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Nasal Eosinophilic Inflammation Contributes to Bronchial Hyperresponsiveness in Patients with Allergic Rhinitis

There are increasing evidences that allergic rhinitis (AR) may influence the clinical course of asthma. We conducted methacholine challenge test and nasal eosinophils on nasal smear to patients with allergic rhinitis in order to investigate the mechanism of connecting upper and lower airway inflammation in 35 patients with AR during exacerbation. The methacholine concentration causing a 20% fall in FEV1 (PC_{20}) was used as thresholds of bronchial hyperresponsiveness (BHR). Thresholds of 25 mg/dL or less were assumed to indicate BHR. All patients had normal pulmonary function. Significant differences in BHR were detected in the comparison of patients with cough or postnasal drip and without cough or postnasal drip. There were significant differences of PC_{20} between patients with cough or postnasal drip and those without cough or postnasal drip (3.41±3.59 mg/mL vs 10.2±1.2 mg/mL, p=0.001). The levels of total IgE were higher in patients with seasonal AR than in patients with perennial AR with exacerbation (472.5±132.5 IU/L vs. 389.0±70.9 IU/L, p<0.05). Nasal eosinophils were closely related to log PC_{20} (r=-0.65, p<0.01). These findings demonstrated that nasal eosinophilic inflammation might contribute to BHR in patients with AR.

Key Words : *Rhinitis, Allergic; Eosinophils; Bronchial Diseases; Methacholine Chloride; Asthma*

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INTRODUCTION

Rhinitis and asthma usually occur together. There are increasing evidences that allergic rhinitis (AR) may influence the clinical course of asthma. AR patients without symptoms of asthma such as episodic cough, dyspnea, and wheezing often have bronchial hyperresponsiveness (BHR) to nonspecific bronchoconstrictors such as methacholine or histamine (1, 2). Methacholine responsiveness in the asthmatic range among the patients with rhinitis is associated with variable airflow obstruction and subclinical asthma (3).

Putative mechanisms linking rhinitis to asthma are explained by direct and indirect effects (4). The direct effects are nasobronchial reflex, postnasal drip of inflammatory cells and/or mediators from the nose into the lower airways, and absorption of inflammatory cells and/or mediators from the nose into the systemic circulation, and ultimately, the lung. The indirect effects are nasal obstruction causing reduction in filtration, humidification, and warming function of the nose (5). Rhinitis patients showed a lower degree of bronchial sensitivity to allergen than asthmatics, but responded to allergen inhalation with changes in airway inflammation and in maximal response plateau, very similar to asthma subjects. These data support the hypothesis that both allergic asthma and AR belong to the same population, and that the differences in symptoms depend on a quantitatively different response to environmental allergen inhalation (5). Eosinophilic inflammation may be present in subjects with AR and BHR even when there are no symptoms of asthma (6).

To investigate the mechanism of connecting upper and lower airway inflammation, we conducted methacholine challenge test and nasal eosinophils on nasal smear to patients with AR.

MATERIALS AND METHODS

Study design

Patients were recruited between 1998 and 2000 from Seonam University Hospital. The first visit included history and diagnostic testing procedures to verify inclusion and exclusion criteria and a questionnaire for symptoms and medications was given and physical examination was performed. After then, nasal smear for eosinophils, skin prick tests (SPT), spirometry, and methacholine provocation test were done.

Subjects

The study was performed as a prospective controlled clinical trial. A total of 35 patients (13 perennial AR with exacerbation and 22 seasonal AR) was included. AR was defined as a positive answer to the question, "Do you have any symptoms such

as sneezing, itching, coryza, and nasal obstruction?" and a positive skin prick test (Allergopharma, Germany) response to 1 or more of 55 inhalant allergens. The type of rhinitis, seasonal or perennial was in agreement with the kind of sensitizing allergen, seasonal or perennial. Seasonal AR patients were currently exposed and symptomatic. All patients did not take anti-allergic therapy during the study period. Exclusion criteria were the history of bronchial asthma, the existence of any nasal disease other than AR, pregnancy, any acute or inflammatory disease, anti-allergic therapy such as antihistamines or topical steroids at study entry, presence of parasitic infections, hypereosinophilia, respiratory infection for 4 weeks prior to the study. All subjects were informed and gave their consent before starting the study. The ethics committee of Seonam University Hospital approved the study protocol.

Recording of symptoms

The patients received a questionnaire to document their symptoms of AR (e.g., rhinorrhea, itching, sneezing, nasal obstruction). The severity of symptoms was scored individually on an arbitrary scale from 0 to 3 (0=free of symptoms, 1=mild, 2=moderate, 3=severe symptoms). The total symptom scores were calculated by adding up all scores.

Nasal swabs for eosinophils

A nasal secretion sample was taken from both nasal cavities by wiping the surface of the inferior turbinate with a cotton-tipped applicator. The sample was smeared over a standard glass slide, fixed, stained, and immediately examined to count the eosinophils. The proportion of eosinophils was expressed as a percentage of the total non-squamous cell count.

