of the study, nor in the writing of the article. The study was approved by the institutional IRB (Comité de Ética en Investigación de la Fundación Neumológica Colombiana).

3 | RESULTS

Sixty-one children with SA were included, 61.3% male. The medians and interquartile ranges by age, weight, and BMI are presented in Table 1. The ACT average was 20 (± 4.13). The median of positive SPT was 2 (IQR: 2-3). The majority of the patients (88.7%) had at least one positive SPT and 87.9% were positive for at least one type of HDM: *Dermatophagoides farinae* (70.7%), *Dermatophagoides pteronyssinus* (56.9%), *Lepidoglyphus destructor* (24.2%), or *Blomia tropicalis* (19%). The median total serum IgE was 348 IU/mL (IQR: 154-760) and the median FENO was 22 ppb (IQR: 9-41).

TABLE 1 General characteristics of the population

Age, years	10.0 (8.0-12.0)
Weight, kg	32.5 (26.0-43.5)
Height, m	1.34 (1.24-1.49)
BMI ^a (kg/m ²)	17.0 (16.0-20.0)
FE _{NO} ^a (ppb)	22.0 (9.0-41.0)
IgE (UI/mL)	348.0 (154.0-760.4)
Positive allergy tests (number)	2.0 (2.0-3.0)

Results presented as median (interquartile range).

^aBMI, body mass index; FE_{NO}, fractional exhaled nitric oxide.

The results of the spirometry are shown in Table 2. The mean pre-bronchodilator values were: %FVC: 109.7% ($\pm 15.5\%$), %FEV₁: 98.4 (± 16.3), VEF₁/FVC: 82% (± 8). Nineteen children (31%) had obstruction (FEV₁/FVC < 80%). The group with obstruction had a higher number of positive SPT (3 [IQR: 2-4]) than the group without obstruction (2 [IQR: 1-3]) (P: 0.005) (Table 3). There were no differences in age, gender, BMI, FE_{NO} and IgE between these two groups.

A weak but significant negative correlation between the number of positive SPT and the FEV₁/FVC ratio was found (Spearman's Rho: -0.34; CI 95%: -0.55 to -0.09; P = 0.008) (Figure 1). There was no significant correlation between FEV₁/FVC and FE_{NO}. Neither the FE_{NO} nor the IgE were correlated with the ACT questionnaire.

4 | DISCUSSION

In this cohort of children from 6 to 15 years old with SA residents at HA (2640 meters) in a tropical middle-income developing country, we found a very high frequency of HDM sensitization (87.9%) and atopic phenotype, defined as at least one positive SPT (88.7% in our study), and high levels of IgE and FE_{NO}. Differently from previous studies in Europe that have shown a low rate of HDM sensitization at HA,^{5,8} our study ratifies observations from other tropical country (Ecuador)^{10,22} and in other more recent European study²³ that have shown high HDM sensitization at HA.

The high frequency of allergic sensitization found in these children with SA has been described in several studies, including the Severe Asthma Research Program (SARP).²⁴⁻²⁶ However, these studies were performed at sea level or low altitude. Our findings suggest that, in tropical countries, altitude does not cause a decrease of the frequency of HDM sensitization. In the same way, the results suggest that the described clinical and functional improvement of asthmatic children and adults at HA^{5,6,9,11,27,28} could be probably not

TABLE 2 Pulmonary function and ACT

Spirometry	
Pre-FVC, L	2.54 (± 0.97)
Pre-FVC, predicted %	109.7 (± 15.5)
Pre-FEV ₁ , L	2.06 (± 0.75)
Pre-FEV ₁ , predicted %	16.3)
FEV ₁ /Pre-FVC	0.82 (± 0.08)
Post-FVC, L	2.64 (± 0.97)
Post-FVC, predicted %	112.8 (± 14.9)
Post-FEV ₁ , L	2.27 (± 0.79)
Post-FEV ₁ , predicted %	105.8 (± 18.1)
FEV ₁ /Post-FVC	0.86 (± 0.06)
Questionnaires	
cACT ^a	20.1 (± 4.13)

Average results ($\pm$ standard deviation).

^acACT, Asthma Control Test.

TABLE 3 Characteristics according to the presence of obstruction ($FEV_1/FVC < 80\%$)

Characteristic	$FEV_1/\text{pre-bronchodilator } FVC < 80\%$	
	No $n = 42$ (69%)	Yes $n = 19$ (31%)
Gender ^a		
Female	19 (44.2%)	5 (26.3%)
Male	24 (55.8%)	14 (73.7%)
Age, years	10 (7-11)	10 (9-13)
BMI ^b , kg/m ²	17 (15-19)	19 (16-20)
FE_{NO} ^b ppb	17 (8-45)	26 (11-39)
IgE (UI/mL)	321.5 (126.3-760.4)	495.8 (180.2-1425.3)
cCAT ^b	20 (16-24)	21 (19-23)
Positive allergy tests (number)*	2 (1-3)	3 (2-4)
At least one positive allergy test ^a	38 (88.4%)	17 (89.5%)
Some mite allergy ^a	35 (87.5%)	16 (88.9%)

^aResults presented as n (%): number (percentage). Other results as the median (IQR: interquartile range).

