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Original article

Characteristics of phenotypes of elderly patients with asthma

Hiroyuki Sano*, Takashi Iwanaga, Osamu Nishiyama, Akiko Sano, Yuji Higashimoto, Katsuyuki Tomita, Yuji Tohda

Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine, Osaka, Japan

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Abbreviations:
ACOS, asthma-COPD overlap syndrome; AHR, Airway hyperresponsiveness; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity of the lung for carbon monoxide; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in one second; HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids; LABA, long-acting $beta_2$-bronchodilator agonists; LAMA, long-acting muscarinic antagonists; OAD, asthma-obstructive airway disease; PC_{20}, provocative concentration that causes a positive reaction to a 20% fall in FEV_1; ROC, receiver operating characteristic

ABSTRACT

Background: The characteristics of phenotypes of elderly patients with asthma are unknown. The aim of this study was to classify these phenotypes using lung function tests and images from high-resolution computed tomography (HRCT), and to identify associations between clinical characteristics and phenotypes.

Methods: A cross-sectional study was conducted in 165 elderly patients (>65 years of age) who underwent a multidimensional assessment of clinical and functional status and comorbidity. The patients were divided into three phenotypes: (1) asthma-predominant, (2) asthma-obstructive airway disease (OAD) overlap without emphysema, and (3) asthma-OAD overlap with emphysema (asthma-emphysema overlap) based on chest HRCT. A receiver operating characteristic (ROC) curve was constructed to evaluate the cutoff for differentiating between the two OAD phenotypes. Multivariate analysis was also used to distinguish between these two phenotypes.

Results: The phenotypes were asthma-predominant in 48 patients (29%), asthma-OAD without emphysema in 36 (22%), and asthma-emphysema in 81 (49%). Patients with asthma-emphysema were more frequent smokers. In multivariate analysis, smoking status (odds ratio 2.92: 95% CI 1.21–7.00, $P = 0.03$) and % predicted $FEV_1 \leq 70\%$ (odds ratio 3.18: 95% CI 1.13–8.92, $P = 0.03$) differed significantly between the asthma-emphysema and asthma-OAD without emphysema phenotypes.

Conclusions: Half of elderly patients with asthma are characterized by asthma-emphysema overlap. Our results showed that elderly patients with asthma who are smokers and have moderate or severe OAD are also likely to have emphysema.

Introduction

Asthma is an allergic disease that commonly develops at a young age, is characterized physiologically by reversible airflow obstruction, and responds well to anti-inflammatory treatment. In contrast, chronic obstructive pulmonary disease (COPD) is characterized by incomplete reversible airflow limitation, is typically caused by tobacco smoking, and develops at an old age. There is a considerable pathologic and functional overlap between these two heterogeneous disorders, particularly among the elderly, who may have components of both diseases. This condition is referred to as asthma-COPD overlap syndrome (ACOS), in which asthma and COPD are at the opposite ends of the disease spectrum.[1,2] ACOS is defined as a post-bronchodilator ratio of forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7 in current international guidelines.

The number of older people with asthma is likely to rise due to the worldwide population trend for longevity and the disproportionate increase in people aged 65 years and older.[3] This is a concern because mortality in older people with asthma is higher

* Corresponding author. Department of Respiratory Medicine and Allergology, Kinki University School of Medicine, 377-2 Ohnohigashi, Osaka-Sayama, Osaka 589-8511, Japan.
E-mail address: hsano@med.kindai.ac.jp (H. Sano).
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than that in young adults.[4] Airway hyperresponsiveness (AHR) and a diagnosis of asthma are associated with a greater decline in FEV_1 in both smokers and nonsmokers[5,6] and asthma is a risk factor for chronic COPD.[7] However, the characteristic features of worsening asthma control in elderly patients are not well understood.[8] Also, since irreversible obstructive airway disease (OAD) often coexists with asthma in elderly patients, the presence of accompanying emphysema requires evaluation by diffusion capacity or computed tomography (CT) of the lung.[9] Therefore, the aims of this study were to define phenotypic subgroups of asthma and determine the proportion of elderly patients aged >65 years in each group, and to characterizes the clinical features of these phenotypes based on lung function and chest CT findings.

Methods

Subjects

A single-center cross-sectional study was conducted in the outpatient department at Kinki University Hospital between October 2011 and September 2012. The subjects were 170 patients with asthma aged ≥65 years old who were recruited from the Department of Respiratory Medicine and Allergology. Diagnoses of asthma and COPD were made by the subjects' physician consistent with the definitions for these diseases in the Global Initiative for Asthma[10] and the Global Initiative for Chronic Obstructive Lung Disease[11] guidelines, respectively. All subjects were assessed at visits in which the disease had been stable for at least 8 weeks since exacerbation, which was defined as an increase in symptoms necessitating a course of oral corticosteroids and/or antibiotic therapy. All subjects provided written informed consent and the study was approved by the Kinki University Hospital ethics committee.

