

Original article

Allergic vs nonallergic asthma: what makes the difference?

Background: The aim of this work was to describe clinical similarities and differences between allergic and nonallergic asthmatics, notably concerning the nasosinusal involvement.

Methods: A total of 165 asthmatics (122 allergics and 43 nonallergics) and 193 controls (40 allergics and 153 nonallergics), recruited in the frame of EGEA study (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy), were included. Asthmatics were included on the basis of positive answer to four standardized items. To establish differences and similarities between allergic and nonallergic asthmatics, general characteristics (age, sex, smoking habits, history of hay fever and allergic dermatitis), history of asthma, severity and nasosinusal involvement were examined. Clinical assessment was based on the answers to a detailed questionnaire, and spirometry.

Results: Greater age, female sex, sinusal polyposis, and FEV₁ below 80% of the predicted value increased the risk of displaying a nonallergic type of asthma, whereas history of hay fever, seasonal exacerbation of asthma, and asthma duration lowered this risk. Unexpectedly, we found no difference in terms of rhinitic symptoms between both groups, probably resulting from distinct causes.

Conclusion: These results give new insights into the contrasts between clinical features of allergic and nonallergic asthma.

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The terminology of extrinsic asthma was first introduced by Rackeman in 1947 (1) and referred to the triggering role of allergens in asthma. By symmetry, he described intrinsic asthma as a disease characterized by later onset in life, female predominance, higher degree of severity, and more frequent association to nasosinusal polyposis. As these asthmatics were not improved by conventional treatment, this author considered their disease as caused by a nonallergic, unknown phenomenon. It is now widely admitted that nonallergic asthma can be objectively distinguished from allergic asthma based on negative skin tests to usual aeroallergens. On the other hand, positive skin test shows a tendency to produce IgE antibodies in response to low doses of allergens. "Atopy" and "atopic" are the terms used to describe this clinical trait and predisposition (2). Allergic clinical manifestations of atopy are of various types, for example rhinitis and asthma. Nowadays the terminology of "extrinsic" and "intrinsic" asthma should no longer be used, and should be replaced by the terminology of "allergic" or "nonallergic" asthma (2).

Whether nonallergic asthma does or does not represent a proper entity was disputed because of marks of allergy in it. Indeed, in an epidemiological study,

Burrows et al. (3) showed a strong association between high levels of serum total immunoglobulin E (IgE) and asthma, which persisted in the subgroup of nonallergic asthmatics. Furthermore, the higher expression of molecules involved in allergy such as interleukin IL-4 (4), IL-5 and its receptor (5), and the high affinity IgE receptor (6), was not different in nonallergic compared to allergic asthma. Walker et al. (7) showed a lower expression of the IL-4 gene in nonallergic asthma. Alveolar macrophage activation turned out to be more important in nonallergic compared to allergic asthma (8).

From a clinical point of view, features of both kinds of asthma were stated on the observation of a limited number of subjects and never in a prospective survey. Furthermore, nasosinusal symptoms had never been specifically compared between both types of asthma. Finally, the classical greater severity of nonallergic asthma is controversial. Ulrik et al. (9) who followed up a cohort of allergic and nonallergic asthmatics for 10 years, found a higher decline in lung function in the nonallergic group. By contrast, Inouye et al. (10) compared the severity of asthma between skin test positive and skin test negative asthmatics, and found no difference between both groups.

The aim of this work was to describe clinical similarities and differences between allergic and non-allergic asthmatics.

Material and methods

Subjects

This study was made within the framework of the EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). Design and phenotype issues had been published elsewhere (11, 12). Briefly, it was a multicenter, case-control survey with a study of asthmatic subjects. Included patients were those of age between 15 years and 65 years, born in metropolitan France, and have a determined place of residence. Controls consisted of subjects randomly selected from the general population and from surgery outpatient clinics. Asthmatics were recruited in hospital clinics depending on answers to a self-questionnaire. Subjects were considered asthmatics if they gave positive answers to four items (below) from standardized questionnaires of the British Medical Research Council/European Coal and Steel Community (BMRC/ECSC) (13), American Thoracic Society (ATS, 14) and European Community Respiratory Health Survey (ECRHS, 15).

