
Clinical, functional, and epidemiological differences between atopic and nonatopic asthmatic children from a tertiary care hospital in a developing country

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Background: Differences between children with atopic asthma (AA) and nonatopic asthma (non-AA) have been shown in epidemiologic studies. In developing countries, even when non-AA is more prevalent than AA among schoolchildren, no data are available regarding clinical, functional, and epidemiological differences between these 2 groups.

Objective: To evaluate differences between Chilean children with AA and non-AA.

Methods: In this cross-sectional study, skin prick tests were performed on all patients (age range, 4–14 years) admitted to our tertiary care hospital with the diagnosis of asthma who were consequently classified as having AA or non-AA. Demographic characteristics, spirometry results, exercise bronchial challenge test results, and eosinophil counts measured in the last 12 months were recorded.

Results: Among the 237 asthmatic children, 62.5% had AA. Non-AA children had a significantly earlier onset of asthma and a more frequent history of pneumonia and tobacco consumption at home. Children with AA had higher nasal eosinophilia levels and a higher prevalence of dermatitis and severe exacerbation episodes of asthma in the past year (emergency department consultation and oral corticosteroids courses). Lung function was similar in both groups. After the multivariate analysis, only the number of oral steroid courses was significantly different between the groups and was associated with AA.

Conclusions: In this selected population of asthmatic schoolchildren, the prevalence of non-AA (37.6%) is not negligible, and some differences between AA and non-AA children exist.

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INTRODUCTION

Several longitudinal studies have hypothesized that different asthma phenotypes exist during childhood, with a broad variety of clinical and functional prognoses.^{1–4} At school-age 2 main phenotypes can coexist: IgE-associated or atopic asthma (AA) and nonatopic asthma (non-AA).¹ An elevated IgE level has been shown to correlate with asthma symptoms or physician-diagnosed asthma even in the absence of atopy, defined by skin prick test (SPT) results, leading to the idea that asthma has almost invariably an allergic basis in both children⁵ and adults.⁶ By the age of 14 years, most children have asthma that seems to be related to IgE level.^{1,7} However, Pearce et al,⁸ in an analysis of numerous studies, showed that only 58% (any positive SPT result) and 66% (high IgE level) of children had AA and suggested that the importance of

atopy as a cause of asthma may have been overestimated. Furthermore, it has been emphasized that among children with the same respiratory symptoms, those who had AA were more likely to label the disease as asthma than were those with non-AA.⁹ Furthermore, epidemiologic studies on asthma from developing countries have shown a low proportion of AA (eg, 21.5% in Peru,¹⁰ 26% in Estonia,¹¹ and 44.2% in Chile¹²).

Some epidemiologic studies have described different risk factors for AA and non-AA children. Male sex and maternal asthma have been described as risk factors for AA, whereas maternal and personal smoking habits, mold stains on the household walls or dampness at home, breastfeeding for less than 3 months, recurrent chest infections, and older siblings have been associated with non-AA.^{13–16} However, to the best of our knowledge, no studies from developing countries have investigated whether AA and non-AA schoolchildren have different clinical, functional, or epidemiological characteristics. The purpose of the present cross-sectional study was to evaluate those differences between AA and non-AA children who were followed up in a tertiary care hospital in Chile.

METHODS

This study was performed at the Pediatric Pulmonary Section, Exzequiel Gonzales Cortez Children's Hospital, Santiago,

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Chile. Children between 4 and 14 years of age with asthma symptoms followed up in our clinic were enrolled in the study and underwent a SPT to be classified as having AA or non-AA. Asthma was diagnosed according to the National Asthma Education and Prevention Program.¹⁷ Exclusion criteria were as follows: pulmonary or cardiac congenital malformations, cystic fibrosis, chronic pulmonary disease, malnutrition, or prematurity. Using a structured computer form, we recorded the following factors from the medical record: demographic and environmental data; parental first-degree history of asthma or allergies; personal medical diagnosis of eczema, rhinitis, or other allergic and respiratory diseases; asthma characteristics; lung function test (spirometry) results; exercise bronchial challenge test results; total peripheral blood test results; and nasal and bronchial eosinophil counts measured in the last 12 months.

