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Clinical Characteristics According to Sensitized Allergens in Adult Korean Patients With Bronchial Asthma

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Purpose: Allergic sensitization is a risk factor for the development of bronchial asthma. This study was conducted to investigate clinical manifestations according to sensitized allergens in adult Korean patients with bronchial asthma. **Methods:** In total, 523 adult patients who were diagnosed with bronchial asthma between March 2002 and March 2008 were included in the study. All patients underwent skin prick tests for approximately 45 allergens or a specific IgE test. Sensitized allergens were grouped into the following categories: house dust mites, fungus, pollen, and animal dander. Atopy was defined as a positive skin prick test response or the presence of a specific IgE to one or more allergens. **Results:** Of the 523 patients, 295 (56%) were sensitized to one or more allergens. A younger median age, greater proportion of males, higher eosinophil counts, and higher total IgE levels were observed in the atopic asthma group compared to the non-atopic asthma group. The PC20 value was negatively correlated with eosinophil counts and total IgE in the atopic asthma group. In the subgroup analysis, patients sensitized to *Cladosporium* showed poorer pulmonary function and a higher response to bronchodilators. In addition, patients sensitized to *Alternaria* showed severer bronchial hyperresponsiveness than non-atopic patients with asthma. Finally, a gradual increase in the number of sensitized allergens was noted with increasing age, eosinophil counts, and total IgE levels. **Conclusions:** We suggest the need for identifying the existence of atopy and exact offending allergens at the time of asthma diagnosis, since significant differences in sex, age, blood test results, and lung function were observed according to atopy and sensitized allergens.

Key Words: Allergens; asthma; Asian Continental Ancestry Group; Koreans; skin tests

INTRODUCTION

Allergic diseases including bronchial asthma can develop in individuals who are sensitized to indoor or outdoor allergens, and subsequently induce immunologic hypersensitivity reactions.[1] This sensitization to allergens is affected by genetic factors, age, exposure time, the degree of exposure to allergens, and concentrations of allergens.[2] In addition, sensitization to indoor allergens and particular outdoor fungal spores increases the risk of bronchial hyperresponsiveness (BHR) and aggravates clinical symptoms in children. Patients sensitized to house dust mites (HDM), animal dander, or fungus show a relatively severe BHR.[3] In contrast, investigators have reported that grass pollens, ragweed pollens, and geographically related pollens do not act as risk factors for bronchial asthma.[4] Since the severity of asthmatic symptoms is related to the degree of allergen exposure,[5] avoidance of HDM improves clinical symptoms and pulmonary function in patients with asthma who have been sensitized to HDM.[6] The common allergens identified by skin prick tests in adult Korean patients with bronchial asthma are reported to be HDM and ragweed pollen.[7,8] However, differences in the clinical features of bronchial asthma according to the offending allergens had not yet been elucidated. Therefore, this study was conducted to investigate the clinical characteristics and distributions of common offending allergens and to determine the relationship between the type and number of sensitized allergens and clinical manifestations in adult Korean patients with bronchial asthma.

MATERIALS AND METHODS

Patients

This retrospective study included a total of 523 patients aged

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≥18 years who presented at Chung-Ang University Hospital with episodic breathlessness, wheezing, cough, and chest tightness and who were diagnosed with bronchial asthma between March 2002 and March 2008. The diagnosis of asthma was based on the presence of characteristic symptoms and lung function (reversibility or BHR). The degree of reversibility in FEV1 was accepted as ≥12% and ≥200 mL from the pre-bronchodilator value. BHR was accepted as positive when the provocative concentration of methacholine was ≤8 mg/mL, causing a 20% fall in FEV1 (PC20).

Skin prick tests

Skin prick tests were performed on all patients using 45 allergens (Bencard, Brentford, UK) including HDM (3 allergens), pollen (27 allergens), animal dander (7 allergens), and fungus (8 allergens). A wheal was used to assess positive responses to allergens after 15 minutes. A wheal identical to or greater than histamine (1 mg/mL) was regarded as positive.

Allergen-specific IgE test

In some patients, serum-specific IgE levels against HDM and fungus were measured using a Pharmacia CAP system (Pharmacia, Uppsala, Sweden). A level of ≥0.35 KU/L was regarded as positive.

Definition of atopy and nonatopy

Atopy was defined as being positive for one or more allergens, whereas nonatopy was defined as being negative for all allergens in a skin prick test or using the CAP system.

