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ORIGINAL ARTICLE

Persistent Airflow Obstruction in Young Adult Asthma Patients

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ABSTRACT

Background: Lung function determined by spirometry and the severity of dyspnea correlate weakly in asthma patients. We attempted to determine the risk factors in asthma patients having persistent airway obstruction despite of having only mild subjective symptoms, and to examine the possibility of improving FEV1 by treating asthma on the basis of the bronchodilator change in FEV1.

Methods: We examined asthma patients in their 20s and who visited Sagamihara National Hospital for the first time over a period of four years, by reviewing their clinical records. They underwent tests on the bronchodilator change in FEV1 and a test of airway hyperresponsiveness to histamine dihydrochloride.

Results: One hundred thirty-eight subjects (mean age, 25.6 years; 51 males, 87 females; current smoking, 30.4%; history of childhood asthma, 48.6%) were enrolled. Among them, 18.8% (26/138) showed persistent airway obstruction (postbronchodilator FEV1/FVC (%) <80%). Using the multiple logistic regression model, we found that history of childhood asthma and smoking history were the significant isolated risk factors for persistent airway obstruction. Moreover, we determined that the factors associated with the reversibility of airway obstruction in asthma patients without subjective symptoms were history of childhood asthma.

Conclusions: In this study, patients not undergoing treatment for asthma were examined. History of childhood asthma and smoking history may be the risk factors for persistent airway obstruction in the asthma patients with mild subjective symptoms. Tests on the bronchodilator change in FEV1 should be performed in patients with history of childhood asthma and smoking history, even if they have only mild subjective symptoms.

KEY WORDS

active smoking, airflow limitation, asthma, beta-agonist, childhood asthma

INTRODUCTION

Bronchial asthma is characterized by symptoms associated with variable airflow obstruction, airway inflammation, and airway hyperresponsiveness. Asthma patients show subjective symptoms (for example, cough, wheezing, and dyspnea) of varying severity. It was reported that lung function determined by spirometry and the severity of dyspnea correlate weakly in asthma patients, and a blunted perception of dyspnea by asthma patients is likely the cause of life-threatening asthma exacerbation.[1-3] Patients who have a blunted perception of dyspnea may have airway remodeling due to persistent airway inflammation. Airway remodeling may lead to irreversible loss of lung function. The most accurate method to detect airway remodeling is bronchial biopsy. However, bronchial biopsy is an invasive examination. Therefore, we focused on persistent airway obstruction, which was examined by lung function tests. The postbronchodilator ratio of forced exhaled volume in 1 second (FEV1) to vital capacity (VC) or forced vital capacity (FVC) is used as a marker of persistent airway obstruction.[4,5] We attempted to determine the risk factors in asthma patients having persistent airway obstruction despite of having only mild subjec-

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tive symptoms, and to examine the possibility of improving FEV1 by treating asthma on the basis of the bronchodilator change in FEV1.

METHODS

STUDY POPULATION

We examined asthma patients with mild asthma on the basis of subjective symptoms (excluding those with acute exacerbation such as episodes of a progressive intensification of shortness of breath, cough, wheezing, or chest tightness, and those with the need for treatment with systemic corticosteroids) who did not use controller medications, who were in their 20s, and who visited Sagamihara National Hospital for the first time from January 2004 to March 2008, by reviewing their clinical records. They underwent tests on the bronchodilator change in FEV1 and a test of airway hyperresponsiveness to histamine dihydrochloride (His) within four weeks of their first visit, under the condition that they did not use a bronchodilator less than 12 hours before the test. The condition of not using controller medications in our study denotes not using drugs, such as inhaled corticosteroids (ICS), a leukotriene receptor antagonist (LTRA), a long-acting inhaled β2 agonist (LABA), theophylline, or sodium cromoglycate for six months, except for a short-acting inhaled β2 agonist (SABA) or a bronchodilator as required. The asthma diagnosis was made in accordance with the American Thoracic Society (ATS) guidelines and was determined as episodes of paroxysms of dyspnea, wheezing, and cough, and an increased airway hyperresponsiveness.[6] Mild asthma symptoms were defined in accordance with the following criteria: 1. asthma symptoms occurred less than once a week for a month, 2. no visit to a medical institution because of asthma exacerbation for one year, and 3. no hospitalization because of asthma exacerbation for three years. Exclusion criteria included an abnormal shadow in chest X-ray films, pregnancy, and other respiratory diseases. One hundred thirty-eight asthma patients were chosen on the basis of the above-mentioned criteria. Moreover, all of the subjects were enrolled with their written informed consent, and methods approved by the ethnical review comittee of our hospital.