Q21 Have you ever had attacks of breathlessness at rest with wheezing? (BMRC/ECSC/ATS questionnaires)

Q22 Have you ever had asthma attacks? (BMRC/ECSC questionnaires). If Yes:

Q22a Was this diagnosis confirmed by a physician? (ATS questionnaire); and

Q22b Have you had an asthma attack in the last 12 months? (ECRHS questionnaire).

A procedure described elsewhere (12) was used to include true asthmatics who might not have answered positively to these four questions, after reviewing elements of medical records that substantiated the diagnosis of asthma. Only indisputable cases were included.

A total of 213 asthmatics and 304 controls were enrolled. Thirty-eight asthmatics were excluded from the controls group so that 266 nonasthmatic controls were studied. Written informed consent was obtained from each subject.

Study design

After inclusion, subjects were invited to follow the following procedure:

1 A detailed questionnaire, divided into two parts, using BMRC/ECSC (13), ATS (14) and ECRHS (15) questions plus additional ones when needed, was administered. The first part consisted of issues

concerning history of asthma attacks, nasosinusual symptoms associated with asthma, and active smoking. The second one concerned medication requirements.

2 Spirometry including measures of forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC). Three measurements were taken for each subject and the best FEV₁ and FVC were retained for analysis if they met ATS acceptability and reproducibility criteria (16).

3 Skin prick tests (17) to allergenic extracts were performed. The battery included 11 aeroallergens: cat, *Dermatophagoides pteronyssinus*, *Blatella germanica*, *Cladosporium*, *Aspergillus*, *Alternaria*, timothy grass, *Parietaria*, ragweed, birch tree and olive tree pollens. Negative (0.9% saline) and positive (histamine) controls were performed. Prick tests were considered positive if the wheal diameter 20 min after allergen injection was at least 3 mm larger than the size of the negative control.

4 A blood sample for multiallergic testing (Multirast Phadiatop, Pharmacia & Upjohn, Uppsala, Sweden) was taken.

Atopy was defined by at least one positive skin prick test associated with multiallergic test positivity. The absence of atopy was defined by the negativity of these two parameters.

Eight subjects of the asthmatic group did not have skin testing, and another eight did not have the multiallergic test. Among the remaining 197 asthmatics, 32 were excluded because of positive Phadiatop and negative skin tests ($n=13$), negative Phadiatop and positive skin tests ($n=12$), and questionable results in Phadiatop ($n=7$). In the control group, eight did not have skin testing, and another 15 did not have the multiallergic test. Among the remaining 243 controls, 50 were excluded because of positive Phadiatop and negative skin tests ($n=10$), negative Phadiatop and positive skin tests ($n=33$), and questionable results in Phadiatop ($n=7$). Finally, we studied a total of 122 allergic asthmatics, 43 nonallergic asthmatics, 40 allergic controls and 153 nonallergic controls.

Evaluation criteria

General characteristics consisted of the following criteria: age, sex, active smoking, history of hay fever and allergic dermatitis in childhood.

History of asthma was assessed by the following criteria: age of first asthma attack, asthma duration, exacerbations of asthma attack according to seasons. Exacerbation signified an increase in the frequency or severity of asthma attack.

Severity was evaluated by three parameters: FEV₁, use of steroids, and severity score. Predicted values of FEV₁ were calculated on the basis of ECSC references (18) for 18-year-old subjects or older, and on the basis of Polgar's references for subjects under 18 years old (19). Steroid use was evaluated qualitatively for inhaled and systemic administration over the last 12 months (i.e. "Did you use systemic (inhaled) steroids over the last 12 months?"). An overall assessment of asthma severity was realized on the basis of a severity score (Table 1) created for this study (20).

Table 1. Severity score

Class 1: Mild	Class 2: Moderate	Class 3: Severe
Less than one asthma attack per week. No Interattack symptoms. No hospitalization in the last 12 months, and no hospitalization ever in intensive care unit, and FEV ₁ $\geq 80\%$ of predicted value	Less than one asthma attack per week, and interattack wheezing or interattack wheezing with shortness of breath, and dyspnea grade 1 or 2, and no hospitalization in the last 12 months, and no hospitalization ever in intensive care unit, and FEV ₁ $< 80\%$ and $\geq 60\%$ of predicted value	Dyspnea grade 3 or 4 or shortness of breath limiting usual activity associated with at least one asthma attack per week, or hospitalization in the last 12 months, or hospitalization ever in intensive care unit, or FEV ₁ $< 60\%$ of predicted value

Dyspnea is graded as follows: grade 0: no dyspnea; grade 1: dyspnea walking fast on flat surface or climbing a gentle slope or stair; grade 2: dyspnea walking normally on flat surface; grade 3: subject stops walking when walking normally on flat surface; grade 4: dyspnea at rest.

