

Nasal eosinophilia can predict bronchial hyperresponsiveness in persistent rhinitis: Evidence for united airways disease concept

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ABSTRACT

Background: Nasal eosinophils may be indicative of bronchial hyperresponsiveness (BHR) in rhinitis concerning the “united airways disease” theory. This study was designed to evaluate the relationship between nasal eosinophilia and BHR in persistent perennial rhinitis patients.

Methods: Thirty-seven patients (12 males and 25 females, mean age: 33.3 ± 10.4 years) were included in the study. Skin-prick test, nasal symptom score, nasal smears, methacholine bronchial challenge test, and nasal rhinometry were obtained in all patients. Eosinophil count in nasal smears was expressed as a percentage of the total cells. None of the patients had asthma.

Results: There was no difference between the number of atopic and nonatopic patients having BHR (4/20 versus 4/17; chi-squared = 0.07; $p > 0.05$). Total nasal flow was lower and percentage of nasal eosinophils was higher in the patients with BHR than in patients without BHR ($p = 0.012$ and $p = 0.009$, respectively). A cutoff point of 68% nasal eosinophils yielded a sensitivity of 100% (63.1–100) and a specificity of 58.6% (38.9–76.5) to determine the presence of BHR. Positive likelihood ratio for the value of eosinophils above cutoff value was 2.42 (1.8–3.3).

Conclusion: This study shows the relationship between nasal eosinophils and BHR in persistent perennial rhinitis patients. Nasal eosinophil percentage below cutoff value indicates that a patient does not have BHR.

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Rhinitis, either allergic or nonallergic, is a disorder characterized by inflammation of the mucous membranes lining the nasal passages. Rhinitis is associated with eosinophilic infiltration of nasal mucosa, particularly, in allergic rhinitis (AR).^{1,2} However, eosinophilia in nasal mucosa is not only confined to AR but also present in nonallergic rhinitis.³

Several clinical and experimental data suggest a similar immunopathology between the upper and lower airways in allergic subjects. The common inflammatory process that develops in the respiratory tract explains some of the complex interactions among different clinical entities such as rhinitis, sinusitis, asthma, bronchial hyperresponsiveness (BHR), and viral infections. There are also noninflammatory mechanisms that may contribute to the link between rhinitis and asthma.⁴ Consequently, some novel terms have been introduced, including “allergic rhinobronchitis,” “one airway one disease,” and “united airways disease.”⁵ BHR is a characteristic feature of asthma and is a consequence of underlying airway inflammation.⁶ BHR is detected both in asthmatic patients and in patients with AR or nonallergic rhinitis, although the exact mechanism is not explained.^{7–9}

Patients with rhinitis who do not report symptoms of bronchial asthma may show BHR, which could indicate the presence of sub-clinical inflammation of the lower airways.⁸ Asthma is more common in perennial AR (PAR) than in seasonal AR.¹⁰ Eosinophils may play a major role for maintenance of inflammation in nasal and bronchial mucosa. There may be a relationship between nasal eosinophilia and BHR in patients with rhinitis regarding the “united airways disease” theory. The aim of this study was to evaluate the presence of and the risk factors for BHR in patients with persistent perennial rhinitis and the relationship between nasal eosinophilia and BHR.

MATERIALS AND METHODS

Patients

Adults with persistent perennial rhinitis with complaints of nasal itching, rhinorrhea, sneezing, and nasal obstruction for at least 2 years were recruited in the study. The diagnosis of PAR was based on the history and sensitization to allergens with a skin-prick test (SPT). Exclusion criteria included (1) positive history for asthma or presence of symptoms that suggests asthma-like wheezing, dyspnea, chest tightness, and cough; (2) preexisting comorbid diseases; (3) use of any medication that causes rhinitis; (4) presence of structural nasal deformities including deviated nasal septum by declaration of patients and anterior rhinoscopic examination; (5) use of H₁-antagonists and/or decongestants within the past 15 days; (6) upper or lower respiratory tract infections; (7) use of corticosteroids or sodium cromoglycate within the past 6 weeks, and (8) concurrent purulent nasal infection. None of the subjects were smokers or had specific immunotherapy. The study was approved by the local ethics committee and informed consent was obtained from the patients.

Study Design

Patients were recruited from the outpatient clinic in our allergy department. The patients were questioned for their medical history to verify inclusion and exclusion criteria and physical examination was performed. SPT was performed to identify sensitization to aeroallergens in the patients using a common panel explained later. If a patient's history was suggestive for sensitization to allergens but SPTs were negative, an intradermal skin test was performed to exclude allergic sensitization. Peripheral venous blood was taken for eosinophil count and serum total IgE determination. A symptom score scale was used to determine nasal complaints of obstruction, itching, sneezing, and rhinorrhea for the following 10 days. The severity score was noted as 0 = absent, 1 = mild (symptom was present but not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep). Nasal smears were obtained from

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all patients and afterward nasal rhinometry measurements, pulmonary function tests, and methacholine provocation tests were performed. All measurements were obtained out of pollen season between November and February to exclude seasonal effects of pollen sensitization.