Sinus radiography

Waters' view, Candler's view, and skull lateral view were taken.

Spirometry

Spirometry was performed according to American Thoracic Society standards (7) using SensorMedics 2200 spirometer (Cardiopulmonary Care Company™, Yorba Linda, California). The representative values for forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were selected according to International Thoracic Society criteria (8), and the reference values were taken from the reports by Choi et al. (9) and by Kim et al. (10).

Bronchial hyperresponsiveness

Methacholine challenge tests were carried out by a modified method described by Chai et al. (11), and were performed in the pollen season. Concentrations of 0.075, 0.15, 0.31, 0.62, 1.25, 2.5, 5, 10, and 25 mg/mL methacholine were prepared by dilution with buffered saline. A Micro-dosimeter (S&M Instrument Co, Doylestown, PA) was used to deliver the aerosol generated by a DeVilbiss 646 nebulizer (Sunrise Medical HHG., Inc., Pittsburgh, PA, U.S.A.). Subjects inhaled 5 breaths of increasing concentrations of methacholine until FEV_1 fell by more than 20% of its basal value or it reached the highest concentration level. The largest value of triplicate FEV_1 at 30, 90 or 180 sec after each inhalation was adopted for analysis. If PC_{20} was less than 25 mg/mL, a subject was considered to have BHR to methacholine.

Allegy skin prick tests

Allergy skin prick tests were performed using 55 common allergen extracts (Allergopharma Co, Germany). None of the subjects had received antihistamines orally for 3 days preceding the study. A positive control of histamine (1 mg/mL) along with a negative diluent control was included in all tests. After 15 min, the mean diameter of a wheal formed by the allergen was compared with that formed by histamine. If the former was same or larger than the latter (A/H ratio ≥ 1.0), the reaction was deemed to be positive. Atopy means one or more positive allergy prick tests.

Blood sampling

Venous blood was collected into the tubes containing 5.0 mL ethylenediaminetetraacetic acid (K3 Vacutainer BD, Rutherfold, N.J.) simultaneously with nasal smear, differential white blood cell count was obtained using of a Coulter STKS instrument (Coulter Corp., Hialeah, Fla.). The total serum IgE was measured by enzyme immunoassay.

Statistical analysis

All data were analyzed using the SPSS version 7.5 for Windows. Data are expressed as mean±SEM. Comparison of continuous variables was performed using chi-square test, Fisher's exact test, and Mann-Whitney U test. Spearman's correlations were used to assess relationships between variables. A p-value of <0.05 was considered significant.

RESULTS

The characteristics of 35 patients (13 perennial AR with exacerbation and 22 seasonal AR) enrolled to the study are given in Table 1. Seasonal AR patients were positive in alder, birch, hazel, rye, timothy, mugwort, ragweed allergens.

Symptom scores

The mean average scores of sneezing, itching, coryza, and

Table 1. Characteristics of patients with allergic rhinitis

	Perennial	Seasonal
Age(yr)	33.5±3.2	29.9±2.4
Male/Female	8/5	13/9
IgE	157.8±74.3	389.0±70.9*
Serum-eosinophils	472.5±132.5	538.9±166.9
Nasal symptom score		
Itching	2.23±0.34	2.04±0.25
Sneezing	2.30±0.26	2.09±0.18
Coryza	2.23±0.28	2.36±0.25
Obstruction	2.76±0.28†	1.95±0.20
PC_{20} (mg/mL)	5.20±2.7	4.80±1.60

*p<0.05 compared with perennial allergic rhinitis with exacerbation, †p<0.05 compared with seasonal allergic rhinitis.
PC_{20} were defined as the methacholine concentration causing a 20% fall in FEV_1.

Table 2. Relationship of bronchial hyperresponsiveness and cough or postnasal drip

		Bronchial hyperresponsiveness	
		Yes	No
Cough or Postnasal drip	Yes	17	2
	No	5	11

Sensitivity=89.4%. Specificity=68.7%. Overall accuracy=80.0%.

nasal obstruction were 2.17, 2.11, 2.31, and 2.25, respectively (2.17±1.03 vs. 2.11±1.21 vs 2.31±1.10 vs 2.25±1.03). Nasal obstruction scores were higher in patients with perennial AR with exacerbation than in patients with seasonal AR (2.76 ±0.28 vs 1.95±0.20, p<0.05).

Nasal eosinophils, IgE, blood eosinophils

The level of total IgE was higher in patients with seasonal AR than in patients with perennial AR with exacerbation (472.5±132.5 IU/L vs 389.0±70.9 IU/L, p<0.05). Nasal eosinophils were 31.7±5.1% (0-95%). There were no differences of nasal eosinophils between perennial and seasonal AR (26.3±6.5% vs 34.8±7.3%). PC_{20} was lower in patients with >10% of nasal eosinophils than in patients with <10% of nasal eosinophils (4.06±1.36 vs 8.02±3.73). However, nasal eosinophils were closely related to log PC_{20} (Fig. 1, r= -0.65, p<0.01). There were no correlations between symptom scores and nasal eosinophils.