Classification of offending allergens

Offending allergens were divided into four allergen groups: HDM, pollen, fungus, and animal dander. Group positivity was defined as being positive for one or more individual allergens within each allergen group. Cockroaches were included in the HDM allergen group.

Statistical analysis

Age is expressed as the median, and other measurements are expressed as the mean. All statistical analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Variables were compared using a chi-square test or Student's *t*-test. Eosinophil counts, serum eosinophil cationic protein (ECP), and total IgE level were log-transformed for statistic analysis. Linear regression was used to eliminate the effects of age, sex, body mass index (BMI), and smoking amounts on the results of pulmonary function tests. The relationship between the number of offending allergens and clinical characteristics was analyzed using correlation coefficients and a regression analysis. A *P* value of <0.05 was considered statistically significant.

RESULTS

Clinical characteristics and the distribution of common offending allergens

The median patient age was 48 years (range, 18-85 years), and 46.3% of patients were men. The mean value of serum total IgE was 158.5 KU/L. The mean FEV1 was 86.4% predicted and the mean FVC was 91.1% predicted. Of 523 patients, 295 (56.4%) showed positive responses to one or more allergens. In these patients, HDM comprised the most common offending allergen, followed by pollen, animal dander, and fungus. With respect to the number of allergic sensitizations, allergic sensitization to only one allergen group was most common (n=165, 31.5%; Table 1).

Differences in clinical characteristics between patients with atopic asthma and those with non-atopic asthma

Patients in the atopic asthma group were younger than those in the non-atopic asthma group (44 versus 55 years, $P<0.05$). The ratio of males to females was higher in the atopic asthma group compared to that in the non-atopic asthma group. Peripheral blood total eosinophil counts and serum total IgE level were also higher in the atopic asthma group ($P<0.05$). However, FEV1 percent predicted, bronchodilator responses (BDRs), and PC20 results were not significantly different between the two groups (Table 2). Linear regression of FEV1 percent predicted,

Table 1. Clinical characteristics of patients with bronchial asthma

No. of patients	523
Age (yr)	48 (18-85)
Sex (male %)	46.3
BMI	23.7±3.4
Smoking amounts (PY)	8.5±15.0
Eosinophil counts (10^9/L)*	199.5 (79.4-631.0)
ECP (μg/L)*	15.9 (6.3-39.8)
Total IgE (KU/L)*	158.5 (31.6-794.3)
FVC% predicted	91.1±17.1
FEV1% predicted	86.4±22.7
BDR (change %)	10.9±11.5
PC20 (mg/mL)	2.2±2.0
Atopy (%)	295 (56.4)
HDM	224 (42.8%)
Pollen	112 (21.4%)
Animal dander	92 (17.6%)
Fungus	56 (10.7%)
Number of the positive allergen groups	
1	165 (31.5%)
2	80 (15.3%)
3	41 (7.8%)
4	9 (1.7%)

PY, pack-years; BDR, bronchodilator response; PC20, provocative concentration of methacholine causing a 20% fall in FEV1.
*Log transformation for statistical analysis.

PC20, and BDR percent adjusted for age, sex, BMI, and smoking amounts were not significantly different between the two groups.

Correlation between the PC20 value and laboratory test results

The PC20 value was negatively correlated with eosinophil counts (r=-0.132, P<0.05) and total IgE levels (r=0.192, P<0.001). In the subgroup analysis, these negative correlations were observed in atopic patients with asthma (eosinophil counts, r=-0.156, P<0.05 and total IgE level, r=0.239, P<0.005), but not non-atopic patients.

Differences in clinical characteristics according to allergen group

Positive responses to each allergen group were more often observed in younger patients and males as compared to non-atopic asthma (P<0.05). Serum total IgE levels were higher in patients who showed positive responses to each allergen groups compared to the non-atopic asthma group (P<0.05). In particular, mean eosinophil counts and serum ECP were higher in positive responders to the animal dander group compared to the non-atopic asthma group (P<0.05; Table 3).

