

RISK FACTORS

Atopy Is Not Associated with Poor Control of Asthma

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Introduction. Atopy is part of the immunopathology of allergic diseases; however, the effect of atopy on the prognosis of asthma in adult patients is not established yet. The aim of this study is to investigate whether there is an association between lack of control of asthma and sensitization to aeroallergens. The relation between rhinitis severity and atopy was also investigated. **Methods.** Six hundred and thirty-nine patients aged ≥ 20 years with uncontrolled and untreated asthma were enrolled. They were followed for 1 year, received inhaled corticosteroids combined with long-acting beta-2 agonists, performed spirometry, skin prick test to aeroallergens, and reported emergency room visits due to asthma. Questionnaires (Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ)) were applied to evaluate asthma symptoms and quality of life. Rhinitis diagnosis and severity were evaluated. **Results.** Baseline data demonstrated that atopic patients were younger and had earlier onset of asthma. Gender, body mass index, and lung function were similar between atopic and nonatopic patients. Low schooling had a borderline association with nonatopic asthma. Follow-up data demonstrated that there was no significant difference between atopic and nonatopic patients in asthma symptoms, quality of life, frequency of patients with uncontrolled asthma, emergency room visit, hospital admission, airway obstruction, nor response to treatment. Rhinitis severity was also similar between atopic and nonatopic individuals. **Conclusions.** In conclusion, positive skin prick test to common aeroallergens was not found to be predictor of asthma control among adults.

Keywords aeroallergen, asthma, atopy, epidemiology, prognosis, skin prick test

INTRODUCTION

Approximately two-thirds of patients with asthma have positive skin prick test or detectable specific immunoglobulin-E (IgE) to aeroallergens (1). Anti-IgE antibody and measures to limit allergen exposure improve symptoms of these patients. These data support the hypothesis that allergy participates in the mechanisms of airway inflammation in asthma (2, 3). Whether allergy takes part in the immunopathology of asthma among patients with negative skin prick test and undetectable specific IgE to aeroallergens is a matter of controversy. Studies have shown that cytokine and cell profiles recovered from their airways are similar to that observed in allergic asthmatics (4, 5). However, other studies support differences in the immunopathologic background (6–8).

Whether atopy is associated with increased asthma severity is a topic not completely elucidated. Studies found that children with atopic asthma have greater risk of exacerbations (9–15) and reduced lung function (13–18). Among adults, two large multicentre epidemiological surveys demonstrated an association between positive skin prick test to moulds and increased asthma severity (19, 20). However, the effect of allergens other than moulds on asthma severity among adult patients is not yet established. Positive skin prick test to nonmold allergens was not associated with asthma severity in some studies (19, 21). In other studies, it was associated with increased asthma severity (20, 22). However, a population-

based study found positive skin prick test to protect from severe asthma (23). The association between atopy and asthma control is further explored in this study. The main objective is to evaluate whether atopy is associated with increased risk of emergency room visits and hospital admissions due to asthma in 1 year of prospective follow-up. Secondary aims were to investigate (i) whether atopy was associated with the severity of asthma symptoms, asthma-related quality of life, and lung function and (ii) whether atopy was associated with rhinitis severity.

METHODS

Population

The study population comprised patients referred to an outpatient reference center for asthma—Program for Control of Asthma in Bahia (ProAR). The main characteristics of this population at enrollment are to be naive of inhaled corticosteroids, to have low family income, and to live in urban area.

Inclusion and Exclusion Criteria

The inclusion criteria were age ≥ 20 years old and to have uncontrolled asthma. Uncontrolled asthma was characterized according to the following criteria: daily symptoms of asthma or more than two nights awake per week due to asthma or use of more than two puffs of short-acting bronchodilator per day to relief asthma symptoms or at least one hospital admission because of asthma in the last year. The exclusion criteria were smoking history more

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than 10 pack/years, diagnosis of other pulmonary morbidities, or any severe extra-pulmonary disease. The study was approved by the institutional review board of the Maternidade Clímério de Oliveira—Universidade Federal da Bahia (UFBA). All the patients signed informed consent.

Study Design

Six hundred and thirty-nine patients were included in the study. These patients were followed up for 1 year. They had five visits throughout the follow-up, named visits I, II, III, IV, and V. The interval between visits was 3 months. At visit I, the inclusion/exclusion criteria were checked, patients had multidisciplinary appointments (physician, nurse, and pharmacist), received medications for asthma (inhaled corticosteroids, long-acting beta-2 agonist and short-acting beta-2 agonist), performed spirometry, skin prick test, and reported emergency room visits due to asthma in the last 12 months. At the follow-up visits (visits II, III, IV, and V), treatment was adjusted by the physician in charge in order to achieve complete symptoms control. At visit V, a subsample of the first 383 patients enrolled in the study answered the Asthma Control Questionnaire (ACQ), the Asthma Quality of Life Questionnaire (AQLQ), performed a posttreatment lung function test, and were submitted to a clinical evaluation of asthma and rhinitis control.