Skin-Prick Test

SPTs were performed by using a common panel including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, grass, tree, and weed pollens; animal dander (cat, dog); animal feathers; and mold (including *Alternaria*, *Cladosporium*, *Aspergillus*, and *Penicillium*) allergen extracts (ALK, Madrid, Spain). Positive and negative controls were histamine and phenolated glycerol saline, respectively. A mean wheal diameter of 3 mm or greater than that obtained with control solution was considered as positive. Intradermal tests were performed with the same allergen panel using aqueous solutions (ALK).

Nasal Smear

Nasal specimens for cell counts were obtained by passing a straight cotton swab along the base of the nose and drawing it under the inferior turbinate with a twisting motion and the collected secretions and cells were smeared onto a glass slide and air-dried. The slides were stained with Wright-Giemsa stain and examined under a light microscope by an experienced hematologist, who was blinded to the clinical status of the patients. At least 300 cells were counted in each slide at high power (oil immersion, $\times 1000$) excluding epithelial cells and eosinophil count was expressed as a percentage of the total cells.

Rhinomanometry

Nasal airflow was measured by active anterior rhinomanometry. Patients wore a facemask and with the mouth closed, breathed through one nostril. A stopper was placed in the contralateral nostril. The instrument (Koko Rhino; CO) was connected to a personal computer. Nasal pressures *via* airflow were reported as the sum of recorded airflow through right and left nostrils in milliliters per second at a pressure difference of 75 and 150 Pa across the nasal passage.

Spirometry and Methacholine Bronchial Challenge

Spirometry was performed with a spirometer (Vitalograph Alpha III; Vitalograph, United Kingdom). In patients with forced expiratory volume in 1 second (FEV_1) $\geq 80\%$ of predicted, methacholine challenge test was performed to evaluate BHR. Methacholine bronchial challenge (MBC) was performed according to the recommendations of American Thoracic Society guidelines.¹¹ Briefly, methacholine was administered using a dosimeter methacholine concentrations from 0.125 to 16 mg/mL (Zan 200; Zan, Oberthulpa, Germany) with doubling doses in each step. Three maneuvers of FEV_1 were performed after each dose and the highest FEV_1 was reported. The challenge was stopped when the FEV_1 dropped by $>20\%$ from the postphysiological saline or when the highest concentration of methacholine had been administered. Subjects were considered to have BHR if they showed a decline in FEV_1 of $\geq 20\%$ at a concentration of methacholine <16 mg/mL. PC_{20} value was calculated from log dose-response curve.¹¹ At the end of a positive challenge, patients received 200 μ g of salbutamol from a metered-dose inhaler to relieve airway obstruction.

Statistical Analysis

The results were presented as mean $\pm$ SD. Comparisons between groups were made using the Mann-Whitney *U* test, χ^2 -test, and parametric and nonparametric *t*-test for unpaired data when appropriate. A value of $p < 0.05$ was considered statistically significant. Spearman test was used for the correlation analysis. SPSS for Win-

dows (Version 13.0; SPSS, Inc., Chicago, IL) was used for the calculations.

The receiver operating characteristic (ROC) analysis was used to determine the cutoff values of the test (percentage of nasal eosinophils) to discriminate between a positive and negative outcome in the MBC. The ROC curves were constructed by plotting the sensitivity against one specificity at each nasal eosinophil percentage and flow level using the MedCalc statistical program. The area under the ROC curve was used to define overall index of diagnostic accuracy of the test. Assay performance was computed using sensitivity, specificity, likelihood ratio (LR), positive predictive value (ppv), and negative predictive value (npv) of the test result. Sensitivity is the percentage of positive tests (above cutoff value) in patients with a positive MBC. Specificity is the percentage of negative tests (below cutoff value) in subjects with a negative MBC. The ppv for nasal eosinophils above cutoff value described the percentage of patients with a positive test and a positive MBC. The npv for nasal eosinophils below cutoff value described the percentage of patients with a negative test and a negative MBC. LR described the ratio between a positive test result with a positive MBC and a positive test result with a negative MBC.

