

IgE-mediated and age-related bronchial hyperresponsiveness in patients with asthma. Relationship to family history of the disease

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Abstract

Objective: to uncover any differences in the age-related and IgE-mediated pathophysiology of the airways in asthmatics.

Methods: we examined the relationship of both IgE-mediated bronchial hyperresponsiveness and the cell content of bronchoalveolar lavage fluid with a family history of asthma in 263 patients with asthma classified according to age at onset.

Results: bronchial hyperresponsiveness decreased significantly as age at onset increased in those without a family history. Responsiveness was significantly higher in patients who were ≥ 60 years of age at onset who had a family history than in those who did not ($P < 0.05$). The proportion of lymphocytes in bronchoalveolar lavage fluid was significantly higher in patients between 50 and 59 years old at onset who had a family history than those who did not ($P < 0.05$). These results suggest that bronchial hyperresponsiveness and the proportion of bronchoalveolar lavage lymphocytes differ according to the presence or absence of a family history, a finding which is closely related to IgE-mediated allergy in elderly patients at onset.

Conclusions: our findings suggest (i) the possibility of asthma induced by non-IgE-mediated allergy in elderly patients and (ii) that bronchial responsiveness is also influenced by IgE-mediated allergy and age at onset.

Keywords: asthma, bronchial responsiveness, bronchoalveolar lavage, family history

Introduction

Asthma is an inflammatory disease of the airways which modulates non-specific bronchial hyperresponsiveness [1–4]. In our previous studies we have demonstrated that a correlation exists between the pathophysiology of the airways and inflammatory cells and that the proportion of inflammatory cells is often influenced by medication [5–8]. Asthma is clinically classified into two types, atopic and non-atopic, on the basis of the presence or absence, respectively, of IgE-mediated reactions [9, 10]. However, a different theory contends that asthma is almost always associated with some type of IgE-related reaction [11, 12]. The presence of an IgE-mediated allergic reaction in patients with asthma is often related to a family history of the disease.

To clarify the differences in age-related and IgE-mediated pathophysiology of the airways, we examined the relationship between a family history of asthma and IgE-mediated allergy, the proportion of lymphocytes in bronchoalveolar lavage (BAL) fluid and bronchial hyperresponsiveness among asthmatics (classified according to age at onset).

Subjects and methods

Subjects

We recruited a total of 263 consecutive asthmatic patients (145 women and 118 men; mean age 60 years, range 31–90 years) from our hospital. Asthma was defined according to the criteria of the International

Consensus on Diagnosis and Management of Asthma [13].

None of the subjects was a current smoker, 154 were non-smokers and 109 were ex-smokers. All ex-smokers had refrained from smoking for at least 5 years before the study; they had an average smoking history of 26.8 ± 12.2 pack-years.

All 263 subjects were treated with β -adrenergic agonists, theophylline, sodium cromoglycate, leukotriene receptor antagonist and corticosteroids. We observed no differences in medication between age-stratified groups with positive or negative family histories.

We determined the age at onset of asthma and family history by a questionnaire administered to patients and/or their families. We excluded subjects with apparent memory impairment. To observe age-related differences among clinical findings, we classified subjects into four groups according to age at onset: group 1, 0–39 years; group 2, 40–49 years; group 3, 50–59 years and group 4, 60+ years.

We classified patients with a history suggestive of third-degree relatives having allergic disease as having a positive family history. All other patients were classified as having a negative family history.

In a preliminary study, there was a high degree of test–retest and interobserver reproducibility. We obtained informed consent from all the participants before the start of the study. The design of the study fulfilled the criteria of the ethics committee of our hospital.

We measured serum levels of total IgE using the radioimmunosorbent test, and estimated serum specific IgE antibodies against inhalant allergens by the Phadebas radioallergosorbent test of the CAP system (Pharmacia Diagnostics AB, Uppsala, Sweden). To standardize for age and sex, serum IgE values were transformed into Z scores, as described by Burrows *et al.* [14].

Spirometric tests were performed by means of a computerized pneumotachograph (Chestac 33, Chest Co., Tokyo, Japan) using a standard technique [15]. Spirometric data were expressed as a percentage of predicted values and any age or height bias was corrected for using standardized residuals [16, 17].

Bronchial responsiveness

We evaluated bronchial responsiveness using an Astograph (TCK6100H, Chest Co., Tokyo, Japan) with direct recording of the dose–response curves of respiratory resistance during a continuous inhalation of methacholine with twofold incremental increases in concentrations ($49 \mu\text{g/ml}$ to 25 mg/ml) [18, 19]. The cumulative dose of inhaled methacholine at the inflection point at which respiratory resistance begins to increase was adopted as the marker of bronchial responsiveness. This was expressed in units, with 1 unit

equalling 1 min of inhalation of aerosol solution at 1.0 mg/ml during quiet tidal breathing. All respiratory medications were stopped for at least 12 h before the examination.