Bronchial hyperresponsiveness

Twenty-two patients had BHR. No significant differences in BHR were detected in the comparison of patients with and without cough, and of patients with and without postnasal drip. Significant differences in BHR were detected in the comparison of patients with cough or postnasal drip, and without

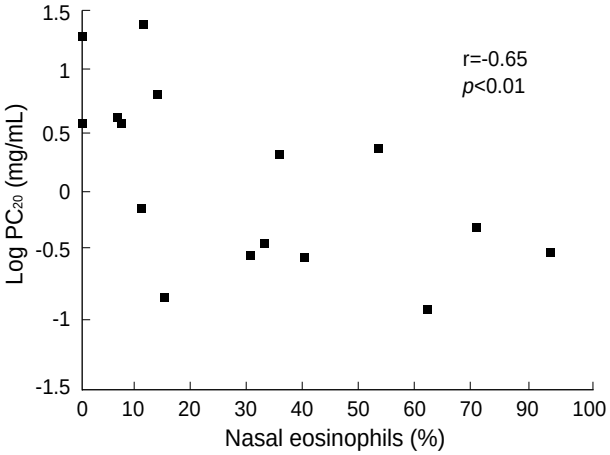

Fig. 1. Correlations between nasal eosinophils and bronchial hyperresponsiveness. PC_{20} values expressed as milligrams per milliter of methacholine.

cough or postnasal drip (Table 2, p<0.01). There were significant differences of PC_{20} in patients between with cough or postnasal drip, and without cough or postnasal drip (3.41± 3.59 mg/mL vs 10.2±1.2 mg/mL, p=0.001).

DISCUSSION

The present study showed that nasal eosinophils were correlated with BHR, suggesting that upper airway eosinophilic inflammation contributes to BHR.

There is a link between AR and asthma. Asthma and rhinitis can be associated with both an IgE-mediated allergic reaction and an inflammatory pattern. Twenty eight to fifty percent of asthmatic patients has AR, compared to 10-20% in the general population. Many patients with AR who have no perceived asthma symptoms have BHR to natural stimuli, such as exercise or to bronchial challenge with chemical stimuli, such as histamine and methacholine, especially during AR exacerbation (3). Simons (12) suggested that the new term "allergic rhinobronchitis" accurately describes chronic allergic inflammation throughout the airways of patients with concurrent AR and asthma. He recommended, the key to management of both disorders lies in addressing the common immunopathologic mechanisms and in preventing and relieving chronic allergic inflammation, not only with appropriate pharmacologic treatment, but also by recommending allergen avoidance and in selected patients, specific immunotherapy. In this study nasal eosinophils were related to BHR, suggesting that the common immunopathologic mechanisms of upper and lower airway inflammation may occur.

AR is characterized by the temporal relationship of symptoms to allergen exposure such as dust mites, pollens, animal dander, and mold spores. Symptom scores may provide a comprehensive picture of airway disease for quality assurance or

research purpose (13). Bousquet et al. (14) demonstrated that quality of life was more affected by rhinoconjuctivitis than by asthma symptoms. Nasal obstruction scores were higher in patients with perennial AR with exacerbation than in patients with seasonal AR, indicating that airway passage be more affected in perennial AR.

The underlying pathologic processes are similar in the upper and lower airways. Patients with grass pollen allergy develop a moderate hyposmia during 3 weeks of natural grass pollen exposure. This is better correlated with inflammatory mediators such as eosinophilic cationic protein in the nasal secretion level than with nasal air flow measured by active anterior rhinomanometry (15). Immune effector cells responsible for allergic reactions in both the lung and the nose include, most prominently, mast cell, T lymphocytes, and eosinophils (16-18). Eosinophils are characteristics for acute and chronic inflammatory changes observed in bronchial asthma and AR, and have also been implicated in many aspects of tissue damage that occurs at sites of chronic inflammation. In this study there are no differences of nasal eosinophils between perennial and seasonal AR.

AR patients who were hyperresponsive to methacholine were at significantly greater risk of developing asthma than those with normal bronchial challenge (19). Upper airway inflammatory processes occurring totally or primarily in the upper airway may participate in the pathogenesis of BHR and asthma (20). Perennial rhinitis is much more important than seasonal rhinitis as a risk factor for developing nonspecific BHR (21). In contrary to that study, we had no differences of BHR between seasonal and perennial AR in this study. Further follow up studies are needed to clarify risk factor for developing bronchial asthma. Rhinitis subjects with nonspecific hyperresponsiveness develop asthma more frequently than those without (3, 19). Inflammatory cells are present, not only in the airways of patients with asthma but also, in airways of patients with seasonal AR, even outside natural exposure.

In summary, the present study shows that there is a relationship of nasal eosinophils and BHR, suggesting that nasal eosinophils may play a role in the development of BHR in rhinitis patients.

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