



Chronic cough and sputum production are associated with worse clinical outcomes in stable asthma



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Summary

Background: Chronic cough and sputum production (chronic mucus hypersecretion) is a poorly described clinical feature of asthma. Our objective was to identify clinical, immunological and computed tomography (CT) measures of airway wall dimensions associated with these symptoms in smokers and never smokers with asthma.

Methods: Cross-sectional data was analysed from 120 smokers and never smokers with asthma. Participants with and without a history of chronic mucus hypersecretion were compared for clinical outcomes, sputum differential cell counts and CT measures of airway dimensions (wall thickness, luminal area and percent wall area).

Results: Chronic mucus hypersecretion occurred in a higher proportion of smokers with asthma (56%) than never smokers with asthma (20%), ($p < 0.001$) and the proportion of patients with these symptoms increased with asthma severity ($p = 0.003$). Smokers with asthma and chronic mucus hypersecretion had worse current clinical control than smokers without those symptoms [ACQ score 2.3 versus 1.6, $p = 0.002$]. A greater proportion of never smokers with chronic mucus hypersecretion required short courses of oral corticosteroids in the last year (58% versus 19%, $p = 0.011$). Sputum neutrophil and eosinophil counts were similar in asthma patients with or without chronic mucus hypersecretion. Of those with severe asthma and chronic mucus

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hypersecretion, a CT measure of airway lumen area was reduced in smokers compared to never smokers (11.4 mm² versus 18.4 mm²; $p = 0.017$).

Conclusions: Chronic mucus hypersecretion occurs frequently in adults with stable asthma, particularly in smokers with severe disease and is associated with worse current clinical control in smokers and more exacerbations in never smokers.

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Introduction

Chronic cough and sputum production due to airway mucus hypersecretion is an important component of several airway diseases including chronic obstructive pulmonary disease (COPD) and asthma. Cigarette smoking is one of the strongest risk factors for chronic bronchitis, also termed chronic mucus hypersecretion, in individuals with and without airflow limitation [1]. Chronic mucus hypersecretion develops in asthma [2–5], at least in part, due to the pro-inflammatory effects on airway epithelial glands of the T-helper type 2 (Th2) cytokines interleukin (IL)-9 and IL-13, as well as IL-1 β and tumour necrosis factor (TNF)- α [6].

The prevalence rates for chronic bronchitis vary between studies, due to differences in the definitions used and in the populations studied, but overall a consistent picture emerges of higher rates in airway disease and with cigarette smoking [5,7]. A systematic review of 38 studies reported a prevalence rate for chronic bronchitis of 6.4% in the general population [8] and with increased rates in smokers without airflow obstruction [2,9]. Higher rates are found in patients with COPD compared to smokers without COPD, with prevalence rates ranging from 27% [10] to over 70% [11–13]. There is more limited information on the prevalence rates for chronic cough and sputum production in asthma [2–5,14]. The Copenhagen City Heart Study and the European Community Respiratory Health (ECRH) survey reported prevalence rates of 39% and 42% respectively in non-smokers with asthma and with higher rates in smokers with asthma [2,14].

Chronic bronchitis in COPD has been associated with worse clinical outcomes [7,10] and increased mortality [9]. Less is known about the clinical features of patients with asthma who give a history of chronic mucus hypersecretion compared to those without these symptoms. Chronic mucus hypersecretion is associated with a significantly greater decline in FEV₁ among smokers with asthma [2], with more severe disease [3] and with chronic persistent airflow obstruction in non-smokers with asthma [4]. The presence of excessive airway mucus in asthma may also contribute to exacerbations and fatal attacks of asthma [15].

Taken together, these findings indicate that whilst chronic mucus hypersecretion is known to occur in asthma and that it may play a role in disease outcomes, the relationships between chronic mucus hypersecretion in smokers and never smokers with asthma with clinical, lung function, immunological outcomes and computed tomography (CT) airway dimensions are unknown. We wished to test the hypothesis that clinical outcomes are worse and/or that inflammatory biomarkers and CT measures of airway dimensions differ, in patients with asthma who give a

history of chronic mucus hypersecretion and that these outcomes are also influenced by smoking status and disease severity. We undertook an analysis of 120 subjects with asthma (smokers and never smokers) of differing severity to test this hypothesis, by examining outcomes in those with symptoms of chronic cough and sputum production compared to those without these symptoms.

Methods

Subjects and study design

A cross sectional study was performed in subjects with asthma recruited to the Glasgow COPD and Asthma Biomarker study [16]. Clinical, physiological, induced sputum cell counts and CT measurements were performed. Participants were recruited with mild, moderate and severe persistent asthma (GINA classification) [17], (both current smokers and never-smokers):

Age range 18–75 years and duration of asthma ≥ 6 months; Symptoms of episodic wheezing, chest tightness and/or dyspnoea; Objective confirmation by airway hyperactivity determined by a positive methacholine challenge or where this was not safe (when FEV₁ < 60% predicted), by evidence of airflow variability with a $\geq 12\%$ and 200 ml increase in FEV₁ following nebulised salbutamol 2.5 mg. The West Glasgow Research Ethics Committee approved the study and all patients gave written informed consent.

Patients had 3 study visits. At the first visit, the medical history was obtained and a methacholine challenge performed. At the second visit, one week later, spirometry and reversibility plus sputum induction were performed and asthma questionnaires completed. The third visit, a month later, was to assess reproducibility of sputum measurements. The CT scan and static lung volumes/diffusion capacity measurements were performed on visit 2 or 3. The participants were recruited over an 18 month period.

Measurements

Questionnaires

A history of chronic mucus hypersecretion was based on the question:

'Do you have a history of persistent sputum >3 months per year'. Asthma control questionnaire (ACQ) score [18] was also obtained. Information was obtained from participants on the number of hospital admissions, accident and emergency visits and emergency oral corticosteroid use in the last year.

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