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Persistent airflow obstruction in patients with asthma: Characteristics of a distinct clinical phenotype☆

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ABSTRACT

Background: Some patients with asthma present persistent airflow limitation but their clinical and inflammatory characteristics have not been extensively described. In this study we aimed to identify differences in the clinical, functional and inflammatory characteristics between patients with asthma with and without persistent airflow obstruction.

Methods: Patients (n = 170) were consecutively recruited from two tertiary Asthma Clinics. Patients' demographics, pulmonary function tests, inflammatory cells in induced sputum, bronchial hyperresponsiveness (BHR, PD15 to methacholine) and treatment regimens were recorded.

Results: Sixty patients (35.3%) presented persistent airflow obstruction. Besides differences in lung function, patients with persistent obstruction presented, lower methacholine PD20, higher exhaled NO, and higher eosinophil and neutrophil counts in induced sputum. The majority (71.7%) of the patients with persistent obstruction fulfilled the ATS criteria for severe refractory asthma (SRA), in contrast to 4.5% in the group without persistent obstruction. A cluster analysis identified three clinically relevant clusters: Cluster 1 (n = 56, not related to persistent airflow obstruction) included non-atopic patients, who did not receive high-dose ICS without SRA; Cluster 2 (n = 53, related to persistent airflow obstruction) included atopic patients, receiving high-dose ICS and/or oral CS, fulfilling SRA criteria; Cluster 3 (n = 61, not related to persistent airflow obstruction) included atopic patients not receiving high-dose ICS, without SRA.

Conclusions: Asthma patients with persistent airflow obstruction present a distinct asthma phenotype, with significant differences in clinical, functional and inflammatory characteristics compared to patients without fixed airway obstruction. These patients present more often severe refractory asthma and require more intense treatment.

1. Introduction

Asthma is a clinical syndrome that is characterized by intermittent respiratory symptoms triggered by several stimuli, including viral infections and environmental allergens, and is associated with chronic airway inflammation and bronchial hyperresponsiveness [1]. Asthma, is a heterogeneous disorder which includes several different phenotypes characterized by differences in age of onset, aetiology, inflammatory profile and response to treatment [2], as well as different endotypes characterized by distinct functional or pathophysiological mechanisms [3]. In the previous years, distinct asthma phenotypes and

Abbreviation List: ANOVA, analysis of variance; ATS, American Thoracic Society; BHR, bronchial hyperresponsiveness; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; FeNO, fraction of exhaled nitric oxide; FVC, forced vital capacity; DLCO, diffusing capacity for carbon monoxide; FRC, functional residual capacity; GINA, global initiative for asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LTRA, leukotriene receptor antagonists; SRA, severe refractory asthma.

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endotypes have been described, yet their characterization is based on a limited number of features and no specific methods or biomarkers have been identified as useful in this process [4,5].

Most asthmatic patients have mild or moderate asthma and can be controlled with low doses of anti-inflammatory drugs. However, a small subgroup of patients present with uncontrolled asthma, frequent exacerbations and rapid decline of lung function, despite avoidance of trigger factors, proper management of comorbidities and use of high-dose anti-inflammatory treatment. For such patients the term severe refractory asthma has been used [6,7]. Moreover, some patients with asthma present persistent airflow limitation [8]. In a recent study, patients with severe asthma and persistent airflow obstruction were characterized by increased airway smooth muscle with ongoing TH1 and TH2 inflammatory responses, but these patients did not present specific characteristics on high-resolution computed tomographic scans or sputum analysis [8]. On the other hand, in severe asthma, more than 50% of the patients develop irreversible airway obstruction [9]. In terms of taxonomy, it is sometimes quite difficult to classify these patients properly, as the presence of persistent airflow obstruction may lead to a diagnosis of COPD, especially in smokers with characteristics of asthma and/or atopy [10,11]. From the clinicians' point of view it is important to identify these patients in order to optimize their treatment, and especially to avoid overtreatment based solely on pulmonary function tests.

The aim of the present study was to evaluate the differences in clinical, functional and inflammatory characteristics between asthmatic patients with and without persistent airflow obstruction. We further used cluster analysis in order to identify and characterize different asthma subtypes based on the presence of persistent airflow obstruction.