BAL

We performed BAL using a previously reported method [5] when the patients were attack-free. A bronchofibrescope was routinely wedged into a segment of the right lung, $3 \times 50 \text{ ml}$ aliquots of sterile isotonic saline at 37°C introduced into the segment and samples immediately aspirated into silicon-treated glassware. The aspirates were filtered through sterile steel mesh and centrifuged at $300 \times g$ for 10 min at 4°C . The cell pellet was resuspended and smear preparations of the cell suspension made. The slides were air-dried and stained with May–Grunwald–Giemsa, after which a differential cell count was performed on 500 cells, excluding epithelial cells. The results were expressed as a percentage of the total number of cells.

Statistical analysis

Results were expressed as mean values (SD) for patients' ages, pulmonary function data and cell counts in BAL fluid. Serum IgE levels and the cumulative dose of inhaled methacholine at the inflection point were reported as the geometric mean and geometric standard deviation of the mean. We used one- and two-way analysis of variance (ANOVA) to compare patients' ages, pulmonary function data, serum IgE levels, bronchial hyperresponsiveness and cell counts in BAL fluid between groups. The positivity of specific IgE antibodies against inhalant allergens was compared between groups using the χ^2 test.

Results

Table 1 shows the mean age and ventilatory function of the subjects with asthma according to age at onset of the disease. We found no statistically significant differences in the frequency of a positive family history, corticosteroid use or standardized residuals of forced vital capacity and forced expiratory volume in 1 s/forced vital capacity among the four groups. The smoking histories of the ex-smokers in each group, expressed in pack-years, were as follows: group 1, 23.1 ± 14.4 ; group 2, 30.6 ± 11.8 ; group 3, 25.4 ± 9.7 ; group 4, 31.8 ± 12.2 . We also compared family sizes and found no significant differences between those with a positive and negative family history.

As shown in Table 2, there were no significant differences in the mean levels of serum IgE and IgE Z scores among the four groups in subjects with a positive family history. However, both values tended to decrease as the age at onset increased among those with a negative family history, with group 4 showing

Table 1. Patient characteristics, lung function and medication use among subjects, by group (age at onset of asthma)

Characteristic	Group ^a			
	1 (n = 62)	2 (n = 65)	3 (n = 76)	4 (n = 60)
Male/female	27/35	26/39	31/45	30/30
Mean age, years (SD) ^b	50.7 (11.9)	56.0 (9.3)	62.6 (5.6)	71.7 (6.1)
No. (and %) with				
Family history of allergy ^c	38 (61.3)	36 (55.4)	37 (48.7)	25 (41.7)
Smoking history	26 (41.9)	28 (43.1)	30 (39.5)	25 (41.7)
Systemic steroid treatment	28 (45.2)	28 (43.1)	28 (36.8)	22 (36.7)
Inhaled steroid treatment	30 (48.4)	28 (43.1)	27 (35.5)	19 (31.7)
Mean FVC (SD)				
% of predicted ^c	98.2 (17.9)	89.3 (20.9)	90.4 (21.4)	85.8 (19.6)
Standardized residual	-0.21 (1.27)	-0.88 (1.72)	-0.89 (1.86)	-1.09 (1.55)
Mean FEV1/FVC (SD)				
%	67.9 (11.6)	62.9 (12.3)	64.7 (13.1)	65.4 (14.4)
Standardized residual	-2.63 (1.91)	-3.20 (2.09)	-2.60 (2.17)	-2.09 (2.45)

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; SR, standardized residual.

^aAge at onset of asthma: group 1, 0–39 years; group 2, 40–49 years; group 3, 50–59 years and group 4, 60+ years.

^bThose in both groups 3 and 4 were significantly older than those in either group 1 or 2 ($P < 0.01$), and those in group 4 were significantly older than group 3 ($P < 0.001$), and those in group 2 were significantly older than group 1 ($P < 0.01$).

^cSignificant difference in group 1 and group 4 ($P < 0.05$).

Table 2. Mean serum IgE levels and Z scores of asthma patients with and without a family history of allergic diseases

Group ^a	With history			Without history		
	n	IgE Serum (IU/ml) ^b	Z score ^b	n	IgE Serum (IU/ml)	Z score
1	38	291.5 (3.8)	0.01 (0.75)	24	269.3 (4.4)	0.20 (1.29)
2	36	219.7 (4.9)	0.16 (1.40)	29	200.4 (3.7)	0.01 (0.92)
3	37	232.0 (3.7)	0.99 (0.80)	39	157.8 (2.8)	-0.19 (0.70)
4	25	319.1 (2.9) ^c	0.40 (1.26) ^c	35	99.7 (3.3) ^c	-0.48 (0.48) ^c

^aAge at onset of asthma: group 1, 0–39 years; group 2, 40–49 years; group 3, 50–59 years and group 4, 60+ years.