OUTCOME VARIABLES

We performed the bronchodilator change tests in FEV1 and airway hyperresponsiveness test within four weeks of the first visit, under the condition that they had not used controller medications or a bronchodilator for more than 12 hours before the test. Lung function was measured using a spirometer (Auto Spiro AS-303; Minato Medical Science Co., Ltd., Osaka, Japan).

We conducted the bronchodilator change tests in FEV1 using β2 agonist inhalation. A normal postbronchodilator FEV1/FVC is more than 80%.[5,7] Rasmussen and Mariotta have shown that airway remodeling is demonstrated by a low postbronchodilator FEV1/FVC, and the cut-off value defined as 80%.[5,7] Persistent airway obstruction was determined as having a postbronchodilator FEV1/FVC(%) <80%. A bronchodilator (salbutamol, 5 mg/ml nebulizer solution) was administered to the subjects. Lung function was measured before bronchodilator administration (pre) and 30 minutes after (post). The best FEV1/FVC was chosen from three measurements.

The airway hyperresponsiveness test was performed as described by Chai *et al*..[8] We prepared histamine dihydrochloride (Sigma, St. Louis, MO, USA) at 0.078, 0.157, 0.316, 0.625, 1.25, 2.5, 5, and 10 mg/ml by diluting it in buffered saline (pH 7.4). All anti-asthma medications were withheld for at least 12 hours before measurement. The subjects inhaled aerosol from a nebulizer (DeVilbiss 646; DeVilbiss, Somerset, PA, USA; 5 L/min) by tidal breathing for 2 min. Isotonic saline was inhaled first to obtain a baseline measurement. Histamine dihydrochloride at increasing concentrations was then inhaled until FEV1 decreased by >20% of its post-saline solution value or until the maximum concentration was reached. Bronchial sensitivity was defined as the provocative concentration (PC) of the agonist leading to a decrease in FEV1 by >20% (PC20). Subjects with HisPC20 of <10 mg/ml were defined as being positive for airway hyperresponsiveness. HisPC20 of more than 2000 μg/ml was considered to indicate a more than moderate sensitivity, as determined from the severity classification based on methacholine bronchial hypersensitivity (MchPC20) reported by Woolcock *et al*..[9]

STATISTICAL ANALYSES

The subjects were divided into two groups (postbrochochodilator FEV1/FVC(%) <80% and ≥80%). Moreover, we classified the subjects on the basis of their showing reversibility of airway obstruction or not. The reversibility of airway obstruction is defined as an FEV1 increase of more than 12% and 200 ml in comparison with the prebronchodilator FEV1 on the basis of the criteria of American Thoracic Society.[10] We used the Mann-Whitney U test and $\chi 2$ test to determine statistically significant differences. Multiple logistic regression analysis was used to determine the association between outcome variables and variables found to be statistically significant by univariate analysis. We performed multiple logistic regression analysis for each outcome variable to estimate the adjusted odds ratios (ORs) for gender, history of childhood asthma, smoking history, serum IgE level, and HisPC20. Adjusted ORs and the corresponding 95% confidence intervals (95% CIs) were calculated.

Analyses were conducted using SPSS 11.0 for Windows (IBM Japan, Tokyo, Japan). $p < 0.05$ was considered statistically significant.

RESULTS

CHARACTERISTICS OF SUBJECTS

The characteristics of all the enrolled subjects and the results of pulmonary function tests are shown in Table 1. One hundred thirty-eight subjects (mean age, 25.6 years; 51 males, 87 females; current smoking, 30.4%; history of childhood asthma, 48.6%) were enrolled.