2. Methods

2.1. Study population

In this study we have recruited 170 consecutive adult patients from an on-going cohort of asthmatic patients who are followed up in the asthma clinics of the1st and 2nd Respiratory Medicine University Departments in Athens. The health system in Greece is based on the assessment by a specialist. The patients were followed up in a tertiary clinic as part of their regular follow-up. Demographic data, smoking status, body mass index (BMI) and type of treatment were recorded for all patients. Diagnosis of asthma was based on the GINA guidelines(1), and early onset asthma was defined as the presence of asthma symptoms before the age of twelve years [2]. All asthmatic subjects were optimally treated for at least 6 months according to GINA guidelines(1) and were adherent to therapy. The latest was checked through the national insurance system. Exclusion criteria were a diagnosis of other respiratory disease, concomitant malignancy and severe heart, liver, renal or collagen disease. Patients with a respiratory tract infection or an asthma exacerbation in the past 8 weeks prior to admission were also excluded. The study was approved by the ethics committees of the Attikon & Sotiria hospitals (approval number 1915, September 2010) and all subjects provided written informed consent.

2.2. Definition of persistent airflow obstruction and severe asthma

Patients were assigned to the group with persistent airflow obstruction if they presented post-bronchodilation FEV_1 values < 70% predicted at all visits, or a single value of post-bronchodilation FEV_1 between 70% and 75% predicted during a 1-year follow up [8]. A FEV_1/FVC ratio less than 75% was also a presupposition in order to define persistent airflow obstruction. All other subjects were considered to be able to achieve a normal or near normal FEV_1 and were classified to the group without persistent airflow obstruction [8]. Patients were characterized as having severe refractory asthma (SRA) according to the ATS workshop consensus [6].

2.3. Study measurements

2.3.1. Sputum induction and processing

Sputum induction was performed as previously described [12,13], using all the modifications for safe measurements according to the underlying asthma severity [14,15]. The process had a total duration of 15 min, where subjects inhaled 3% saline at room temperature by an ultrasonic nebulizer (DeVilbiss Co., Heston, UK). Sputum supernatant was removed with centrifugation and total cell count was evaluated with a haemocytometer using Trypan Blue stain. Slides were prepared by cytospin (Shandon, Runcorn, UK) and were stained with May-Grunwald and Giemsa for differential cell counts. A blind observer performed counting of a minimum 500 inflammatory cells in each sample. Sputum samples were considered acceptable if they had a volume of at least 2 ml after final expectoration and the percentage of squamous cells on the prepared slides was <10%. Total cell count was expressed as the number of cells $\times 10^6$/ml and sputum inflammatory cells as percentage (%) of non-squamous cells.

2.3.2. Lung function

Forced expiratory volume in 1 s FEV_1were measured using Master Screen Body (Viasys Healthcare, Jaeger, Hoechberg, Germany) according to the American Thoracic Society guidelines [16]. Bronchial hyperresponsiveness (BHR) was measured as PD_{20} to methacholine using a commercially available system (APS; Viasys Healthcare, Jaeger, Hoechberg, Germany) according to the ATS guidelines [17].

2.3.3. Measurement of exhaled nitric oxide

The fraction of exhaled NO (FeNO) was measured using a portable NO analyser (NIOX MINO, Aerocrine, Solna, Sweden) [18].

2.3.4. Characterization of atopic status

Atopic status was confirmed by a positive skin prick test to any of twenty common aeroallergens.

2.4. Statistical analysis

Categorical variables are presented as n (%), whereas numerical variables are presented as mean ± standard deviation (SD) or median (interquartile ranges) for normally distributed and skewed data, respectively. Normality of distributions was checked with Kolmogorov–Smirnov test. Comparisons between patients with fixed and non-fixed airway obstruction were performed using chi-square tests for categorical data, as well as unpaired t-tests or Mann–Whitney U-tests for normally distributed or skewed numerical data, respectively.

A two-step cluster analysis was performed in order to classify patients in asthma subtypes. Uniform cluster analysis methodology was applied to each population using a two-step approach as previously described [19]. In the first step, hierarchical cluster analysis using Ward's method generated a dendrogram for estimation of the number of likely clusters within the studied population. This estimate was prespecified in a k-means cluster analysis that was used as the principal clustering technique. Variables chosen for cluster modelling were selected on the basis of their considered contribution to characterizing the asthma phenotype.

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