^bSignificantly higher than in those with a negative family history ($P < 0.05$).

^cSignificantly higher than among those in group 1 ($P < 0.05$).

significantly lower serum IgE values and IgE Z scores than group 1 ($P < 0.05$). Both values were significantly lower among group 4 subjects with a negative family history than in those with a positive family history ($P < 0.05$).

The frequency of subjects with specific IgE antibodies against commonly inhaled allergens decreased as age at onset increased, and the frequency was significantly lower in group 4 subjects with a negative than a positive family history ($P < 0.05$; Table 3).

The proportion of BAL eosinophils was not related to age at onset and did not differ significantly between subjects with and without a family history (Table 4). The proportion of lymphocytes in BAL fluid ranged from 14.4 to 20.6% in subjects with a negative family history and from 15.8 to 25.2% in subjects with a positive family history, but these differences were not significant. As shown in Table 4, the proportion of BAL

Table 3. Frequency of specific IgE antibodies against inhalant allergens in asthma patients with and without family histories of allergic diseases

Group ^a	With history		Without history ^b	
	n	No. (%) with antibodies	n	No. (%) with antibodies
1	38	24 (63.2)	24	16 (66.7)
2	36	16 (44.4)	29	11 (37.9)
3	37	18 (48.6)	39	13 (33.3)
4	25	10 (40.0) ^c	35	5 (14.3)

^aAge at onset of asthma: group 1, 0–39 years; group 2, 40–49 years; group 3, 50–59 years and group 4, 60+ years.

^bSignificant differences between groups 1 and 3 ($P < 0.05$), groups 1 and 4 ($P < 0.01$) and groups 2 and 4 ($P < 0.05$).

^cSignificantly higher than among those without a family history ($P < 0.05$).

Table 4. Bronchoalveolar lavage cell content in subjects in relation to family history of allergic diseases

Cell content	Mean value (SD) by group ^a and family history							
	Group 1		Group 2		Group 3		Group 4	
	FH+ (n = 19)	FH- (n = 14)	FH+ (n = 14)	FH- (n = 10)	FH+ (n = 18)	FH- (n = 21)	FH+ (n = 9)	FH- (n = 10)
Total cells/ml, × 10 ⁵	126.9 (75.9)	198.6 (101.5)	184.1 (90.7)	192.0 (97.9)	133.5 (88.2)	171.7 (95.8)	171.4 (92.0)	185.0 (92.0)
Macrophages (%)	77.6 (11.4)	64.5 (27.3)	76.1 (16.5)	73.8 (21.4)	66.6 (19.2)	74.9 (20.7)	64.1 (19.9)	67.9 (17.5)
Lymphocytes (%)	17.8 (11.1)	14.4 (13.9)	15.8 (12.0)	14.4 (6.8)	24.5 (16.0)	14.5 ^b (12.5)	25.2 (14.7)	20.6 (17.1)
Neutrophils (%)	2.1 (2.7)	10.8 (21.6)	1.2 (1.4)	1.7 (2.6)	5.6 (13.0)	6.9 (19.7)	6.2 (10.8)	7.6 (13.3)
Eosinophils (%)	2.5 (2.4)	10.3 (16.4)	7.0 (13.3)	10.1 (17.4)	3.6 (9.0)	3.7 (7.2)	4.5 (6.7)	3.9 (3.2)

FH+, positive family history; FH-, negative family history.

^aAge at onset of asthma: group 1, 0-39 years; group 2, 40-49 years; group 3, 50-59 years and group 4, 60+ years.

^bSignificantly lower than in patients with a family history ($P < 0.05$).

lymphocytes was significantly lower among group 3 subjects with a negative family history than those with a positive family history ($P < 0.05$).

Bronchial responsiveness decreased from 0.924 to 1.199 units of methacholine in subjects with a positive family history as age at onset increased. We found no significant differences in this value among the four groups classified according to age at onset. In contrast, in subjects with a negative family history, bronchial

responsiveness decreased markedly with age at onset, from 0.812 to 5.010 units of methacholine. Among those with a negative family history, the responsiveness in group 1 ($P < 0.05$) and group 2 patients ($P < 0.01$) was significantly greater than among those in group 4. Responsiveness was significantly lower in group 4 subjects without a family history than among those with one, as shown in Figure 1 ($P < 0.05$).

