Original Article

Ongoing Allergic Rhinitis Impairs Asthma Control by Enhancing the Lower Airway Inflammation

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What is already known about this topic? Allergic rhinitis is common in asthma and has an impact on asthma condition. The pathophysiologic events critical to the clinical manifestations of allergic rhinitis and asthma are similar.

What does this article add to our knowledge? This study provides data regarding the mechanism of interactions between the upper and lower airways. Ongoing allergic rhinitis is associated with incomplete asthma control by enhancing lower airway inflammation.

How does this study impact current management guidelines? Evaluation of the activity of allergic rhinitis is useful for assessing the impact of rhinitis on asthma, and adequate control of allergic rhinitis may improve asthma condition.

BACKGROUND: The relationship between allergic rhinitis and asthma is well accepted; however, little is known about the mechanism that underlies the interactions between the upper and lower airways.

OBJECTIVE: To investigate the symptomatic and inflammatory linkages between allergic rhinitis and asthma in patients with atopy.

METHODS: We enrolled 520 patients with asthma who were taking inhaled corticosteroids, and examined them by using the Asthma Control Questionnaire, spirometry, exhaled nitric oxide fraction (FENO), visual analog scale for nasal symptoms, allergic rhinitis questionnaire, and serum specific IgE (study 1). The symptomatic and inflammatory marker responses to nasal corticosteroids in patients with incompletely controlled asthma (Asthma Control Questionnaire > 0.75) and moderate-to-severe persistent allergic rhinitis were also observed (study 2).

RESULTS: A total of 348 patients (66.9%) had atopy and allergic rhinitis. There was a striking difference in the proportion of patients with incomplete asthma control, depending on the presence as well as the activity of rhinitis (no rhinitis, 11.0%; mild intermittent, 20.4%; moderate-to-severe intermittent, 44.6%; mild persistent, 53.1%; moderate-to-severe persistent, 65.7%). The FENO levels were increased with the activity of rhinitis, and the nasal visual analog scale was positively correlated with the FENO levels ($r = 0.31$; $P < .0001$). The additive treatment with nasal corticosteroids improved the nasal visual analog scale, Asthma Control Questionnaire, and FENO levels, and the changes in these variables were correlated with each other in all parameters (all $P < .001$).

CONCLUSION: This observational study of patients with atopy indicates that the ongoing allergic rhinitis is related to worsening of asthma by enhancing the lower airway inflammation. © **2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:172-8)**

Key words: *Airflow limitation; Airway inflammation; Atopy; Exhaled nitric oxide; Inhaled corticosteroids; Nasal corticosteroids*

Allergic rhinitis is common in asthma.[1] Previous studies provided evidence that the presence of rhinitis increases the social burden of asthma.[2,3] Patients with asthma and with concomitant rhinitis experience more asthma-related hospitalizations and physician visits, and higher medical costs than patients with asthma alone. Moreover, results of several studies indicated a link between the severity and/or control of rhinitis and asthma.[4-7] However, these studies defined allergic rhinitis by clinical symptoms and/or patient questionnaire, and many studies were *post hoc* analyses. To date, the relationships between the upper and lower airway conditions have not been fully examined in patients with confirmed atopic allergic rhinitis and asthma.

The mechanism that underlies the interaction between the upper and lower airways is still unclear, although pathophysiologic events critical to the development and clinical manifestations of

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Abbreviations used
ACQ- Asthma Control Questionnaire
AR- Allergic rhinitis
ARIA- Allergic Rhinitis and its Impact on Asthma
FVC- Forced vital capacity
FENO- Exhaled nitric oxide fraction
FEV_1- Forced expiratory volume in 1 second
ICS- inhaled corticosteroid
VAS- Visual analog scale

allergic rhinitis and asthma are similar.[8-11] Previous studies showed that nasal allergen challenge induces eosinophilic inflammation in the upper and lower airways, and causes airflow limitation in patients with allergic rhinitis.[10] Bronchial allergen provocation can induce nasal and bronchial symptoms as well as reductions in pulmonary and nasal function.[11] Moreover, several studies have reported that treatment of concomitant rhinitis was related to reductions in the risk of emergency department visits and hospitalizations for asthma[12,13] and that nasal corticosteroid therapy is related to improved respiratory symptoms and patient quality of life in mild intermittent asthma.[14,15] Analysis of these data suggests symptomatic and inflammatory linkages between the upper and lower airways in allergic rhinitis and asthma.