Table 1 The characteristics of the subjects in the classification based on postbronchodilator FEV1/FVC

n	138
Male/Female	51/87
Age (years)	25.6 (25.1-26.1)
Current smoking (%)	30.4
Pet ownership (%)	51.4
History of childhood asthma (%)	48.6
Onset of asthma (years)	15.2 (13.5-16.9)
Blood IgE level (IU/ml)	1362 (631-2094)
Blood eosinophil count (%)	6.6 (5.8-7.4)
FEV1 (L)	2.94 (2.83-3.04)
FEV1 (%, predicted)	89.5 (87.2-91.8)
FEV1/FVC (%)	81.3 (79.7-82.9)
Improvement rate of postbronchodilator FEV1 (ml)	199 (154-243)
Improvement rate of postbronchodilator FEV1 (%, predicted)	7.2 (5.6-8.9)
logHisPC$_{20}$	3.11 (3.03-3.20)

Date are presented mean difference (95% CI) or percentage of patients or number.

EXAMINATION OF PERSISTENT AIRWAY OBSTRUCTION

The features of the groups of postbronchodilator FEV1/FVC (%) <80% and ≥80% groups are shown in Table 2. Among the subjects, 18.8% (26/138) showed persistent airway obstruction. There were no significant differences in mean age and the percentage of pet ownership between the two groups. Moreover, there were no significant differences in laboratory examination results on common allergens and blood eosinophil count. We found significant differences in current smoking ($p = 0.042$), history of childhood asthma ($p < 0.001$), age at onset of asthma ($p < 0.001$), blood IgE level ($p = 0.005$), and logHisPC$_{20}$ ($p = 0.044$) in univariate analysis. In the multiple logistic regression model, history of childhood asthma, and smoking history were the significant isolated risk factors for persistent airway obstruction (Table 3).

REVERSIBILITY OF AIRWAY OBSTRUCTION

The features of the two groups of subjects classified on the basis of their showing the reversibility of airway obstruction or not are shown Table 4. The subjects were divided into two groups (increase FEV1 ≥12% and 200 ml group and increase FEV1 <12% or 200 ml group). Among the subjects, 23.9% (33/138) showed reversibility of airway obstruction. There

Table 2 The classification based on postbronchodilator FEV1/FVC

	Postbronchodilator FEV1/FVC <80%	Postbronchodilator FEV1/FVC ≥80%	*P*-value
n	26	112	-
Postbronchodilator FEV1/FVC (%)	71.5 (68.6-74.5)	88.8 (87.9-89.8)	-
Postbronchodilator FEV1 (%, predicted)	78.2 (71.8-84.7)	100.1 (97.6-102.7)	-
Improvement rate of postbronchodilator FEV1 (%)	12.9 (7.8-18.0)	5.9 (4.4-7.4)	<0.001
Gender · male (%)	57.7	32.1	0.015
Age (years)	26.5 (25.2-27.7)	25.4 (24.9-26.0)	0.123
Current smoking (%)	46.2	26.8	0.042
Pet ownership (%)	50.0	51.8	0.870
History of childhood asthma (%)	76.9	38.4	<0.001
Onset of asthma (years)	9.1 (5.5-12.9)	16.6 (14.8-18.4)	<0.001
Blood IgE level (IU/ml)	3270 (160-6379)	865 (529-1202)	0.005
RAST house dust mite (%)	80.0	84.0	0.693
fungus (%)	12.5	7.2	0.384
pet (%)	25.0	21.2	0.579
Blood Eosinophil count (%)	7.8 (6.0-9.7)	6.4 (5.5-7.2)	0.156
Prebronchodilator FEV1 (L)	2.65 (2.42-2.87)	3.00 (2.89-3.11)	0.007
Prebronchodilator FEV1 (%, predicted)	73.7 (69.2-73.6)	93.2 (91.0-95.3)	<0.001
Prebronchodilator FEV1/FVC (%)	70.1 (66.6-78.2)	83.9 (82.5-85.3)	<0.001
logHisPC20	2.93 (2.70-3.16)	3.16 (3.06-3.25)	0.044

Date are presented mean difference (95% CI) or percentage of patients or number.