Evaluated rhinitic symptoms included paroxysmal sneezing, usual rhinorrhea, and nasal obstruction (outside of colds). An evaluation of seasonal exacerbations of rhinorrhea was obtained by asking subjects if they had predominance or recrudescence of this symptom in some specific months. Nasal polyposis and sinusitis were also evaluated. For those items, a comparison with allergic and nonallergic controls was performed.

Data analysis

Categorical variables were analyzed with the Chi-squared test. When the expected sample size was under 5, Fisher's exact test was used. When variables were in class, we used an overall Chi-squared test, and a Chi-squared test for each class. Continued variables were analyzed by Student's *t*-test. Multivariate logistic regression analysis was used to assess the independent factors increasing the risk of nonallergic asthma compared to allergic asthma. We performed a backward stepwise analysis leading to an estimated odds ratio (OR), together with its confidence interval and degree of significance. The variables included in the model were those for which the *P*-value was lower or equal to 0.25 in the univariate analysis. A *P*-value less than 0.05 was considered as statistically significant. The SAS software package version 6.12 (SAS Institute Inc., Cary, NC) was used for all computations.

Results

Patients characteristics

Allergic patients were significantly younger than non-allergic patients, whether they were asthmatics or not (Table 2). There were significantly more women among nonallergic asthmatics than among allergic asthmatics with a respective sex ratio male:female of 0.8 and 1.2 ($P=0.024$). Smoking status did not differ between all groups. History of hay fever was significantly more frequent in allergic patients compared to nonallergic patients but was, however, more frequent in nonallergic asthmatics than nonallergic controls (35.7% vs 10.5%, respectively, $P<0.05$). In the allergic asthmatic group, 38.3% of the patients reported a history of allergic dermatitis, which is higher than the three other groups.

Characteristics of asthma

First asthma attacks appeared earlier in life in allergic asthmatics (15.8 ± 1.3 vs 32.2 ± 2.3 , $P=0.0001$, Table 3) and asthma duration was similar in both groups (18.5 ± 1.3 vs 15.1 ± 2.2 , $P=0.17$). By contrast, 72.3% ($n=81$) and 36.6% ($n=15$) of allergic and nonallergic

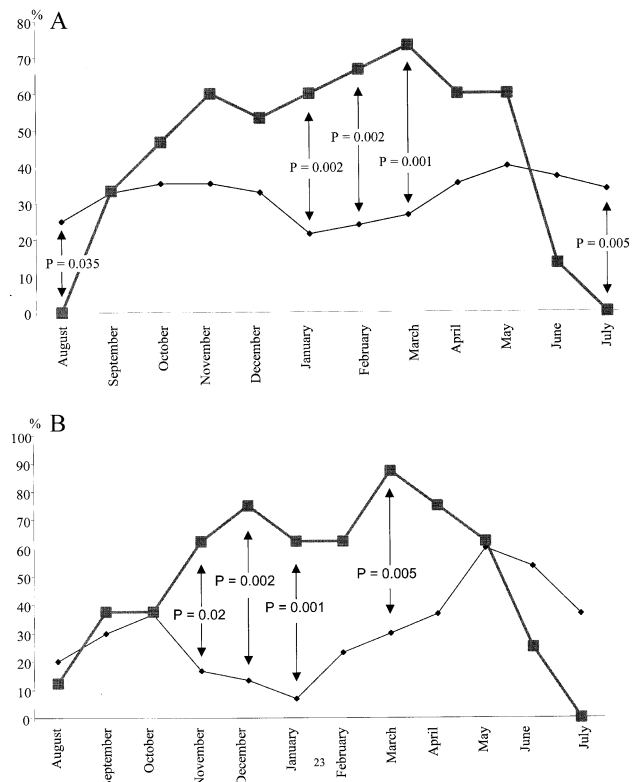


Figure 1. Month of exacerbation of symptoms in asthmatics displaying exacerbations of this symptom in some specific month: A) month of asthma exacerbation; B) month of rhinorrhea exacerbation. Allergic asthmatics: gray shadow; nonallergic asthmatics: black shadow. Only significant *P*-values are shown.

asthmatics, respectively, reported an increase in their attack on some specific months ($P=0.001$). Among them (Fig. 1A), asthma exacerbations mostly occurred in the autumn and winter months in nonallergic asthmatics, and the difference was significant for January ($P=0.002$), February ($P=0.002$) and March ($P=0.001$). Conversely, nonallergic asthmatics had less exacerbations in summer and the difference was significant for July ($P=0.005$) and August ($P=0.035$) compared to allergic asthmatics.