Clinical Evaluation of Asthma and Rhinitis Control at Visit V

Evaluation of asthma control at visit V was carried out by a physician. Patients were classified into two groups: controlled and uncontrolled asthma. Patients were considered to have controlled asthma if they fulfilled all of the following criteria: ≤ 1 day of symptoms of asthma per week, no emergency room visits in the last year, ≤ 2 night awakes because of asthma per month, ≤ 1 use of short-acting bronchodilator per week, and no missing days at school or work because of asthma. Patients were considered to have uncontrolled asthma if they did not fulfill at least one of the above criteria and were using at least 1200 mcg/day of inhaled budesonide associated with long-acting beta-2 agonist. Patients with persistent symptoms but using less than 1200 mcg/day of inhaled corticosteroid were not classified in the uncontrolled asthma group because they were undertreated indeed.

Evaluation of rhinitis control at visit V was carried out by a physician. Patients were classified according the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria (mild or moderate/severe). A trained technician applied a questionnaire to evaluate the severity of nasal obstruction, sneezing, itching, and running nose in the preceding 7 days. In this questionnaire, the patient classified each symptom as absent (0), mild (1), moderate (2), or severe (3). The sum of each symptom score defined a final score ranging from 0 to 12.

Description of Lung Function and Skin Prick Test

A Koko spirometer (software PDS Instrumentation, Inc., Louisville, CO, USA) was used according to the

American Thoracic Society recommendations for lung function measurements. Brazilian-predicted values were used for normality. The forced expiratory volume in the first second (FEV₁) was expressed as the percentage of predicted value and was used to quantify the degree of airway obstruction.

Atopy was assessed with an immediate-type hypersensitivity skin prick tests with aeroallergen extracts, performed in the forearm. The following antigens were used: *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, and cat and dog epithelium (FDA Allergenic, Rio de Janeiro, Brazil), being the most common aeroallergens in Salvador—Bahia. The wheal diameters of the reactions were measured 15 min after puncture. The test was considered positive when at least one antigen induced a reaction with a diameter 3 mm greater than that of the negative control with saline solution. The sum of the larger diameters of the reactions to the various antigens was used to measure the intensity of the atopic status. The median of this variable was a cutoff value to classify patients as mildly or highly atopic.

Statistical Analysis

In order to establish if atopy impacts on asthma control, comparisons were made between patients with positive and negative skin prick tests. The primary end points to estimate asthma control during the study were events of emergency room visits and hospital admissions reported in the follow-up. These end points were available for the 639 patients enrolled in the study. Secondary end points were lung function, symptoms score (ACQ questionnaire), and quality of life score (AQLQ questionnaire) at visit V. The secondary end points were available for the first 383 consecutive patients enrolled in the study.

An index to estimate response to treatment was created. The studied population was not under regular use of inhaled corticosteroid before the study. Therefore, reduction in the number of emergency room visits during the study was attributed to the use of the inhaled corticosteroids during the study. The number of emergency room visits in the year before the study, reported by the patient at visit I, was the baseline information to estimate the percentual reduction of this event during the study. Patients were classified into two categories: $>90\%$ reduction in the number of emergency room visits and $<90\%$ reduction in the number of emergency room visits.

Nominal variables were expressed as proportions. Ordinal and continuous variables were expressed as quartiles. The Chi-square test was used to compare nominal variables and the Mann–Whitney test was used to compare ordinal and continuous variables. Spearman test was used for correlations between the intensity of atopy (sum of the larger diameters of the skin prick test) with end points that evaluate asthma control and response to treatment. The statistical analysis was performed using a software program (SPSS for Windows; SPSS Inc., Chicago, IL, USA) and all the tests were two-tailed.

RESULTS

The studied population comprised 639 patients, 515 (81%) patients were female, 338 (53%) patients had rhinitis, median age was 47 (37–57), and median baseline FEV₁ was 69 (55–84). Table 1 compares the baseline characteristic of atopic and nonatopic patients. At this moment, patients were not using inhaled corticosteroids and were very symptomatic. Fifty-six percent of the studied population had a positive skin prick test for at least one common aeroallergen. Patients with positive skin prick test were younger and had an earlier asthma onset. No statistically significant difference was observed in gender, body mass index, and lung function. However, illiterate patients had a trend toward association with negative skin prick test ($p = .06$).