RESULTS

Thirty-seven consecutive patients (12 male and 25 female patients) were included in the study. The age of the patients ranged between 19 and 56 years (mean age, 33.3 ± 10.4 years). Twenty patients were atopic according to skin test results. Three patients had sensitization to *Dermatophagoides*, five patients had sensitization to tree and weed pollens, four patients had sensitization to molds, one patient had sensitization to animal feathers, and one patient had sensitization to cat dander. Six patients were sensitized with multiple allergens (three with *Dermatophagoides* plus molds, two with *Dermatophagoides* and pollen, and one with animal dander and pollen). All patients had FEV_1 values $>80\%$ of predicted and underwent MBC. Eight patients had positive response to MBC. The numbers of atopic and nonatopic rhinitis patients were similar regarding BHR (4/20 in those with positive BHR versus 4/17 in those with negative BHR; $\chi^2 = 0.07$; $p > 0.05$).

Rhinosinusitis was diagnosed in one patient who did not have BHR by consideration of clinical symptoms and computerized tomography evaluation of paranasal sinuses. Nasal polyp at nasal examination was determined in one patient who had BHR. Clinical comparisons of the atopic and nonatopic patients with AR and those with positive and negative BHR are presented in Table 1.

As shown in the Table 1, rhinitis patients with atopy were younger than those nonatopic patients ($p = 0.004$). The mean age of the two groups concerning BHR was similar. FEV_1 (percent of predicted) and nasal symptom scores did not differ between atopic and nonatopic patients or between those with positive and negative BHR. Patients with BHR had decreased total nasal flow and increased percentage of nasal eosinophils when compared with those patients without BHR ($p = 0.012$ and 0.009 , respectively). When we considered only those patients with BHR, nasal eosinophilia was negatively correlated with PC_{20} values ($r = -0.41$; $p = 0.013$); however, it was not correlated with total nasal flow ($r = -0.31$; $p = 0.06$). Total nasal flow and nasal eosinophilia were not different between the atopic and nonatopic groups. Total IgE levels were similar in all groups.

The estimated area under the ROC curve for percentage of eosinophils was 0.80 (95% confidence interval [CI], 0.63–0.91; Fig. 1). Distribution of nasal eosinophil percentages in the patients with and without BHR is shown in Fig. 2. A cutoff point of 68% of nasal eosinophils yielded a sensitivity of 100% (63.1–100) and a specificity of 58.6% (38.9–76.5) to determine a positive MBC test. The ppv for nasal eosinophil percentage above 68% was 40% (18.6–64.6) and the npv was 100% (80.5–100). Positive LR for the value of eosinophils above cutoff value was 2.42 (1.8–3.3).

Table 1 Clinical data of patients with perennial rhinitis according to presence of atopy and bronchial hyperresponsiveness

	Atopy			Bronchial Hyperresponsiveness		
	Yes (n = 20)	No (n = 17)	p	Yes (n = 8)	No (n = 29)	p
Age (yr)	29.1 ± 8.*	38.3 ± 10.8	0.004	35.7 ± 10.5	32.7 ± 10.5	>0.05
Duration of rhinitis (yr)	5.9 ± 6.3	6.3 ± 6.0	>0.05	6.5 ± 4.1	6.0 ± 6.6	>0.05
FEV ₁ (% predicted)	100.8 ± 8.6	96.9 ± 14.4	>0.05	90.5 ± 13.0	102.2 ± 9.2	>0.05
Nasal symptom score	1.60 ± 0.71	1.42 ± 0.92	>0.05	1.77 ± 0.97	1.47 ± 0.75	>0.05
Total nasal flow (mL/s)	644.6 ± 171.2	527.8 ± 250.5	>0.05	414.1 ± 248.7#	639.7 ± 182.7	0.012
Nasal eosinophils (% of total cells)	57.7 ± 39.9	51.9 ± 43.6	>0.05	89.0 ± 12.8§	45.7 ± 41.4	0.009
Total IgE (IU/dL)	254.9 ± 302.2	150.7 ± 274.4	>0.05	367.1 ± 447.9	160.2 ± 225.0	>0.05

*Atopic patients are younger than nonatopic patients ($p = 0.004$).

#Total nasal flow is lower in the patients with bronchial hyperresponsiveness ($p = 0.012$).

§Percentage of eosinophils in nasal mucosa is higher in the patients with bronchial hyperresponsiveness ($p = 0.009$).

FEV₁ = forced expiratory volume in 1 s.