Severity of asthma

FEV₁ was higher in allergic asthmatics compared to nonallergic asthmatics (Table 3). The use of inhaled and

Table 2. Characteristics of the patients

	Allergic asthma	Nonallergic asthma	Allergic controls	Nonallergic controls
Age (years $\pm$ SEM)	34.3 $\pm$ 1.3	47.3 $\pm$ 1.7*	34.1 $\pm$ 1.5	43 $\pm$ 1.2*
Sex ratio (M/F)	1.2†	0.8	1	0.87
Active smoking (g/day $\pm$ SEM)	2.3 $\pm$ 0.5	1.4 $\pm$ 0.6	3 $\pm$ 0.8	3.8 $\pm$ 0.6
History of hay fever (%)	66.7	35.7 °	60	10.5*
History of allergic dermatitis (%)	38.3‡	9.3	12.5	11.8

* $P<0.05$ vs allergic asthma and allergic controls.

† $P<0.05$ vs nonallergic asthma.

‡ $P<0.05$ vs the three other groups.

Table 3 Characteristics of asthma. Steroid use concerns the last 12 months. Severity score graded as described in Table 1. The total of the three classes does not reach 100% because of missing values: 7.4% and 4.6% for allergic and nonallergic asthmatics, respectively, $P > 0.05$

	Allergic asthma	Nonallergic asthma	P-value
History of asthma			
Age of first asthma attack (years $\pm$ SEM)	15.8 $\pm$ 1.3	32.2 $\pm$ 2.3	0.0001
Asthma duration (years $\pm$ SEM)	18.5 $\pm$ 1.3	15.1 $\pm$ 2.2	0.17
Exacerbations in specific months (%)	72.3	36.6	0.001
Severity			
FEV ₁ (%) $\pm$ SEM)	91.2 $\pm$ 1.7	79.2 $\pm$ 3.6	0.003
Inhaled steroids (%)	73.5	90.5	0.02
Systemic steroids (%)	50.4	74.4	0.006
Severity score			
Class 1: Mild (%)	16.4	4.6	0.02
Class 2: Moderate (%)	41.8	30.2	0.006
Class 3: Severe (%)	34.4	60.5	0.02

systemic steroids in the last 12 months was more frequent in nonallergic asthmatics. The severity score was higher in nonallergic asthmatics with 60.5% and 34.4% ($P = 0.005$) of nonallergic and allergic asthmatics, respectively, having a class 3 severity score in the subclass analysis.

Symptoms of rhinitis

The prevalence of rhinitic symptoms was not statistically different between both groups of asthmatics (Table 4), but there was a trend for a higher rate of paroxysmal sneezing in allergic asthma (84.2% vs 74%, $P = 0.085$). Paroxysmal sneezing and rhinorrhea were significantly less frequent in nonallergic controls as compared to the other three groups and nasal obstruction was less frequent in nonallergic controls as compared to allergic asthmatics. Among subjects displaying rhinorrhea, respectively 73.8% ($n = 31$) and 60% ($n = 9$) in allergic and nonallergic asthmatics had a predominance of this symptom on specific months but the difference was not significant (data not shown). Among them (Fig. 1B), rhinorrhea exacerbations occurred mainly in the autumn and winter months in nonallergic asthmatics and the difference was significant for November ($P = 0.02$), December ($P = 0.002$), January ($P = 0.001$) and March ($P = 0.005$). Symmetrically, allergic asthmatics experienced a recrudescence of rhinorrhea in the summer as compared to nonallergic asthmatics, but the difference was not significant.