Spirometry was performed using a heated Fleisch-type pneumotachograph (model 3810, Hans Rudolph Inc, Kansas City, MO) with the MedGraphics CPF-S processing system (Medical Graphics Corp, St Paul, MN). At least 3 technically acceptable curves were obtained. Values of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) did not differ from the nearest lower value by more than 5% or 100 mL. Recorded values were obtained from the best curve with the highest sum of FEV₁ and FVC, according to the American Thoracic Society guidelines.¹⁸ A positive bronchodilator response was defined as an FEV₁ improvement of more than 15% after the administration of salbutamol metered-dose inhaler (200 µg) applied with a large volume spacer device (Volumatic, Allen & Hanburys, Middlesex, England). A bronchial challenge test using the free-running technique was performed by asking the children to run for 6 minutes. The challenge was considered acceptable when the maximal heart rate achieved twice that of the baseline or more than 90% of the maximum predicted for age. Peak expiratory flow (PEF) was measured with a mini-Wright flow meter at 1, 3, 5, 10, and 15 minutes after exercise. The response to exercise was quantified as the maximum decrease in PEF, expressed as a percentage of the preexercise value. After completion of the exercise challenge test, all study participants inhaled salbutamol (200 µg) from a spacer (Volumatic) to ensure that pulmonary function returned to baseline. The exercise challenge test result was defined as positive if the postexercise PEF decreased at least 15% with respect to the baseline value. The spirometry and the exercise challenge test were performed on different days by 2 different specialists (D.P. and H.P., respectively) and when the child had been free of respiratory symptoms for at least 4 weeks. Use of inhaled salbutamol was previously discontinued for 12 hours, but use of inhaled corticosteroids was maintained.

Peripheral eosinophilia was defined as cells representing 4% or more of the differential count in whole blood. Standard techniques were performed for sampling nasal and induced sputum eosinophils.¹⁹ The cutoff point for nasal and bronchial eosinophilia was established as 5% or more.

SPTs to 39 common inhalant and food allergens were performed on the forearms, as well as positive (histamine) and negative (solvent) controls. The following allergens were used: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, American cockroach, German cockroach, dog dander, cat dander, feathers, *Aspergillus*, *Penicillium*, meadow grass, meadow fescue, rye grass, Bermuda grass, *Chenopodium multifidum*, ribwort plantain, red sorrel, *Taraxacum officinale*, common silver birch, *Platanus orientalis*, ashleaf maple, common ash, acacia, cypress, poplar, privet, white elm, *Azara microphylla*, *Morus nigra*, willow, egg white, egg yolk, soya bean, peanut, wheat, fish, milk, and latex (all from Leti, Spain) and *Blomia tropicalis* (from Allerbio, France). Atopy was defined as a positive reaction (wheal size diameter that measured 3 mm or more after subtraction of the control value) to one or more allergens. The SPT was performed by only one specialist (P.T.), who was blinded to the clinical characteristics of the child's asthma. A child was defined as having AA when he or she had a positive SPT result; otherwise, the child was considered to have non-AA.

The Ethics Committee of the Hospital approved the study, and full informed and signed consent was obtained from all parents.

Statistical analysis of the differences between AA and non-AA children was performed with the χ^2 test for categorical variables, the *t* test for continuous variables, and the Mann-Whitney *U* test for ordinal variables. Odds ratio (ORs) and 95% confidence intervals (CIs) were also calculated. A multivariate logistic regression was built using the type of asthma (AA or non-AA) as the dependent variable and those factors that were statistically significant ($P < .05$) in the univariate analysis as independent variables. When the same factor was measured in 2 different ways (ie, history of pneumonia episodes or recurrence of pneumonia [≥ 2 episodes]), the more significant of the 2 was incorporated in the multivariable analysis. Adjusted ORs were calculated from the logistic regression model. All analyses were performed with the Stata statistical software, version 7.0 (Stata Corp, College Station, TX).