Objective and procedures

To identify the clinical characteristics of comorbidity of COPD in elderly patients with asthma, the subjects were divided into three phenotypes: asthma-predominant, based on the absence of airflow obstruction; asthma-OAD overlap, defined as irreversible airway obstruction without emphysema on chest high-resolution CT (HRCT); and asthma-emphysema overlap, a combination of airflow obstruction and emphysema.

Measurements

Physicians interviewed each patient to establish details of medical history, family history, smoking history and respiratory symptoms based on questionnaires. Subjects were defined as never, former or current smokers of tobacco (cigarettes, cigars or pipes). Cumulative cigarette consumption was calculated in pack-years, with 1 pack-year equivalent to 20 cigarettes per day for 1 year.

Blood samples

Blood was collected for measurement of total serum IgE and complete blood count. Total and specific IgE were measured with a third-generation chemiluminescent enzyme immunoassay (Immulite 2000; Siemens Medical, Deerfield, IL, USA). Atopy was defined as any specific IgE to common allergen >0.35 kU/L.

Pulmonary function tests

Spirometry was performed with a portable spirometer (Minato, Tokyo, Japan) according to American Thoracic Society (ATS) criteria.[12] FEV_1 and FVC were measured and FEV_1 was used to evaluate airway obstruction. After several practice measurements with a trained technician, measurements for data collection were taken three times. The greatest FEV_1 from acceptable tests for each subject was selected. The subjects were instructed to take complete inspirations and expirations that lasted approximately 3 s.[13] Reversibility of the reduction in FEV_1 was measured 15 min after inhalation of 20 μg procaterol.

AHR is expressed as the methacholine concentration that caused a 20% decrease in FEV_1 from baseline (PC_{20}). The test was administered at least 8 h after the last dose of short-acting bronchodilators and 24 h after inhaled corticosteroids (ICS) or long-acting bronchodilators.

The diffusion capacity of the lung for carbon monoxide (DLCO) was determined using the single-breath method. Alveolar volume (VA) was measured during the single-breath maneuver using helium as the inert gas. A % predicted DLCO ≤80% indicates emphysema of the lung. ATS guidelines were followed for all lung function tests.[14]

Fraction of exhaled nitric oxide (FeNO)

FeNO was measured online by NOA280i (Severs, GE Analytical Instruments, Boulder, CO, USA) at a constant expiratory flow rate (50 mL/s) before any forced expiratory maneuvers, consistent with published guidelines.[15] All readings were obtained by technical staff.

High-resolution computed tomography (HRCT)

The severity of radiological emphysema on chest HRCT (2-mm sections at 15-mm intervals) was visually assessed by three independent pulmonologists using the Goddard scoring system.[16] Six images of three lung slices (the right and left lungs were evaluated separately) were analyzed for each patient. Each image was classified and scored as normal (score 0), ≤5% affected (score 0.5), ≤25% affected (score 1), ≤50% affected (score 2), ≤75% affected (score 3) and >75% affected (score 4). The mean score of the six images was taken as representative of the severity of emphysema. Each image was then classified as normal (score 0), very mild (>0 to ≤0.5), mild (>0.5 to ≤1), moderate (>1 to ≤2), and (E) severe (>2).

Emphysema was diagnosed as airway obstruction on a pulmonary function test (FEV_1/FVC <0.7) and the presence of emphysema on a chest image (emphysema score >0).

Statistical analysis

Differences in continuous variables between groups were analyzed by Kruskal–Wallis test followed by post hoc analysis by Dunn test. For categorical variables, a χ^2 test (or Fisher exact test for small proportions) was used, $P < 0.05$ was considered significant. A receiver operating characteristics (ROC) curve was constructed to evaluate the best cutoff for differentiating asthma-emphysema overlap from asthma-OAD overlap. Multivariate logistic regression analysis was used to distinguish asthma-emphysema from asthma-OAD without emphysema, with the results reported as the odds ratio (OR) with a 95% confidence interval (CI). All analyses were performed using SPSS ver. 19.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics

Of the 170 elderly patients with asthma enrolled in the study, we excluded five patients due to an absence of lung function tests or HRCT, leaving 165 patients in the analysis. The demographic and clinical features of the study population are shown in Table 1. There were 92 males (54.1%), the average age was 73.8 ± 5.4 years old, and 89 patients (52.4%) had a smoking history, including 47% with >10 pack-years. An atopic disposition was present in 76 patients and the