This study is based on the concept that allergic rhinitis may be a contributor to impaired asthma control with the possibility that the upper and lower airway inflammation is linked. In study 1, a cross-sectional survey was performed for assessing the linkages between the upper and lower airway conditions in patients with atopy and with allergic rhinitis and asthma. In the current guidelines for allergic rhinitis, intranasal corticosteroids are recommended as the first-line treatment for persistent moderate-severe disease.[1] Therefore, the symptomatic and inflammatory marker responses to the addition of nasal corticosteroids to asthma treatment in patients with incompletely controlled asthma and moderate-severe persistent allergic rhinitis were also observed (study 2).

METHODS

Study subjects

All the subjects were recruited from July 2012 to December 2012 to avoid the influence of the cedar pollen season in Japan. Subjects older than 20 years old were considered eligible if they satisfied the standard criteria for asthma.[16] The patients had a history of episodic dyspnea, wheezing, and documented reversible airway obstruction. According to the Global Initiative for Asthma,[16] asthma treatment included inhaled corticosteroids (ICS) with or without inhaled long-acting β2-agonist, leukotriene receptor antagonist, or theophylline. It is known that asthma conditions, including lung function and airway inflammation, are modified by tobacco smoking, exacerbations of asthma, and corticosteroid therapy.[16-18] Subjects were excluded if they were current smokers or had experienced an asthma exacerbation or had been treated with systemic and/or nasal corticosteroids during the 8 weeks before the study. Also, patients with poor adherence to the treatment (defined as <80% adherence calculated by dividing the number of days supplied for a medication by the number of days between the office visits) or with other pulmonary diseases, such as chronic obstructive pulmonary disease or bronchiectasis, which could influence asthma control, were excluded. Serum-specific immunoglobulin (Ig) E for common inhaled allergens (house dust mite, cedar, ragweed, cocksfoot, dog, and cat) was examined by using the ImmunoCAP system (Pharmacia Diagnostics, Uppsala, Sweden). Positive specific IgE (>0.7 UA/mL) to at least one allergen was assumed to confirm atopy. Allergic rhinitis was defined as the presence of atopy and a positive answer to the rhinitis questionnaire based on allergic rhinitis and its impact on asthma (ARIA).[1] This study was approved by the local ethics committee (institutional review board 526) and registered with the University Hospital Medical Information Network (000008609). Informed written consent was obtained from each participant.

Study design

This was a multicenter, prospective, observational study. We studied the medical records, including medication use and smoking history. After the inclusion period, a cross-sectional survey, by using the asthma control questionnaire (ACQ), spirometry, exhaled nitric oxide fraction (FENO), visual analog scale (VAS) for nasal symptoms, the allergic rhinitis questionnaire, and serum-specific IgE, was performed (study 1). After this survey, the patients with incompletely controlled asthma (ACQ score >0.75) and moderate-severe persistent rhinitis were selected, and additive therapy with 200 μg nasal mometasone furoate per day was administered for 4 weeks if the patient agreed to participate. We used the nasal symptom VAS, ACQ, spirometry, blood eosinophil counts, and FENO at the start and end of the nasal corticosteroid therapy (study 2). The baseline treatment for asthma was continued without any changes during the study period. The flow diagram of the study is shown in Figure E1 (in this article's Online Repository at www.jaci-inpractice.org).

Questionnaire and VAS

The patient questionnaire for rhinitis approved by the Japanese ARIA and the Global Initiative for Asthma committee was used to assess the presence of symptoms of allergic rhinitis.[1,4] The activity of allergic rhinitis and the impact on the quality of life were also evaluated.[1] The ACQ-5 is a composite control measure that assesses the asthma condition according to 5 items, each of which can be rated on a 7-point scale.[19] The overall score was the mean of the 5 responses, and ACQ $\leq$ 0.75 was considered to indicate well-controlled asthma.[19] Both questionnaires have been used in earlier studies in Japan.[4,20] Furthermore, the VAS, which ranges from 0 cm (absence of symptoms) to 10 cm (very severe symptoms) for all combined nasal symptoms, was self-assessed by the patient.[21,22]

Pulmonary function and exhaled nitric oxide measurement

The forced vital capacity (FVC) and FEV_1 were measured by using a dry rolling seal spirometer (CHESTAC-8800; Chest, Tokyo, Japan). The FENO was measured by an online electrochemical nitric oxide analyzer (NIOX MINO; Aerocrine, Solna, Sweden) as previously described.[23]

Statistical analysis

All data were expressed as mean (SD) values for continuous variables. For categorical variables, the numbers of observations and percentages were given in each category. Comparisons among different subgroups were performed by the Fisher exact