RESULTS

Of the 265 children with asthma symptoms initially followed up in our clinic, 28 were misclassified (premature and/or severe pneumonia in the neonatal period). Therefore, 237 children with asthma (60.8% males) were included in the study, of whom 148 (62.5%) had AA and 89 (37.6%) had non-AA. No significant differences were found in gestational age, birth weight, duration of exclusive breastfeeding, parental history of asthma, rhinitis, or dermatitis between the 2 groups. However, AA children were older than non-AA children (106.5 ± 35.0 vs 85.9 ± 38.8 months; $P < .001$) (Table 1). The presence of rhinitis or a history of drug, food, or insect allergy was similar between groups; however, dermatitis was more prevalent among AA than among non-AA children (35.4% vs 21.7%; $P = .03$; OR, 2.7; 95% CI, 1.4–5.1) (Table 1). The age of the mattress, the frequency of

Table 1. Demographic Characteristics in Atopic and Nonatopic Asthmatic Schoolchildren*

Characteristics	Atopic (n = 148)	Nonatopic (n = 89)
Male	62.8	57.3
Age, mo	106.5 ± 39†	85.9 ± 35
Gestational age, wk	39.1 ± 1.0	39.3 ± 0.4
Birth weight, kg	3,347 ± 440	3,459 ± 428
Exclusive breastfeeding, mo	4.8 ± 2.0	4.5 ± 2.2
Paternal asthma	10.3	13.6
Paternal rhinitis	11.7	17.1
Paternal dermatitis	6.9	8.0
Maternal asthma	18.1	17.1
Maternal rhinitis	16.7	19.3
Maternal dermatitis	7.6	12.5
Dermatitis	35.4†	21.7
Rhinitis	64.7	62.2
History of insect allergy	25.8	18.1
History of drug allergy	24.2	22.2
History of food allergy	8.9	4.2
Time of use of the mattress, y	3.8 ± 0.4	3.6 ± 0.4
Mattress vacuum cleaning	23.6	26.2
Rugs at home	49.6	45.8
Dry plants at home	18.3	23.9
Green plants at home	78.5	78.1
Mold stains or dampness at home	39.7	31.1
Dog at home	59.1	63.4
Cat at home	36.2	37.8

* Data are presented as percentages or mean ± SD.

† $P = .001$, atopic vs nonatopic asthmatic children.

‡ $P < .05$, atopic vs nonatopic asthmatic children.

its vacuum cleaning, the presence of rugs or of dampness or mold stains on the household walls, and the existence of pets and plants (dry and green) at home were similar between groups (Table 1).

Paternal and maternal smoking consumption was similar in both groups (36.5% vs 32.8% and 23.7% vs 28.1%, respectively), but there were more indoor smokers (other than parents) in the homes of the non-AA children (22.2% vs 10.8%; $P = .04$; OR, 2.4; 95% CI, 1.0–6.0). No differences were found in kerosene, gas, and wood fuel heating systems used at home between AA and non-AA children (51.9% vs 49%, 20.8% vs 19%, and 2.5% vs 4.3%, respectively); however, the non-AA children used more electric systems than the AA ones (17% vs 5%; $P = .03$; OR, 3.9; 95% CI, 1.0–18.6).

Non-AA children had a significantly higher proportion of history of pneumonia episodes and recurrence (≥ 2 episodes) than AA children (56% vs 33.6%; $P = .001$; OR, 2.5; 95% CI, 1.4–4.5; and 31.0% vs 18.2%; $P = .03$; OR, 2.0; 95% CI, 1.0–4.0, respectively). The proportion with a history of acute otitis media was also higher among children with non-AA vs AA (16.6% vs 8%; $P = .06$; OR, 2.3; 95% CI, 0.9–6.2). Furthermore, the proportions with a history of croup and sinusitis were slightly higher among non-AA vs AA children

(8.9% vs 5.3%; $P = .90$; and 3.9% vs 1%; $P = .10$; respectively).

