

COMORBIDITIES

Impact of Schizophyllum sensitization on decline of lung function in asthmaHaruhiko Ogawa¹, Masaki Fujimura², Yasuo Takeuchi³, and Koichi Makimura^{4*}

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Abstract

Objective: There is increasing interest in the association between the severity of asthma and fungal sensitization, and lung function decline in relation to mold and dampness in the home has recently been reported. This study was performed to determine the correlation between sensitization to *Schizophyllum commune* and decline of lung function, and to elucidate the outcomes and risk factors, especially from *Schizophyllum* allergy. **Methods:** The medical records of 50 patients with asthma who satisfied the following inclusion criteria were collected and reviewed retrospectively: (1) at least 5 years of follow-up with five evaluations; (2) intradermal skin tests including *S. commune* performed at the initial assessment; and (3) severity ranging from mild-to-moderate. Lung function decline (evaluated as adjusted delta FEV1/year) was compared in a cross-sectional manner with regard to gender, age, BMI, smoking habit, allergological characteristics and exacerbation frequency. **Results and Conclusions:** There were significant differences in lung function decline between females and males ($p < 0.05$), positive and negative results of late-phase skin reaction to *S. commune* ($p < 0.001$), and positive and negative late-phase skin reaction to *Aspergillus* ($p < 0.05$). Lung function decline was correlated with exacerbation frequency ($r = 0.428$, $p = 0.002$). On multiple regression analysis, the probability of lung function decline in asthma was found to be significantly associated with female gender and positive late-phase skin reaction against *S. commune*. Our results suggested that sensitization to *S. commune* may be one of the risk factors involved in lung function decline in asthmatic patients.

Keywords

Basidiomycetous fungus, decline of lung function in asthma, exacerbation frequency, fungal sensitization, *schizophyllum commune*

History

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Introduction

It is important to assess the etiological and exacerbating agents as future risk factors in both achieving and maintaining asthma control [1]. Rapid decline in lung function is emphasized in the Global Initiative for Asthma guidelines (GINA) 2011 as an important future risk factor. In particular, there is increasing interest in the association between severe asthma and fungal sensitization [2], and lung function decline in relation to mold and dampness in the home has recently been reported [3].

Schizophyllum commune is a basidiomycetous (BM) fungus that can cause allergic bronchopulmonary mycosis (ABPM) [4]. Our recent studies suggested that *S. commune* is

an important causative fungal antigen [5] and an aggravating factor of bronchial asthma [6]. Therefore, this BM fungus may be a candidate organism influencing the clinical manifestations of asthma via sensitization to this fungus, similar to *Aspergillus* [7]. Multivariate analysis demonstrated that sensitization to *S. commune* is correlated with both asthma severity and exacerbation frequency [6], and it has therefore become important to determine the correlation between sensitization to *S. commune* and decline of lung function. The present study was performed to elucidate the outcomes and risk factors, especially related to *Schizophyllum* allergy [8], for decline in forced expiratory volume in 1 s (FEV1) in patients with well-controlled, stable asthma.