Table 2 compares asthma control and treatment requirements during the study. At this moment, 84% of the patients were using >800 mcg/day of budesonide for asthma. The frequency of patients using >800 mcg/day of budesonide was similar between atopic and nonatopic patients. The

TABLE 1.—Baseline characteristics of patients with atopic and nonatopic asthma (visit I).

	Atopic (n = 361)	Nonatopic (n = 278)	p-value
Female (%)	283 (78)	232 (83)	.10
Age (years)	45 (35–55)	50 (39–59)	<.01
Illiterate ^a (%)	28 (10)	35 (15)	.06
Body mass index	27 (23–31)	26 (23–30)	.70
Smoke history ^b (pack/years)	0 (0–0)	0 (0–0)	.78
Age of asthma onset (years)	9 (3–23)	18 (6–33)	<.01
Duration of asthma symptoms (years)	30 (19–43)	29 (15–42)	.15
Number of emergency room visits in the year before the study	6 (2–20)	7 (3–23)	.20
Number of hospital admission in the year before the study	0 (0–1)	0 (0–1)	.45
FEV ₁ % of predict	70 (55–85)	68 (55–83)	.39

Notes: ^aData available for 514 patients: 285 were atopic and 229 were nonatopic. Continuous and ordinal variables expressed in median and interquartile range.

^bAll the patients included in the study have <10 pack/years of smoke history.

TABLE 2.—Indicators of asthma control and treatment requirement during follow-up.

	Atopic (n = 361)	Nonatopic (n = 278)	p-value
Use >800 mcg/day of budesonide in the follow-up (%) ^a	185 (84)	137 (81)	.44
Use of long-acting beta-2 agonist in the follow-up (%) ^a	193 (87)	138 (83)	.25
Number of emergency room visits in the follow-up	0 (0–2)	0 (0–2)	.57
Patients with emergency room visit in follow-up (%)	156 (43)	117 (42)	.77
Patients with hospital admission in follow-up (%)	11 (3)	16 (6)	.10
Patients with ICU admission in follow-up (%)	1 (<1)	1 (<1)	.68
ACQ score at visit V ^a	1.85 (1.00–2.89)	1.85 (1.00–2.89)	.56
ACQ score ≥0.75 at visit V ^b	29 (52)	22 (45)	.43
AQLQ final score at visit V ^a	3.94 (2.83–5.06)	3.80 (2.82–5.47)	.92
FEV ₁ % of predict at visit V ^a	68 (52–80)	69 (57–84)	.17
Uncontrolled asthma—clinical evaluation at visit V (%) ^c	27 (21)	18 (17)	.40
Patients with <90% reduction in emergency room visits (%) ^d	76 (30)	60 (30)	.98

Notes: ^aData available for the first 383 patients admitted in the study. 219 were atopic and 164 were nonatopic.

^bData available for 104 patients: 55 were atopic and 49 were non atopic. Patients with ACQ score >0.75 (uncontrolled asthma) and insufficient treatment with inhaled corticosteroids (<1.200 mcg/day of budesonide) were excluded of this analysis.

^cData available for 234 patients: 127 were atopic and 107 were non atopic. Patients with uncontrolled asthma attributable to insufficient treatment (<1.200 mcg/day of budesonide) were excluded of this analysis.

^dData available for 452 patients: 253 were atopic and 199 were nonatopic. Patients without emergency room visits in the year before enrollment were excluded from this analysis.

number of emergency room visits and the frequency of patients with at least one emergency room visit due to asthma during the study were similar between groups. The frequency of patients with at least one hospital admission due to asthma during the study was similar between groups. Symptoms score, asthma-related quality of life, lung function, and the frequency of patients with uncontrolled asthma at visit V were similar between groups. The frequency of patients with <90% reduction in emergency room visits during the study was similar between groups.

Table 3 demonstrates that the frequency and severity of rhinitis at visit V were similar between atopic and nonatopic patients. Adherence to nasal corticosteroids was low but was similar between groups. Tables 4 and 5 show no difference in asthma control and rhinitis severity between patients who were mildly and highly atopic.