Discussion

Atopic asthma is caused by IgE-mediated allergy, which is clinically evaluated according to serum IgE levels, skin reactivity and radioallergosorbent test score to inhalant allergens and bronchial challenge with corresponding allergens. Patients with atopic asthma often have a family history of allergic diseases, suggesting that IgE-mediated allergy is closely related to a family history of allergic diseases. It is generally believed that true allergic asthma very seldom begins in elderly patients and that, when it does occur, it is actually intrinsic asthma. However, late-onset asthma has been reported to be not uncommon among patients over 65 [20]. Litonjua *et al.* suggested that in elderly men, sensitization to cat allergens is associated with asthma, and that sensitization predates airway hyperresponsiveness to methacholine [21].

In the present study, we first compared clinical data among subjects with and without steroid administration to examine the influence of steroids. Since none of these measures differed significantly among the groups (aside from BAL eosinophils), we investigated them in relation to an association with family history. Although memory disturbance and prior diagnostic accuracy may affect the result, there were no significant

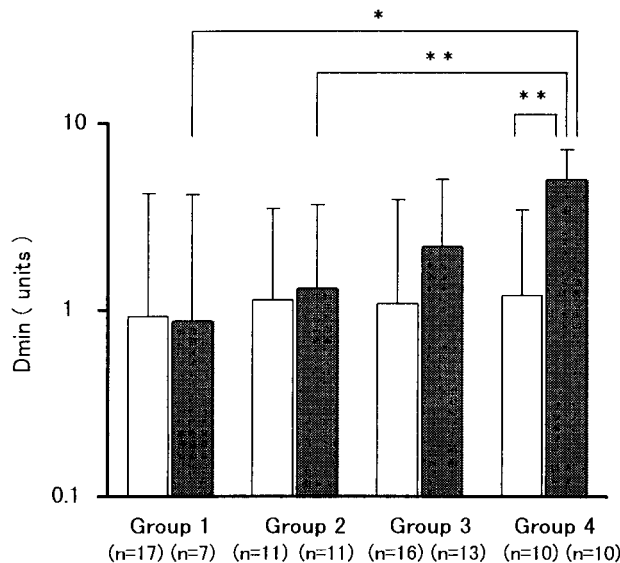


Figure 1. Bronchial hyperresponsiveness to methacholine (Dmin) in patients with (□) and without (■) a family history of asthma, stratified according to age at onset of asthma: group 1, 0-39 years; group 2, 40-49 years; group 3, 50-59 years and group 4, 60+ years. * $P < 0.01$; ** $P < 0.05$.

differences in the frequency of a positive family history among groups classified according to age (data not shown). The frequency of patients with a family history of asthma decreased as age at onset increased. However, the frequency of specific IgE antibodies and age- and sex-standardized IgE Z scores did not differ significantly between subjects with and without a family history in any group classified according to age at onset, except in those who had been over 60 at onset (group 4).

These results suggest that asthma in younger patients is often induced by IgE-mediated allergy—despite a lack of a family history of asthma. In contrast, when no family history of asthma is present, it is possible that asthma in patients aged over 60 at onset is caused by non-IgE-mediated allergy.

Airway inflammation is a common pathological feature in asthma, particularly in late asthmatic reaction [22–24]. BAL cell analyses have shown that airway inflammation modulates non-specific bronchial responsiveness, in which lymphocytes, neutrophils and eosinophils participate in the inflammatory process [1–4, 25–27]. In our study, the proportion of BAL eosinophils did not differ significantly among the four groups classified according to age at onset, or between subjects with and without a family history of asthma. The proportion of BAL lymphocytes has been reported to be higher in asthmatics than in healthy subjects [28]. Our study revealed that the proportion of BAL lymphocytes did not differ among the four groups when there was a negative family history. In contrast, a significant increase in BAL lymphocytes was observed in older patients with a family history. The results also showed that the proportion of BAL lymphocytes is influenced by IgE-mediated allergy in elderly patients with asthma.

We found no differences in bronchial responsiveness among subjects with a positive family history in any of the four groups. In contrast, bronchial responsiveness decreased as age at onset increased in subjects without a family history, and differed between patients with and without a family history with onset over the age of 60. These results suggest that bronchial responsiveness is also influenced by IgE-mediated allergy and the patient's age at onset. It is possible that the responsiveness in older subjects without a family history is not related to IgE-mediated allergy.

Key points

- Both serum IgE values and IgE Z scores were significantly lower in asthmatic subjects who were over 60 years old at onset who had a negative family history than in those with a positive family history.
- Bronchial hyperresponsiveness decreased significantly as age at onset increased in patients without a family history.

- The proportion of lymphocytes in bronchoalveolar lavage fluid was significantly higher in patients between 50 and 59 years old at onset who had a family history than those who did not.
- Bronchial hyperresponsiveness and the proportion of lymphocytes in bronchoalveolar lavage fluid differed according to the presence or absence of a family history, a finding which is closely related to IgE-mediated allergy in elderly patients at onset.

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