Non-AA children had their onset significantly earlier than AA children (15.5 ± 24.8 vs 24.6 ± 36 months; $P = .04$). Furthermore, some interesting differences were found in terms of the clinical manifestations of asthma in the previous 12 months: the number of acute exacerbations of asthma and the duration of those episodes were similar among groups; however, AA children had significantly more severe episodes than non-AA children (ie, emergency consultations [1.8 ± 2.4 vs 0.9 ± 1.8 ; $P = .05$] and need of oral steroid bursts [1.1 ± 1.4 vs 0.6 ± 0.9 ; $P = .03$] in the previous 12 months) (Table 2). The number of hospital admissions caused by an asthma exacerbation in the previous year was similar in both groups. Exercise-induced asthma, nocturnal cough, cough after cry, or chronic cough were also similar between the 2 groups (Table 2). No clear seasonal predominance of asthma episodes was found between the groups (data not shown). The proportion of inhaled corticosteroids used in the previous year and their doses were similar in the 2 groups of children (ie, beclomethasone, 547 ± 131 vs 549 ± 157 $\mu\text{g/d}$, and budesonide, 466 ± 230 vs 488 ± 145 $\mu\text{g/d}$, for AA and non-AA children, respectively). The current clinical classification of asthma severity was also similar between AA and non-AA children: 10.1% and 12.4% for those with mild persistent asthma, 81.1% and 76.4% those with for moderate persistent asthma, and 8.8% and 11.2% for severe persistent asthma, respectively (Table 2).

The proportion of peripheral blood eosinophilia in the previous 12 months was similar in both groups; however, the proportion of eosinophilia in the nasal smear was higher in AA than in non-AA children (24.4% vs 3.7%; $P = .02$). Eosinophilia in induced sputum was higher among AA chil-

Table 2. Characteristics of the Clinical Presentation of Asthma in Atopic and Nonatopic Asthmatic Schoolchildren*

Characteristics	Atopic (n = 148)	Nonatopic (n = 89)
Age of asthma onset, mo	24.6 ± 36†	15.5 ± 2.5
In the past year		
Duration of asthma exacerbation, d	10.9 ± 7.4	10.8 ± 5.3
Asthma exacerbations	4.9 ± 2.6	4.7 ± 2.5
Oral steroids courses	1.1 ± 1.4†	0.6 ± 0.9
Emergency department visits	1.8 ± 2.4†	0.9 ± 1.8
Hospital admissions	11.4	14.2
Intensive care unit admissions	0.7	3.5
Cough after exercise	79.3	85.5
Nocturnal cough	50.8	58.4
Cough after crying or laughing	14.7	17.4
Inhaled corticosteroids users	89.2	88.9
Current asthma severity classification		
Mild persistent	10.1	12.4
Moderate persistent	81.1	76.4
Severe persistent	8.8	11.2

* Data are presented as percentages or mean ± SD.

† $P < .05$, atopic vs nonatopic asthmatic children.

dren, although this finding did not reach statistical significance (Table 3). The percentage of positive exercise bronchial challenge test results was higher among AA children; however, this difference was not statistically significant (Table 3). No differences were found in the prebronchodilator and postbronchodilator values of FVC, FEV₁, forced expiratory flow between 25% and 75%, and FVC/FEV₁ in the previous year (Table 3).

In the multiple logistic regression analysis, only the oral steroid courses still maintained a significant association with atopic asthma (adjusted OR, 2.58; 95% CI, 1.11–5.97; *P* = .03); age was marginally related (adjusted OR, 1.02; 95% CI, 0.99–1.03; *P* = .06) (Table 4).

The 25 most prevalent allergen sensitizations among the AA children were *D pteronyssinus* (58.8%), *D farinae* (57.4%), rye grass (25.7%), meadow fescue (25.0%), cat dander (21.8%), meadow grass (21.6%), Bermuda grass (18.9%), *Alternaria* (13.5%), German cockroach (12.8%), American cockroach (12.2%), *C multifidion* (12.1%), *B tropicalis* (11.5%), *Penicillium* (11.5%), wheat (10.8%), dog dander (10.1%), *P orientalis* (10.1%), ribwort plantain (9.5%), red sorrel (9.5%), acacia (9.5%), peanut (8.1%), *A microphylla* (8.1%), willow (7.4%), soya (7.4%), feather (6.8%), and *Aspergillus* (6.1%).