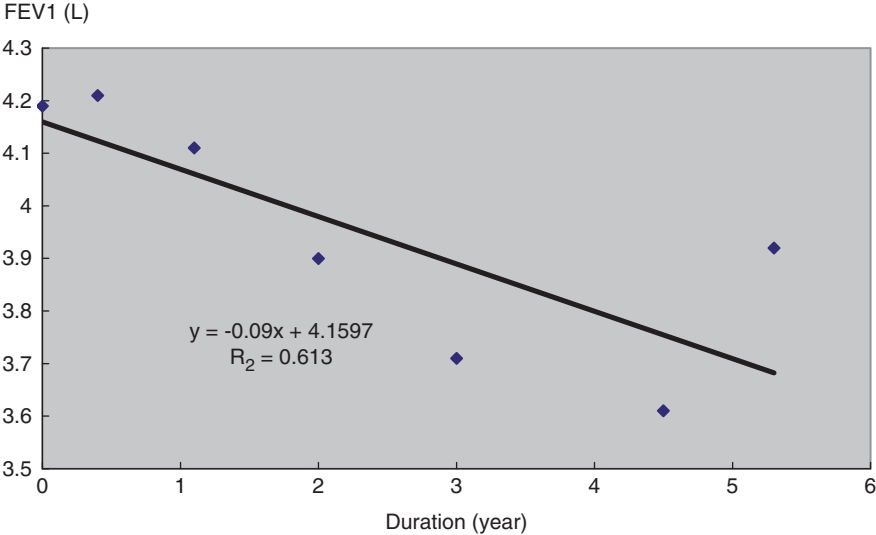
Methods**Subjects**

The medical records of 50 patients with asthma who satisfied the following inclusion criteria were collected and reviewed retrospectively: (1) at least 5 years of follow-up with five evaluations; (2) intradermal skin tests, including *S. commune*, performed at the initial assessment; and (3) asthma severity

*Dr. Ogawa, Dr. Takeuchi, and Dr. Makimura all belong to Fungus association cough research society. Especially Dr. Makimura contributed to identifying fungi. Dr. Fujimura is a general conductor of this study.

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Figure 1. An example for calculating the rate of decline in postbronchodilator forced expiratory volume in 1 second (Δ FEV1/year) in a subject. We used single regression analysis to calculate the annual decline in postbronchodilator FEV1 in each subject. $Y = 4.160 - 0.09 \times X$; $R^2 = 0.61$; (Δ FEV1/year = -0.09 L/year).



ranging from mild-to-moderate (classified in accordance with GINA).

The following information was collected from the medical records of all of the patients: name, date of birth, gender, BMI, smoking habit, and the results of examinations such as blood tests, chest radiography and postbronchodilator FEV1. In addition, allergic status was determined by allergological tests such as intradermal skin tests and serological tests.

Lung function decline (evaluated as adjusted delta FEV1/year [9]) was compared in a cross-sectional manner with regard to gender, age, BMI, smoking habit, allergological characteristics and exacerbation frequency.

This retrospective study was approved by the Institutional Review Board (reference number 2011002).

Rate of lung function decline evaluated as adjusted delta FEV1/year

The rate of decline in postbronchodilator FEV1 (delta FEV1 ml/year) of each subject was calculated and then adjusted with his/her predictive FEV1 (adjusted delta FEV1/year) [9]. We used single regression analysis to calculate the annual decline in postbronchodilator FEV1 in each subject (Figure 1). Postbronchodilator FEV1 was measured using a computerized spirometer (Chestac-9800; Chest Co., Tokyo, Japan) 30 min after inhalation of 300 µg of salbutamol sulfate.

Results

The clinical records of the 50 asthmatic subjects were analyzed. The mean observation period was 5.4 ± 0.9 years. The characteristics of all of the asthmatic patients were as follows (Table 1): Age = 55.1 ± 14.0 year, BMI = 25.0 ± 5.1 kg/m², Duration of asthma = 2.9 ± 2.4 years, Total IgE = 378.2 ± 596.8 IU/ml, %FVC = 113.6 ± 20.0, %FEV1 = 95.7 ± 19.5, FEV1/FVC % = 80.6 ± 16.5. There were only four current smokers in this study. The rate of positive colonization by *A. fumigatus* in the patients with positive results for specific-IgE against *A. fumigatus* was 35.7%, while that in patients with negative results was 27.8%. The rate of positive results of colonization or skin reactions against *A. fumigatus* did not differ between the two groups.

Table 1. Characteristics of the 50 patients with asthma at the initial assessment.

Male/female	26/24
Age (years)	55.1 ± 14.0
BMI (kg/m ²)	25.0 ± 5.1
Duration of asthma (years)	2.9 ± 2.4
Smoking (never/former/current)	(40/6/4)
Controllers	
Dose of ICS (400/800/1600 µg/day*)	(17/32/1)
LABA (±)	(20/30)
LTRA (±)	(45/5)
SRT (±)	(7/43)
Pulmonary function tests	
FVC (% predictive)	113.6 ± 20.0
FEV1(% predictive)	95.7 ± 19.5
FEV1/FVC ratio (%)	80.6 ± 16.5

All data are expressed as mean ± SEM
FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity;
ICS = inhaled corticosteroid; LABA = long-acting β2 agonist;
LTRA = leukotriene receptor antagonist; SRT = slow-release theophylline
*Beclomethasone dipropionate equivalent

Fungal cultures for BM fungi were obtained from the sputum of 17 asthmatics (34.0%); however, no sputum samples yielded *S. commune*. The positive ratio for colonization by BM fungi did not differ significantly between groups divided according to the positive results of allergological tests, such as immediate or late-phase skin reactions.