Clinical characteristics according to allergic sensitization to common allergens

Positive responses to each allergen of *Dermatophagoides pteronyssinus* (Dp), *Dermatophagoides farinae* (Df), cockroach, cat, dog (data not shown), *Cladosporium*, *Aspergillus*, and *Alternaria* (Table 4) were observed in younger patients and markedly more often in males than in non-atopic patients with asthma (P<0.05). Higher mean eosinophil counts and serum total IgE levels (P<0.05) were also observed. Patients allergic to the remaining aller-

Table 2. Clinical characteristics according to atopy

	Atopic asthma (n=290)	Non-atopic asthma (n=233)	*P* value
Age (yr)	44 (18-85)	55 (19-85)	<0.001
Sex (male %)	54.6	35.5	<0.001
BMI	23.6±3.5	23.9±3.4	NS
Smoking amounts (PY)	7.6±13.6	9.5±14.5	NS
Eosinophil counts (10^9/L)*	253.4 (102.2-628.3)	183.6 (66.9-503.9)	<0.001
ECP (μg/L)*	17.0 (6.3-46.0)	14.5 (5.6-37.5)	NS
Total IgE (KU/L)*	177.5 (44.5-707.5)	72.4 (17.4-302.4)	<0.001
FVC % predicted	90.9±17.8	91.5±16.3	NS
FEV1 % predicted	86.4±23.2	86.3±22.1	NS
BDR (%change)	10.8±12.3	11.0±10.3	NS
PC20 (mg/mL)	2.2±2.1	2.2±1.8	NS

PY, pack-years; BDR, bronchodilator response; PC20, provocative concentration of methacholine causing a 20% fall in FEV1.
*Log transformation for statistical analysis.

Table 3. Clinical characteristics according to allergen groups compared with the non-atopic asthma group

	Non-atopic asthma (n=233)	HDM (n=224)	Pollen (n=112)	Fungus (n=56)	Animal dander (n=92)
Age (median, yr)	55	40‡	40‡	46‡	33‡
Sex (male %)	35.5	57‡	55*	59*	60†
BMI	23.9±3.4	23.6±3.6	24.1±3.5	24.0±4.0	23.4±3.5
Smoking amounts (PY)	9.5±14.5	8.5±13.6	9.1±13.4	9.0±11.5	8.1±16.6
Eosinophil counts (10^9/L)§	183.6 (66.9-503.9)	251.8 (103.8-611.1)	230.0 (90.1-587.5)	315.1 (149.0-666.4)	316.0 (140.2-712.5)‡
ECP (μg/L)§	14.5 (5.6-37.5)	16.0 (5.8-44.2)	17.6 (7.7-40.2)	19.6 (7.8-49.1)	22.1 (8.3-58.4)*
Total IgE (KU/L)§	72.4 (17.4-302.4)	284.6 (76.8-1054.5)‡	272.8 (67.5-1102.5)‡	351.1 (72.6-1696.8)‡	319.7 (103.3-988.8)‡
FVC % predicted	91.5±16.3	90.4±17.8	92.4±17.6	89.7±17.9	91.6±19.4
FEV1 % predicted	86.3±22.1	85.9±22.9	89.1±21.2	82.2±23.3	88.2±22.9
BDR (% change)	11.0±10.3	11.2±13.1	10.1±10.5	12.8±12.9	10.4±11.9
PC20 (mg/mL)	2.2±1.8	2.9±2.0	2.5±2.2	1.8±1.8	2.4±2.2

PY, pack-years; BDR, bronchodilator response; PC20, provocative concentration of methacholine causing a 20% fall in FEV1.
*P<0.05, †P<0.01, ‡P<0.001. §Log transformation for statistical analysis.

gens showed no statistical differences (data not shown).

Specifically, patients sensitized to *Cladosporium* showed lower FEV1 percent predicted than the non-atopic asthma group (74.2% versus 86.3%, $P<0.05$), and had a significantly increased BDR (% change; 17.1% versus 11.0%; $P=0.05$). The linear regression of FEV1 percent predicted and BDR (% change) adjusted for age, sex, BMI, and smoking amounts was also significantly different between patients sensitized to *Cladosporium* and non-atopic patients with asthma, respectively ($P<0.05$, $P<0.05$). Patients sensitized to *Alternaria* showed severer BHR than non-atopic patients with asthma (PC20, 1.4 versus 2.2 mg/mL, $P<0.05$; Table 4).

Correlation between the number of sensitized allergens and laboratory test results

The numbers of sensitized allergens were significantly correlated with patient age ($r=-0.386$, $P<0.001$), eosinophil counts ($r=0.15$, $P<0.05$), and serum total IgE levels ($r=0.221$, $P<0.001$) (Fig. 1). However, no significant correlation was observed between pulmonary function test results and the numbers of sensitized allergens.