Nasal polyposis and sinusitis

The prevalence of surgery for nasal polyposis (Table 4) was significantly higher in nonallergic asthmatics than in allergic asthmatics: 21% ($n = 9$) vs 3.3% ($n = 4$), $P = 0.001$). Aspirin-induced asthma (AIA) was not involved in this difference as a single case of AIA was found in each group. Respectively 74.4% ($n = 32$) and 57.5%

Table 4 The prevalence of rhinitic symptoms in allergic and nonallergic asthmatics

	Asthmatics		Controls	
	Allergic	Nonallergic	Allergic	Nonallergic
Paroxysmal sneezing	84.2	72.1	75.0	36.0*
Rhinorrhea	37.5	34.9	37.5	18.3*
Nasal obstruction	43.3†	39.5	32.5	29.4
History of polypectomy	3.3	21.0*	2.6	0.0
Sinusitis	57.5	74.4*	52.5	42.5

Values are expressed as percentages.

* $P < 0.05$ compared to the three other groups.

† $P < 0.05$ compared to nonatopic controls.

($n = 69$) of the nonallergic and allergic asthmatics (Table 4) displayed a history of sinusitis, and the difference was significant ($P = 0.05$). For these two items, the difference is significant as compared with the two groups of controls.

Multivariate analysis

The following items were included in the logistic regression model: age (expressed in decades), sex, active smoking, history of hay fever and allergic dermatitis in childhood, paroxysmal sneezing, history of nasal polypectomy and sinusitis, age of first asthma attack, asthma duration, asthma exacerbations in specific month, and FEV₁ below 80% of predicted value. The factors increasing the risk of displaying nonallergic asthma compared to allergic asthma are (in decreasing order) (Table 5): history of nasal polypectomy, female sex, FEV₁ < 80% of predicted value, and greater age. By contrast, we found three parameters that lowered the risk of being a nonallergic asthmatic: history of hay fever, seasonal exacerbations and asthma duration.

Discussion

The aim of our work was to study the similarities and differences between allergic and nonallergic asthmatics enrolled in the EGEA study. The positivity of at least one skin prick test is usually used in epidemiology as a single diagnostic criteria for atopy. However, we chose to keep two diagnostic criteria to obtain contrasted groups and to lower the risk of misclassification of patients. Indeed, 25 patients were excluded because of discordance between skin prick tests and multiallergic tests.

Twenty-five percent of asthmatics were nonallergic. This proportion is high as the relative prevalence of nonallergic asthma is considered to reach 10%. This relatively high proportion of nonallergic asthmatics in our survey is probably related to the hospital-based recruitment. Accordingly, in similar studies, nonallergic asthma reaches up to 30% (21). The higher rate of nonallergic asthmatics in a selected population is probably due to a bias in the recruitment of more

Table 5. Logistic regression analysis: nonallergic asthmatics compared to allergic asthmatics

	OR	95% CI	P value
Nasal polyposis	19.03	3.22–112.48	0.001
Sex (F/M)	5.69	1.75–18.54	0.004
FEV ₁ <80% of predicted value	4.45	1.35–14.62	0.014
Age	2.48	1.60–3.85	0.0001
Asthma duration	0.94	0.90–0.98	0.005
Seasonal exacerbation	0.21	0.07–0.63	0.005
Hay fever	0.20	0.07–0.59	0.004

CI: confidence interval; OR: odds ratio.

severe patients. Indeed, we confirm herein that non-allergic asthma is more severe than allergic asthma. Aas's score (22) and the Global Initiative for Asthma (GINA) score (23) were not available for this study because they need quantitative evaluation of medication requirements and follow-up of respiratory function. We used a score that has been established for this study (20), including anamnestic, clinical and functional items that are all to be found in the literature for assessment of asthma severity (24). We found this score to be higher in nonallergic asthma. Furthermore, lower FEV₁ increased by five-fold the risk of nonallergic asthma. Asthma duration, which is known to correlate positively with degree of bronchial obstruction (25), could not explain this difference. Indeed, asthma duration lowered the risk of nonallergic asthma. Thus, our study confirmed that asthma is more severe in nonallergics than in allergics. This result, admitted in clinical practice, had not been clearly demonstrated so far. Inouye et al. (10) compared asthma severity in two groups of asthmatics with negative and positive skin tests to aeroallergens. They found greater exercise limitation, more frequent asthma-related symptoms, and a greater use of oral steroids in negative skin test group, suggesting more severe asthma. Nevertheless, these differences disappeared after adjusting for age and asthma duration. Furthermore, bronchial obstruction assessed by FEV₁ was not significantly different between both groups. Accordingly, Cline et al. (26) did not find positivity of skin tests to be related to FEV₁ nor to asthma severity. In contrast, Ulrik et al. (9) followed for 10 years a cohort of allergic and nonallergic asthmatics (31 and 43.5 year olds, respectively) and compared the decline of their lung function. They found a 25 ml and 50 ml FEV₁ annual decrease in allergic and nonallergic asthmatics, respectively ($P < 0.05$), whereas FEV₁ was not different between groups at the outset of the study.