The intensity of atopy (sum of the larger diameters of the skin prick tests) of the 639 patients did not correlate with the ACQ score at visit V ($p = .88$), AQLQ final score at visit V ($p = .68$), FEV₁ at visit V ($p = .18$), number of emergency room visits during follow-up ($p = .74$), number of hospital admissions during follow-up ($p = .26$), score of rhinitis symptoms at visit V ($p = .18$), nor with a reduction in the number of emergency room visits in the follow-up ($p = .35$). Among the 361 atopic patients, these correlations were not significant either: ACQ score at visit V ($p = .42$), AQLQ score at visit V ($p = .49$), FEV₁ at visit

TABLE 3.—Comparisons of rhinitis severity at follow-up.

	Atopic (n = 219)	Nonatopic (n = 164)	p-value
Rhinitis diagnosis (%)			
No rhinitis	26 (12)	23 (14)	.75
Mild rhinitis	123 (56)	93 (57)	
Moderate to severe rhinitis	70 (32)	48 (29)	
Rhinitis symptom score	4 (2–7)	3 (1–6)	.25
Regular use of nasal corticosteroid in the follow-up (%)	101 (46)	73 (44)	.77

Note: Data available for the first 383 consecutive patients admitted in the study.

TABLE 4.—Asthma control at follow-up according to the intensity of atopy.

	Mildly atopic (n = 193)	Highly atopic (n = 168)	p-value
Use >800 mcg/day of budesonide in the follow-up (%) ^a	96 (85)	89 (82)	.61
Use of long-acting beta-2 agonist in the follow-up (%) ^a	99 (88)	94 (87)	.90
Number of emergency room visits in the follow-up	0 (0–2)	0 (0–2)	.82
Patients with emergency room visit in follow-up (%)	84 (44)	72 (43)	.90
Patients with hospital admission in follow-up (%)	4 (2)	7 (4)	.20
Patients with ICU admission in follow-up (%)	0 (0)	1 (<1)	.46
ACQ score at visit V ^a	2.00 (1.21–2.85)	1.86 (1.28–2.84)	.99
Environment AQLQ score at visit V ^a	3.88 (2.50–5.00)	3.38 (2.25–5.50)	.78
AQLQ score at visit V ^a	3.96 (2.86–4.95)	3.88 (2.71–5.51)	.85
FEV ₁ % of predict ^a	71 (54–84)	68 (51–78)	.28
Uncontrolled asthma (%) ^{b,c}	13 (21)	14 (21)	.99
Patients with <90% reduction in emergency room visits (%) ^{d,e}	40 (30)	36 (30)	.95

Notes: Only patients with positive skin prick test were analyzed in this table.

^aData available for the first 219 consecutive patients with positive skin prick test admitted in the study *111 patients were mildly atopic and 108 were highly atopic.

^bPatients with uncontrolled asthma attributable to insufficient treatment (<1,200 mcg of budesonide) were excluded of this analysis

^cData available for 127 patients: 61 patients were mildly atopic and 66 were highly atopic.

^dPatients without emergency room visit in the year before enrollment were not analyzed

^eData available for 253 patients: 134 patients were mildly atopic and 119 were highly atopic.

TABLE 5.—Rhinitis severity at follow-up according to the intensity of atopy.

	Mildly atopic (n = 111)	Highly atopic (n = 108)	p-value
Rhinitis diagnosis (%)			
No rhinitis	15 (13)	11 (10)	.65
Mild rhinitis	63 (57)	60 (56)	
Moderate to severe rhinitis	33 (30)	37 (34)	
Rhinitis symptom score	4 (2–7)	4 (2–8)	.25
Regular use of nasal corticosteroid in the follow-up (%)	50 (45)	51 (47)	.66

Note: Data available for the first 219 consecutive patients with positive skin prick test admitted in the study.

V ($p = .78$), number of emergency room visits during follow-up ($p = .69$), number of hospital admissions during follow-up ($p = .32$), score of rhinitis symptoms at visit V ($p = .52$), and reduction in the number of emergency room visits in the follow-up ($p = .60$).

An additional comparison between patients with negative skin prick tests and patients with positive skin prick test to *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, and cat or dog antigen, analyzed separately, was performed. A positive skin prick test to these allergens was not significantly associated with emergency room visits, hospital admission, ACQ score, AQLQ score, regular use of inhaled medication for asthma or rhinitis, lung function, rate of uncontrolled asthma at visit V, reduction in emergency room visits after treatment, or rhinitis severity in the follow-up ($p > .05$).