Table 3 In the multiple logistic regression model in the postbronchodilator FEV1/FVC

	Persistent Air Flow Limitation (postbronchodilater FEV1/FVC (%) <80%) Odds ratio (95% CI)
Gender (male)	1.49 (0.57-3.92)
History of childhood asthma	2.74 (1.02-7.31)
Current smoking	3.72 (1.21-11.45)
Blood IgE (every level be elevated 10 times)	1.67 (0.77-3.63)
$HisPC_{20}$ (<2000 μg/ml)	1.00 (0.39-2.55)

Table 5 In the multiple logistic regression model the bronchodilator change in FEV1

	The low bronchodilator change (Increase FEV1 ≥12% or 200 ml) Odds ratio (95% CI)
History of childhood asthma	3.49 (1.36-8.95)
Blood Eosinophil count (>6%)	1.41 (0.61-3.28)
$HisPC_{20}$ (<2000 μg/ml)	2.20 (0.82-5.90)

Table 4 The classification based on the increase FEV1 in comparison with the pre-bronchodilator FEV1

	Increase FEV1 ≥12% and 200 ml	Increase FEV1 <12% or 200 ml	*P*-value
n	33	105	
Postbronchodilator FEV1/FVC (%)	81.7 (78.7-84.6)	86.8 (85.1-88.5)	<0.001
Postbronchodilator FEV1 (%, predicted)	94.1 (85.9-102.3)	96.8 (94.1-99.6)	0.022
Improvement rate of postbronchodilator FEV1 (%)	20.6 (17.5-23.7)	3.0 (2.0-4.0)	<0.001
Improvement rate of postbronchodilator FEV1 (ml)	530 (442-620)	93 (62-124)	<0.001
Gender · male (%)	48.5	33.3	0.117
Age (years)	26.4 (24.5-27.5)	25.4 (24.8-26.0)	0.094
Current smoking (%)	24.2	32.4	0.377
Pet ownership (%)	30.3	53.3	0.431
History of childhood asthma (%)	75.8	40.0	<0.001
Onset of asthma (years)	9.8(6.4-13.2)	16.9 (15.0-18.8)	<0.001
Blood IgE level (IU/ml)	1846 (606-3087)	1210 (314-2107)	0.086
Blood Eosinophil count (%)	8.3 (6.4-10.3)	6.1 (5.2-7.0)	0.027
Prebronchodilator FEV1 (L)	2.67 (2.48-2.86)	3.02 (2.90-3.14)	0.010
Prebronchodilator FEV1 (%, predicted)	77.9 (74.5-81.4)	93.1 (90.6-95.6)	<0.001
Prebronchodilator FEV1/FVC (%)	72.0 (69.0-74.9)	84.3 (82.7-85.8)	<0.001
logHisPC20	2.90 (2.69-3.10)	3.18 (3.09-3.28)	0.009

Date are presented mean difference (95% CI) or percentage of patients or number.

were no significant differences in the mean age, the percentage of pet ownership and the percentage of subjects currently smoking between the two groups. By univariate analysis, we found significant differences in history of childhood asthma ($p < 0.001$), age at onset of asthma ($p < 0.001$), blood eosinophil count ($p = 0.027$), and $logHisPC_{20}$ ($p = 0.009$). In the multiple logistic regression model, history of childhood asthma was the significant isolated factors for reversibility of airway obstruction (Table 5).

DISCUSSION

We examined persistent airway obstruction on the basis of changes in postbronchodilator FEV1/FVC. The response to a bronchodilator is the simplest test for assessing airway obstruction. It was surprising that persistent airway obstruction conventionally found in patients with severe asthma was also found in patients with mild asthma symptoms. It was suggested that persistent airway obstruction is associated with history of childhood asthma and current smoking in this examination. It was reported by Rasmussen *et al*. that a low postbronchodilator FEV1/VC ratio was related to childhood asthma, male sex, airway hyperresponsiveness and low lung function in childhood.[4] These findings were compatible with those of our study.