Higher age and female sex are associated with an increasing risk of nonallergic asthma as compared to allergic asthma. These two characteristics were included in the first description by Rackeman (1). However, only age has been clearly identified so far to significantly discriminate between both kinds of asthma (9, 10). In the study by Ulrik et al. (9), there was no sex difference

between both groups. Age of first asthma attack was significantly lower in allergic asthmatics in the univariate analysis but this parameter is not found to be an independent risk factor in the logistic regression.

As previously reported (10), clinical history of atopy was significantly more frequent in allergic asthmatics, and hay fever was the factor that most lowered the risk of displaying nonallergic asthma in the logistic regression.

Seasonal asthma exacerbations lowered the risk of displaying nonallergic asthma. This is confirmed by a recent work (27) concerning 888 asthma cases, in which we found, respectively, 44.5% and 27.8% of seasonal recrudescence of asthma in allergic and nonallergic asthmatics ($P < 0.0001$). This may be related to seasonal variations of allergenic exposure. However, and surprisingly, seasonal exacerbations of asthma were also found among nonallergic asthmatics. Unlike allergics, non-allergic asthmatics displayed exacerbations in winter months and a similar difference was found for rhinorrhea. This result suggests a higher sensibility of non-allergic asthmatics' nasal and bronchial epithelia to nonallergenic stimuli, like cold air, wind or respiratory viruses. This hypothesis is supported by the results of a work performed within the frame of the EGEA study, which found out that nonallergenic factors, such as air conditioning, pollutants and strong smells, trigger asthma attacks in nonallergics (data not published).

Symptoms of rhinitis are known to be associated with asthma in varying frequency. Pedersen et al. (28) found a prevalence of 28% rhinitic patients, defined by paroxysmal sneezing and rhinorrhea, in an asthmatic population. However, the allergic status of patients was unknown and no control subjects were included. In another study from an Iowa population, 78% of allergic asthmatics were rhinitic (29). Conversely, we have formerly shown in a study of rhinitic patients that about 50% were asthmatics, this frequency being higher in allergics (30). The prevalence of rhinitic symptoms had not been formerly compared between allergic and nonallergic asthmatics. Unexpectedly, the prevalence of rhinitic symptoms was similar in both groups, irrespective of allergic status. These results are in keeping with a recent publication from the ECRHS (31). The authors found that the probability of displaying asthma among non-allergic subjects was strongly associated with perennial rhinitis, with an OR of 11.6 (95% CI: 6.2–21.9) whereas the OR reached 8.1 (95% CI: 5.4–12.1) for allergic subjects. They concluded that the relationship between rhinitis and asthma exists, even when there is no underlying allergic disorder that might predispose to both upper and lower airway diseases. Nevertheless, we can speculate that rhinitis results from distinct causes in both groups of asthmatics. Indeed, rhinitic symptoms are probably due to allergic rhinitis in allergic asthmatics. This is suggested by the higher frequency of allergic rhinitis in allergics and by the similar prevalence of

rhinitic symptoms in allergic subjects, whatever their asthmatic status, with a lower prevalence in nonallergic controls. On the other hand, rhinitic symptoms observed in nonallergic asthmatics are probably due to sinus pathology. This is suggested by the higher prevalence of nasal polyposis and sinusitis in this group compared to the other three. These results are in keeping with a study comparing the prevalence of nasal polyposis between asthmatics with negative and positive skin tests (32) in which, respectively, 12.5 and 5.5% of nasal polyposis ($P < 0.05$) was found.

In conclusion, our study confirms that phenotypes of allergic and nonallergic asthma are highly distinct, despite the immunological similarities recently published. The frequency of rhinitis symptoms is equivalent in both groups of asthma. However, the seasonality of these symptoms differs between groups, related to allergic diathesis in allergies, and associated with sinus polyposis in nonallergics.

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