^bBMI, body mass index; FE_{NO} , fractional exhaled nitric oxide; cACT, Asthma Control Test.

* $P < 0.005$.

only related to a lower HDM concentration and sensitization at HA.^{7,29} We tested sensitization to four HDM species (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*, and *Lepidoglyphus destructor*) the which are frequently found, but not exclusively, in house dust in the tropical and subtropical regions in the world.³⁰

Allergic sensitization is the underlying pathogenic mechanism in at least 50% of people with asthma and is much higher in children. HDM are a major perennial allergen source and a significant cause of allergic asthma worldwide.²⁹ Although HDM are globally ubiquitous, their presence could vary geographically depending on environmental conditions like altitude, temperature, and humidity.²⁹ The

prevalence, natural history, risk factors, sensitizers and triggers of allergies, and HDM sensitization could be different in the tropics and are not well defined.³⁰ It is known that exposure and sensitization to mite allergens in the first years of life are associated with increased risk of asthma and late-onset wheeze,³¹ have a significant effect on lung function in pediatric populations with wheeze and is associated with poor clinical outcomes in respiratory health.³² Children with allergic asthma related with HDM sensitization and high levels of IgE and FE_{NO} , like the vast majority of children of our cohort, have a pattern of chronic inflammation in the airway mediated by type-2 helper T-cells.

We found a high proportion (31%) of children with obstruction; this is a frequent feature in children with SA.³³ In our study, the presence of obstruction was associated with a higher number of positive SPT. This correlation, although weak, was significant (Rho: -0.34 ; CI 95%: -0.55 to -0.09 ; $P = 0.008$) (Figure 1), and this has been documented in other studies.^{25,33} Children with asthma, atopy, and decrease of pulmonary function could have an increased risk of progressive loss of lung function.

Interestingly, we did not find obesity in this cohort of children with SA despite the fact that the global prevalence of overweight and obesity in Colombian children and adolescents was 16.6% in 2010.³⁴ A frequent association between asthma and obesity has been described in children and its presence has been linked to an increased severity of asthma and difficulty of achieving control of the disease.^{35,36} We do not have an apparent explanation for the absence of obesity in this group of children.

This study found high levels of FE_{NO} , regardless of the use of inhaled steroids, with levels as high as 47 ppb. This increase has been associated with the severe asthma atopic phenotype. In our study, we find a weak, marginal, but non-significant correlation between FE_{NO} values and the FEV_1/FVC ratio (the higher the FE_{NO} value the lower

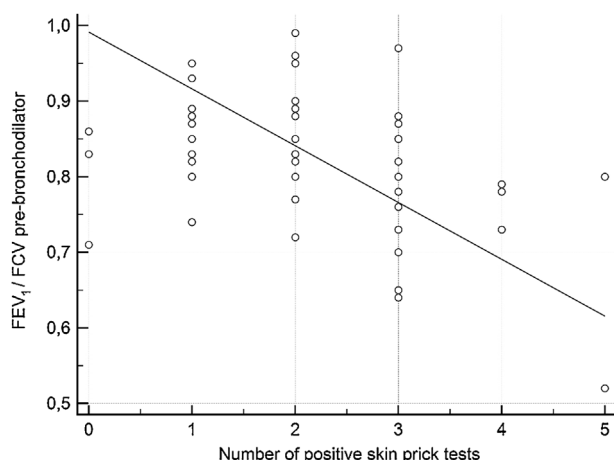


FIGURE 1 Correlation between FEV_1/FVC and positive SPT. Weak but significant correlation between FEV_1/FVC ratio and the number of positive allergy tests (Spearman's Rho: -0.34 ; CI 95%: -0.55 to -0.09 ; $P = 0.008$)

the FEV₁/FVC ratio); this result is similar to that found by Elmasri in his study on FE_{NO} levels in children with asthma and atopy.³⁷ We do not have reference values for FE_{NO} at the altitude of Bogotá (located at 2640 meters). Some studies have shown an inverse relationship between FE_{NO} and altitude.³⁸

Our study is innovative in showing a high prevalence of HDM sensitization in children with SA residing at HA in a tropical middle-income developing country, particularly because it has been described lower HDM sensitization at HA in non-tropical countries. The high prevalence of HDM sensitization at HA is relevant because a significant proportion of the world population resides in the tropics above 2500 meters. The study has the limitation of not having control groups residents at different altitudes and with different severity of asthma. The short- and long-term clinical outcomes of these children are the subject of another study.

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