DISCUSSION

The prevalence of atopy and allergic diseases has recently increased, probably due to environmental risk factors such as increased exposure to inhalant allergens, changes in lifestyle, and air pollution. According to the Global Initiative for Asthma (GINA) guidelines, etiologic factors for the development of bronchial asthma include both host and environmental risk factors. Among these factors, allergens play a crucial role in the development of asthma, and for this reason, the avoidance of sensitizing allergens is an important way of preventing and treating bronchial asthma.[1]

Table 4. Clinical characteristics according to sensitized allergens compared with the non-atopic asthma group

	Non-atopic asthma (n=233)	*Cladosporium* (n=18)	*Aspergillus* (n=35)	*Alternaria* (n=19)
Age (yr)	55	45‡	48†	37†
Sex (male %)	35.5	61*	63†	68†
BMI	23.9±3.4	22.9±4.0	23.4±3.8	24.1±4.9
Smoking amounts (PY)	9.5±14.5	8.0±12.5	8.7±13.5	9.4±15.1
Eosinophil counts (10^9/L)§	183.6 (66.9-503.9)	217.4 (82.3-574.1)†	347.3 (175.0-689.3)‡	349.9 (209.3-585.2)‡
ECP (μg/L)§	14.5 (5.6-37.5)	16.1 (6.0-43.4)	15.2 (6.3-36.9)	23.2 (10.9-49.1)
Total IgE (KU/L)§	72.4 (17.4-302.4)	146.8 (33.2-648.4)‡	594.3 (140.4-2514.7)‡	614.0 (137.5-2742.5)‡
FVC % predicted	91.5±16.3	85.3±13.5	88.3±16.3	91.4±17.5
FEV1 % predicted	86.3±22.1	74.2±18.1*	80.1±22.6	82.7±17.4
BDR (change %)	11.0±10.3	17.1±13.7*	12.2±13.1	12.6±12.3
PC20 (mg/mL)	2.2±1.8	1.6±1.5	2.0±2.1	1.4±1.3*

PY, pack-years; BDR, bronchodilator response; PC20, provocative concentration of methacholine causing a 20% fall in FEV1.
*$P<0.05$, †$P<0.01$, ‡$P<0.001$. §Log transformation for statistical analysis.

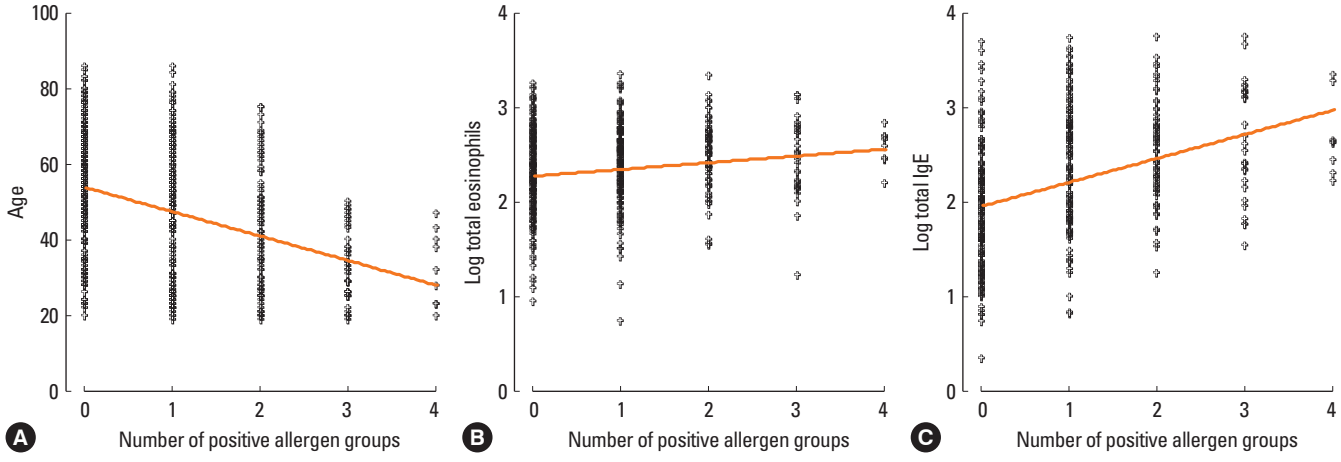

Fig. 1. Correlation of the number of positive allergen groups and other factors.
Age ($r=-0.386$, $P<0.001$) (A), Log10 Total eosinophils ($r=0.15$, $P<0.05$) (B), Log10 Total IgE ($r=0.221$, $P<0.001$) (C).