To exclude the effects of smoking on lung function decline, the data of four current smokers were excluded from the statistical analysis. The mean delta FEV1/year was -27.3 ± 31.0 ml/year and adjusted delta FEV1/year was -0.011 ± 0.014/year. There were significant differences in lung function decline (evaluated as adjusted delta FEV1/year) between females (-0.016 ± 0.017/year) and males (-0.007 ± 0.008/year) ($p < 0.05$), positive (-0.020 ± 0.014/year) and negative (-0.007 ± 0.011/year) results of late-phase skin reaction to *S. commune* ($p < 0.01$), and positive (-0.022 ± 0.018/year) and negative (-0.010 ± 0.013/year) late-phase skin reaction to *Aspergillus* ($p < 0.05$). There were no significant differences in lung function decline between positive and negative results of culture sputum, or presence and lack of comorbidity (allergic rhinitis,

Table 2. Results of multiple regression analysis.

Variables	B	95%CI		Standardized Coefficients β	p Value
gender (female)	0.007	0	0.014	0.264	$p < 0.05$
Positive late-phase skin reaction against <i>Schizophyllum commune</i>	0.008	0.000	0.016	0.287	$p < 0.05$
Positive late-phase skin reaction against <i>Aspergillus fumigatus</i>	0.007	–0.003	0.018	0.172	NS
Exacerbation frequency	0.001	0	0.002	0.193	NS

Table 3. Characteristics of asthmatic patients according to the results of late-phase skin reaction to *Schizophyllum commune*.

	Positive group (n = 16)	Negative group (n = 30)	p Value
Gender (male/female)	(6/10)	(16/14)	NS
Age (year)	54.6 ± 11.2	53.8 ± 15.2	NS
BMI	24.5 ± 4.5	24.8 ± 5.5	NS
Duration of asthma (years)	2.8 ± 2.6	2.7 ± 2.2	NS
Dose of ICS (400/800/1600 µg/day*)	(10/6/0)	(11/19/0)	NS
LABA/LTRA/SRT	(8/15/4)	(10/26/2)	NS
IgE (IU/ml)	385.3 ± 535.0	329.9 ± 645.3	NS
%FVC	113.7 ± 15.7	115.1 ± 21.2	NS
%FEV1	96.2 ± 20.6	95.6 ± 18.0	NS
FEV1%	76.1 ± 12.1	82.0 ± 20.4	NS
Bronchial reversibility (%)	6.9 ± 7.8	5.6 ± 5.2	NS
Exacerbation frequency (times)	3.4 ± 3.7	0.6 ± 1.0	$p < 0.05$
Decline of lung function in FEV1 (ml)	47.2 ± 28.3	19.4 ± 28.6	$p = 0.001$
Adjusted decline of lung function	0.020 ± 0.014	0.007 ± 0.011	$p < 0.01$

All data are expressed as mean ± SEM

FEV1 = forced expiratory volume in 1 s;

FVC = forced vital capacity;

ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist;

LTRA = leukotriene receptor antagonist; SRT = slow-release theophylline

*Beclomethasone dipropionate equivalent

sinobronchial syndrome, and aspirin-induced asthma). Adjusted delta FEV1/year was correlated with exacerbation frequency ($r = 0.428$, $p = 0.002$), but showed no correlations with age, obesity, pulmonary function, of total IgE level.

Multiple regression analysis was performed including gender, positive results of late-phase skin reaction against *S. commune* or exacerbation frequency and the probability of lung function decline in asthma was found to be significantly associated with female gender and positive late-phase skin reaction against *S. commune* (Table 2).

The characteristics of the asthmatic patients according to sensitization to *S. commune* are shown in Table 3. There were no significant differences in drug therapy for asthma between the *Schizophyllum*-sensitized group and non-sensitized group. There were significant differences between the two groups in the degree of adjusted decline and exacerbation frequency.