Smoking is responsible for the development and persistence of airway inflammation. Acute exposure to cigarette smoke triggers bronchoconstriction and symptoms in people with asthma.[11,12] Even nonsmoking patients with asthma may have significant exposure to passive smoke. Compared with nonsmokers with asthma, smokers with asthma have more severe symptoms,[13,14] increased rates of hospitalization[15] and accelerated decline in lung function.[16,17] Particularly high rates of adults presenting with acute asthma have been noted to hospital emergency de-

partments.[15] It was considered that smoking is implicated in airway damage and contributes to airway remodeling.[18,19]

Among patients with mild subjective symptoms, 23.9% showed reversibility of airway obstruction in our study. It has been reported that 25% of bronchial asthma patients in early stages showed an FEV1 increase of more than 12% in comparison with the pre-bronchodilator FEV1 in the reversibility test of airway obstruction and that 23% of moderate to severe asthma patients exhibited an incomplete reversibility of airway obstruction.[20,21] However, the exact prevalence of airway obstruction is unclear. In our study, history of childhood asthma, blood eosinophilia count and the increase in airway hyperresponsiveness were associated with having the irreversibility of airway obstruction in asthma patients without subjective symptoms. The severity of airway hyperresponsiveness has been shown to be an independent predictor of annual decline in lung function in general population.[22] Moreover, it is reported that there is a positive correlation between airway hyperresponsiveness and the rate of decrease in FEV1 in mild to moderate asthma.[23] In another study, the only independent factor associated with persistent airflow limitation was found to be sputum eosinophilia.[24] Irreversible airway obstruction was associated with increased disease severity and increased asthma-related morbidity and mortality.[25] In our study, history of childhood asthma was associated with having the reversibility of airway obstruction in asthma patients without subjective symptoms. It is possible for asthma patients having the reversibility of airway obstruction to improve FEV1 by treatment for asthma. The bronchodilator change tests in FEV1 may be worth in patients having history of childhood asthma. We consider that the reversibility of airway obstruction using bronchodilator is useful to find residual airway inflammation and structural change in asthma patients.

It is reported that most former asthma patients who were considered to be in asthma remission showed a persistent increase in airway responsiveness with or without airflow obstruction, and subjective symptoms may be insufficient to determine true remission.[26] It is difficult to determine true remission of childhood asthma. Persistent airway obstruction was associated with history of childhood asthma in this study. It is possible that airway inflammation has not disappeared completely in patients with history of childhood asthma. In our study as well as 18.8% of patients with mild subjective symptoms showed a low postbronchodilator FEV1/VC. It is difficult to determined asthma severity on the basis of only subjective symptoms. Early detection of persistent airway obstruction, particularly in asthma patients with mild symptoms, leads to adequate therapies in the earlier stages. In this study, patients not undergoing treatment for asthma were examined. These patients may regain their post-bronchodilator FEV1/FVC ≥80% after anti-inflammatory treatment of asthma. History of childhood asthma and smoking history may be the risk factors for persistent airway obstruction in the asthma patients with mild subjective symptoms. The later progress needs the investigation again.

History of childhood asthma and smoking history may be the risk factors of persistent airway obstruction in the asthma patients with mild subjective symptoms. Tests on the bronchodilator change in FEV1 should be performed in patients with history of childhood asthma and smoking history, even if they have only mild subjective symptoms.

Our study has limitations. First, this study design was a complete survey in our hospital but was not a prospective study. It will be necessary to investigate prospectively in the future. Second, we limited our subjects to young adults with asthma because we wanted to examine our hypothesis without the effects of underlying diseases, aging, long-term smoking, and long-term medication. This theme should be investigated in all age groups in the future. Third, we were also unable to examine sputum eosinophil count and histopathological findings, which were reported to be superior for the monitoring of airway inflammation. We need to perform these measurements in the future.

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