Rackermann[9] first introduced intrinsic and extrinsic concepts to bronchial asthma. He classified asthma according to skin test results into extrinsic/allergic asthma and intrinsic/non-allergic asthma. Thereafter, intrinsic asthma was considered to be a form of asthma that showed negative skin test results, late onset of symptoms, and idiopathic or infectious etiologies. Amin et al.[10] demonstrated that no differences existed between atopic and non-atopic patients in terms of lung function, symptomatic scores, or PC20, but differences were observed in the pathologic characteristics. For example, cellular patterns of inflammation in atopic patients are characterized by infiltration of eosinophils, mast cells, and T lymphocytes in bronchial biopsy. The thickness of the reticular basement membrane is also significantly higher in atopic asthma.[11] Just as importantly, some lung function reports have shown that the speed of bronchoconstriction and the speed of reversal of bronchoconstriction to methacholine after β_2-agonist inhalation is higher in non-atopic patients with asthma as compared to atopic patients.[12]

Asthma is probably not a single disease, but rather a complex of multiple, separate syndromes.[13] In this study, PC20 values were negatively correlated with eosinophil counts and total IgE in the atopic asthma group, but not in the non-atopic asthma group. This result suggests that atopic asthma and non-atopic asthma show different phenotypes and that eosinophilic inflammation exerts a critical role in the pathogenesis of atopic asthma. Consistent with our results, Janseu et al.[14] demonstrated that since BHR is related to an increase in eosinophil counts and positive skin prick tests, elevated eosinophil counts play an important role in the pathogenesis of asthma.

In contrast, recent studies have proposed that no need exists to classify asthma into extrinsic and intrinsic types.[15] Non-atopy may be attributable to insufficient skin test allergens, test timing, testing techniques, and possible false negativity. All types of asthma may develop after allergic sensitization and show various clinical features according to genetic and environmental factors. Consistently, in our study, significant differences in sex, age, or blood test results were observed between the atopic asthma group and the non-atopic asthma group; however, pulmonary function tests, BHR, and BDR showed no significant differences (Tables 2, 3).

With respect to fungal allergens, patients sensitized to *Cladosporium*, *Aspergillus* and *Alternaria* showed characteristic findings in blood tests and clinical characteristics. In particular, patients sensitized to *Cladosporium* showed poorer pulmonary function and higher responses to bronchodilators than non-atopic patients with asthma, suggesting that patients showing positive responses to *Cladosporium* should be carefully assessed for the presence of asthma. In addition, patients sensitized to *Alternaria* presented severer BHR than non-atopic patients with asthma. Since fungal spores are ubiquitous and small in size (usually <10 μm), they can easily penetrate the lower airways of the lung and induce allergic reactions.[16] Sensitivity to fungal allergens has been recognized as a risk factor for the development of asthma and may be related to persistent asthma, severe asthma, and potentially fatal asthma exacerbations.[17] Many studies have reported that particular allergens, especially HDM, cat, dog, *Aspergillus* and *Alternaria* are related to the development of asthma.[18,19] In our study, patients sensitized to fungal allergen had decreased lung function and more severe BHR.

Additionally, as the number of offending allergens increased, the patients were found to be older, and peripheral blood eosinophil counts and serum total IgE levels increased; however, no significant differences were observed in pulmonary function test results (Fig. 1). Neimeijer et al.[20] reported that in patients with asthma, the prevalence of atopy decreases as patients become older, which is consistent with our result. In an animal model, Regal et al.[21] demonstrated through an experimental study using Guinea pigs that asthma develops more frequently at a younger age.

The results of this study are subject to some limitations. First, since this study analyzed clinical and laboratory data at the time of initial diagnosis, we could not identify the prevalence of asthma, treatment outcomes, and changes in pulmonary function test results after treatment. Second, since serum-specific IgE levels were not measured in all patients, the possibility of false positivity or false negativity of skin prick tests cannot be excluded.

Taken together, this study identified the clinical characteristics and common offending allergens contributing to asthma. More than half of adult patients with bronchial asthma are sensitized to allergens. In addition, significant differences were observed in sex, age, blood test results, and a correlation between BHR severity with eosinophil counts and total IgE between the atopic asthma group and non-atopic asthma group. These results suggest that atopic asthma and non-asthma are different phenotypes. Furthermore, patients sensitized to fungi showed a difference in lung function. In particular, patients sensitized to *Cladosporium* or *Alternaria* had severe BHR or poor lung function. As a result, we suggest the need to identify the existence of atopy and the exact offending allergens at the time of asthma diagnosis.

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