DISCUSSION

In this study, positive skin prick tests to common aeroallergens were not associated with emergency room visits, hospital admissions, symptoms score, or quality of life in patients with asthma. These end points are proxies of asthma control during the follow-up. The results also demonstrated that approximately 20% of the patients

with asthma remained uncontrolled after 1 year of follow-up, in spite of 1200 mcg/day of inhaled corticosteroid. These patients represent the phenotype of severe asthma. There was no difference in the frequency of severe asthma between atopic and nonatopic patients in this study. These data suggest that aeroallergens do not predict worse prognosis in adult patients with asthma. Three multicenter, population-based surveys in the United States and Europe demonstrated that positive skin prick test to aeroallergens was less frequent among patients with severe asthma than patients with mild asthma (23–25). Our interpretation of these latter studies is that aeroallergens have less important role in the immunopathology of severe asthma among adult patients. The literature seems to be consistent with our conclusions.

Among children allergy seems to have a more important role in the immunopathology and severity of asthma. Studies in children demonstrated that positive skin prick test to aeroallergens is associated with increased asthma severity (9–18). In our study, atopic asthma was associated with younger age and earlier onset of asthma. Moore et al. (23) also observed that adult patients with early-onset asthma have more positive skin prick tests to aeroallergens than patients with late-onset asthma.

Patients enrolled in this study were very symptomatic and were not using inhaled corticosteroids at baseline. This population has low income and was not able to afford treatment. During the follow-up, 84% of the patients were using >800 mcg/day of budesonide for asthma. This is probably the reason why approximately 70% of patients had >90% reduction in the number of emergency room visits during the study. The frequency of patients with >90% reduction in the number of emergency room visits was similar between atopic and nonatopic patients. These data indicate that atopy did not influence the response to treatment. This conclusion was not biased by imbalance on treatment between groups because the rate of patients using high dose of inhaled corticosteroids was similar. To our

knowledge, this is the first study that evaluates the effect of atopy on response to treatment of asthma.

Another observation in our study was a trend toward an association between low schooling and nonatopic asthma in adults. The International Study of Asthma and Allergies in Childhood (ISAAC) study demonstrated a positive correlation between gross national income and atopic wheeze in children (26). Both low schooling and low-income relate to a wide range of environment exposures that may inhibit atopy, such as increased infections.

Data in the literature about the relation between atopy and rhinitis severity are scarce. One small cross-sectional survey failed to demonstrate an association between atopy and self-reported severity of rhinitis (27). Another study found a weak association between more severe tomography abnormalities of the paranasal sinuses and nonatopic rhinitis (28). Romanet et al. (25) in a population-based cross-sectional survey enrolling 165 asthmatics and 193 controls found similar frequency of rhinitis between allergic and nonallergic patients with asthma. However, non-atopic patients had more polyps and sinusitis, while patients with positive skin prick test had more allergic symptoms. Our data are in accordance with the previous literature in general, since it suggests that the frequency and severity of rhinitis in patients with asthma is not affected by the atopic status.

Another important aspect is that we studied a low-income population. The ISAAC study found that the association between atopy and asthma symptoms is evident among affluent populations (26). This may explain the lack of association between asthma control and atopy in our study contrasting to the presence of association between positive skin prick tests to *Dermatophagoides pteronyssinus* and increased asthma severity in a multi-center cross-sectional survey in Europe (20).

The prospective data collection, the sample size, and the various instruments we used to measure control of asthma favor the reliability of our conclusions. Besides, this study was conducted in the main reference clinic of ProAR, a program of remarkable impact in public health (29). However, some limitations can be identified. Four aeroallergens were used in the skin prick test. It probably did not affect the conclusions because these four aeroallergens are responsible for 90% of the positive skin prick test in our environment (30). Although a skin test panel with more allergens could increase slightly the proportion of atopic asthmatics, there is no reason to suppose it would affect the final results. The high rate of nonatopic asthma in this study is mainly explained by the specificities of the population. A higher rate of negative skin prick test is expected among patients with moderate/severe asthma (25).

In order to evaluate if our results on the lack of difference between atopic and nonatopic patients was caused by insufficient sample size, we performed a post-hoc analysis. Considering 452 subjects evaluated for the reduction in emergency room visits, 35% of nonatopic subjects with less than 90% reduction in emergency room visits, and 25% of atopic subjects with less than 90% reduction in emergency room visits, we will be able to

reject the null hypothesis with probability (power) of 64%. However, the power to rule out a 15% difference (22.5% atopic vs. 37.5% nonatopic) was 94%. The type I error probability associated with this test of this null hypothesis was 0.05.

In conclusion, positive skin prick tests to common aeroallergens were not predictors of poor asthma control nor response to treatment in an urban population of adult patients with low income. It was not associated with increased rhinitis frequency or severity either.

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