DISCUSSION

This cross-sectional study from a tertiary care hospital shows that only 62.5% of asthmatic schoolchildren have AA and that therefore non-AA should not be underestimated. There are certain clinical differences between those 2 groups:

Table 3. Laboratory and Lung Function Test Results of Atopic and Nonatopic Asthmatic Schoolchildren*

Test results	Atopic (n = 148)	Nonatopic (n = 89)
Peripheral blood eosinophils ≥4%, %	54.7	50.9
Nasal eosinophils ≥5%, %	24.4†	3.7
Bronchial eosinophils ≥5%, %	14.6	3.9
Positive exercise challenge test result, %	48	28
Baseline		
FVC, L	2.42 ± 0.79	2.33 ± 0.77
FEV ₁ , L	1.98 ± 0.63	1.9 ± 0.65
FVC/FEV ₁	81.5 ± 12.3	82.3 ± 8.9
FEF _{25–75} , L/s	2.3 ± 1.9	2.0 ± 0.8
Postbronchodilator, % increase		
FVC	1.3 ± 5.7	2.17 ± 2.9
FEV ₁	5.8 ± 7.1	6.3 ± 5.6
FVC/FEV ₁	5.8 ± 5.6	4.3 ± 4.7
FEF _{25–75}	23.2 ± 28.5	20 ± 21

Abbreviations: FEF_{25–75}, forced expiratory flow between 25% and 75%; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

* Data are expressed as percentages or mean ± SD.

† *P* < .05, atopic vs nonatopic asthmatic children.

Table 4. Multivariate Analysis for Factors Related to Atopic or Nonatopic Asthmatic Children*

Factors	Adjusted OR (95% CI)	<i>P</i> value
Age	1.02 (0.99–1.03)	.06
Dermatitis	3.16 (0.90–11.14)	.07
Indoor smokers other than parents	1.08 (0.94–1.25)	.27
Electric systems for heating	1.11 (0.98–1.27)	.10
History of pneumonia episodes	0.77 (0.52–1.15)	.21
Age of asthma onset	1.02 (0.99–1.04)	.09
Emergency consultations in the previous 12 mo	0.85 (0.42–1.74)	.66
Oral steroids bursts in the previous 12 mo	2.58 (1.11–5.97)	.03
Eosinophilia in nasal smear	0.97 (0.88–1.08)	.61

Abbreviations: CI, confidence interval; OR, odds ratio (adjusted for all variables in the table).

* Only factors that were significant in the univariate analysis were included. Atopic asthma was considered as a reference group.

non-AA children have a significantly earlier onset of asthma, more past pneumonia episodes, and heavier tobacco consumption at home than AA children. On the other hand, AA children have more severe exacerbations of asthma in the previous year (ie, more emergency department visits and more oral corticosteroids courses). As could be expected, markers of atopy (nasal eosinophilia) and allergic diseases (dermatitis) were significantly more frequent among AA than among non-AA children, although the results of the lung function and of the exercise challenge tests were similar. After the multivariate analysis, only the number of oral steroid courses was related to atopic asthma.

Although the present study was performed in a selected population (children who have more problems with their asthma were followed up in our institution), some factors previously reported in epidemiologic studies as being more prevalent among non-AA children (smoking, pneumonia, or age of onset) are also risk factors present in our cross-sectional study. An epidemiologic study from Sweden¹³ performed in children 7 to 8 years old, another one from Albania¹⁴ performed in young adults, and recently one from Spain¹⁶ of children 9 to 12 years demonstrated that maternal smoking was a risk factor among non-AA children but not AA children. A birth cohort study from the Isle of Wight reported that recurrent chest infections at 2 years of age were an independent risk factor only for non-AA.¹⁵ Previously, Halonen et al²⁰ in the Tucson cohort study found that those *Alternaria*-negative asthmatic children had twice the frequency of lower respiratory tract infections in the first year of life than those *Alternaria*-positive ones. Respiratory syncytial virus infection by the age of 3 years is a risk factor for later wheeze, independently of atopy (non-AA children).⁷ We might speculate that the more frequent early respiratory infections among non-AA children could be related to the different origin of AA and non-AA phenotypes. Non-AA children produce more interleukin 10, whereas AA children