Discussion

As there is evidence of a close link between severe asthma exacerbation and rapid decline in lung function [2,10,11], a rapid decline in lung function is an important issue in the assessment of future risk in asthma control. In the present study, the influences of various factors on the acceleration in the decline of FEV1 in asthmatic patients were investigated. In this study, there were no significant correlations between age, BMI [12], comorbidity of asthmatics, such as allergic rhinitis and/or sino-bronchial syndrome [9], and lung function decline.

Several epidemiological studies have documented sex-related differences in asthma prevalence, incidence, and hospitalization rates, and these differences changed considerably with age [13]. In the present study, a significant correlation was observed between gender and lung function decline. It has been reported that the prevalence of ABPM caused by *S. commune* is greater in women than in men [14]. However, gender showed no correlation with *Schizophyllum* sensitization.

Smoking is associated with accelerated decline of lung function [15] and is known to greatly increase the morbidity and mortality rates associated with asthma. In the present study, the number of current smoking asthmatic patients was too small to allow analysis of the effects of cigarette smoking on lung function decline in asthmatics.

Detection of *A. fumigatus* in sputum was reported to be associated with *A. fumigatus*-IgE sensitization, neutrophilic airway inflammation, and reduced lung function [16]. Although the development of fixed airflow obstruction in asthma is believed to be due to the damaging effects of airway colonization with filamentous fungi, including *A. fumigatus* [17], Benghida et al. [18] reported that sensitization to *Aspergillus* does not have a deleterious effect on the decline in respiratory function in asthmatics. Our data indicated that lung function decline was significantly correlated with positive results not of immediate-phase but of late-phase skin reaction against *A. fumigatus*.

BM fungi were reported to be frequently obtained from the sputum samples of chronic idiopathic cough patients [19]. In

the present study the fungi were also detected from asthmatic patients, but none yielded *S. commune* in sputum cultures. Thus, our results suggested that the colonization by *S. commune* is not necessary in the process of sensitization to this fungus in asthmatics [20]. Various fungal components, such as conidia, spores, hyphae, fragments hyphae, cell wall constituents and voltaic organic compounds, may act as antigens in fungal sensitization [2].

Exacerbations of asthma are considered as multicomponent events associated with an increased risk of future exacerbations and accelerated decline in lung function [21]. Exacerbations, indicating intermittent periods of worsening airway inflammation, were reported to be associated with marked lung function decline in asthma [22]. Our data demonstrated that lung function decline is significantly correlated with the frequency but not the severity of exacerbation. As a positive result of late skin reaction to *S. commune* has been shown to also be correlated with exacerbation frequency, it has been demonstrated that sensitization to this fungus is correlated with lung function decline directly or indirectly via exacerbation frequency.

In the present study, positive specific IgE responses and immediate skin reactions to *Alternaria*, *Cladosporium*, *Trichophyton* [11] or *Aspergillus* were not associated with lung function decline. However, these results did not entirely exclude the roles of these fungi in the decline of lung function. Historically, fungal sensitization has been defined on the basis of positive specific IgE responses and immediate skin reactions, regardless of whether fungal culture is positive or not [2]. It is remarkable that the factors correlated with lung function decline were positive results of late-phase skin reaction to *Aspergillus* and *S. commune*, which were not previously thought to be of concern as the basis of fungal sensitization. In considering fungal sensitization with asthma, allergic reactions such as lymphocyte reactions that occur after type-I allergic reactions should be taken into consideration.

Although we compared the *Schizophyllum*-sensitized group and non-sensitized group, we found no differences in clinical manifestations other than the degree of adjusted decline and exacerbation frequency. Multiple regression analysis demonstrated that the probability of lung function decline in asthma was significantly associated with female gender and positive results of late-phase skin reaction against *S. commune*.

Conclusions/key findings

Our series of studies demonstrated that sensitization to *S. commune* [23] is one of the important future risks of asthmatic patients with regard to both exacerbation frequency and rapid decline in lung function. It was suggested that *S. commune*-sensitization may be related to risk in asthma control. Further studies with regard to *Schizophyllum* allergy [8] may be helpful for clarifying the potential mechanisms of lung function decline in asthmatic patients.

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Declaration of interest

All authors declare that they have no competing interests that might be perceived to influence the results and discussion reported in the present manuscript. This study was supported in part by a grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (23591142).

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