synthesize more interleukin 4 and interleukin 9.²¹ It has been postulated that non-AA could be related to interleukin 8 and neutrophil responses.²² In the present study, AA children had higher eosinophil counts than non-AA ones, although it was only significant in the nasal smear. However, it is possible that the treatment with inhaled corticosteroids may have influenced the eosinophil presence. Parasitosis infestation is a well-known cause of high eosinophil counts, but the prevalence of parasitosis in Santiago is low. Finally, the fact that disease occurred significantly earlier in non-AA children could be related to the higher prevalence of early respiratory infections among them compared with the AA children, as was reported in the epidemiologic study from Tucson^{2,3,20} and recently in a clinical setting in Italy.²³

In Chile, the prevalence of current asthma is 18.2% and 10.2% for children 6 to 7 years and 13 to 14 years old, respectively,²⁴ and 44.1% of children start wheezing in the first 3 months of age.²⁵ Acute respiratory diseases account for nearly 80% of children's visits to health care centers during the winter, and wheezing with pneumonia is the leading cause of hospitalization²⁶; 52% of children are exposed to intradomiciliary tobacco smoke,²⁵ and 16.2% of children 13 to 14 years old report tobacco smoking in the past 12 months.²⁷

In terms of the severity of the disease and health care utilization characteristics, although AA children had a similar number of asthma episodes as non-AA children, the AA children had more emergency department consultations and oral corticosteroids courses. Indeed, after the multivariate analysis, the only factor significantly related to AA was oral steroid courses. Again the findings about asthma severity and atopy were similar to those reported in the epidemiologic studies from Melbourne²⁸ and Tucson.³ Atopy has been reported as an independent risk factor for persistent asthma in adolescence.²⁹ Non-AA children were more likely to outgrow their asthma by the age of 11 years than AA children.²⁰ Implications of defining these 2 subgroups of asthmatic children could have importance when selecting therapy, as suggested by Szeffler et al.³⁰

A different evolution in lung function between AA and non-AA children has been traditionally reported in epidemiologic studies^{3,4,31,32} (ie, non-AA wheezy children are born with lower lung function, which improves later with age; in contrast, AA children experience deterioration throughout their lives). Furthermore, in a case-control study, AA children had lower lung function than non-AA ones.³³ However, a clinical study reported similar lung function measurements and equivalent results of the methacholine bronchial challenge test between AA and non-AA children.³⁴ Nevertheless, Mochizuki et al³⁵ reported higher methacholine hyperresponsiveness among non-AA children. In contrast, hyperresponsiveness to adenosine monophosphate,³⁶ exhaled nitric oxide,^{34,37} and markers of remodeling³⁸ were more prevalent in AA compared with non-AA children. These results suggest that, beyond the epidemiological and clinical differences previously described, there are also immunopathophysiological and genetic differences between AA and non-AA children.³⁹

In the present study, the AA children had a slightly higher number of positive exercise bronchial challenge test results than non-AA children, although the pulmonary function was similar. However, these findings could be affected by the inhaled corticosteroid therapy our children were receiving. Another potential limitation of our study is the recall bias inherent in all cross-sectional studies.

In conclusion, in this selected population of asthmatic schoolchildren from a developing country, the prevalence of non-AA (37.6%) was not negligible. Non-AA children had significantly more tobacco consumption at home, more history of pneumonia, and an earlier onset of asthma. On the other hand, AA children had more episodes of severe asthma exacerbations (emergency department consultation and oral corticosteroid courses).

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