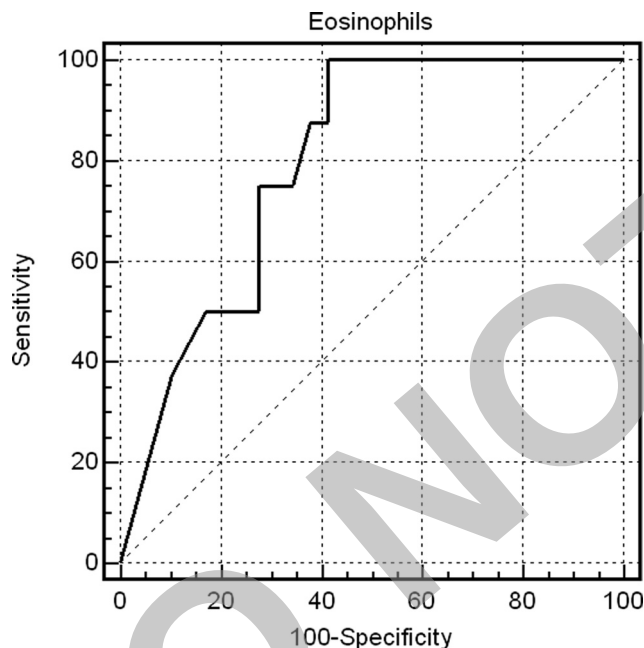


Figure 1. Receiver operating characteristic curve for the percentage of nasal eosinophilia and nonspecific bronchial provocation test.

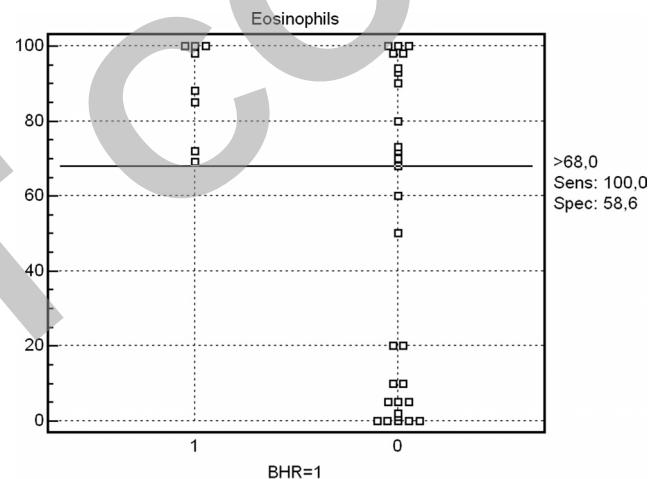


Figure 2. Distribution of nasal eosinophil percentages in the patients with and without bronchial hyperresponsiveness (BHR).

DISCUSSION

Rhinitis represents a global health problem affecting between 10 and 25% of the world population. The impact of the disease is often underappreciated with significantly impaired quality of life a profound socioeconomic impact with direct medical costs and considerable indirect costs relating to absence from work and schools and reduced productivity. Another important issue for rhinitis is that it is a risk factor for developing asthma. The current classification system is based on the recent document on Allergic Rhinitis and Its Impact on Asthma.¹² Two broad categories are recognized: an allergic group comprising individuals with an allergy to an identifiable allergen and a nonallergic group comprising a heterogeneous collection of subjects, some with a known cause and others with an unknown etiology. It is thought that nonallergic rhinitis may account for up to 25% of all rhinitis patients and constitute a contributing factor in up to 60% but little was known about its pathophysiology until today.^{13–15}

The present study showed that nasal eosinophilia is associated with BHR in patients with persistent perennial rhinitis. Although

atopy has not been found an important determinant for BHR, previous studies revealed mainly immunopathological, epidemiological, and therapeutic evidences supporting a relationship between AR and BHR. Hence, united airways disease has been suggested particularly between AR and asthma but little is known about the lower airways in nonallergic rhinitis. We could not make a subgroup analysis because of small numbers of patients with BHR in nonallergic rhinitis patients. Since earlier times it has been known that patients with AR and no history of asthma may develop bronchoconstriction and produce inflammatory cells and mediators in bronchoalveolar lavage fluid when challenged with inhaled bronchial allergens.¹⁶ Although there is a relation between asthma and AR, asthma is more commonly encountered in patients with PAR than in patients with seasonal AR.¹⁶ This correlates with observations that positive SPTs to house-dust mites or animal dander, but not to grass pollen, predict development of asthma.¹⁷

Eosinophilic inflammation in the lower airways has been shown to be related with BHR in asthmatic subjects.¹⁸ In view of the united airways disease concept, it might be speculated that nasal eosinophilia is related to BHR. In a previous study, nasal eosinophil count has been found to be related to BHR in atopic children with rhinoconjunctivitis and asthma.¹⁹ Although our patients were not asthmatic, we found a negative correlation between PC₂₀ values and nasal eosinophil percentage in those patients with BHR. We added the evidence that a percentage of eosinophils in nasal

mucosa are related to BHR in perennial rhinitis patients, supporting the united airways disease concept. Similarly, we indicated that BHR is present both in allergic and in nonallergic rhinitis, suggesting that united airways disease is not a phenomenon only in allergic perennial rhinitis but also in nonallergic perennial rhinitis. The present study also showed that nasal eosinophil percentage could be used to predict BHR in persistent rhinitis patients. A cutoff value of a test helped to differentiate those patients with disease above the threshold value. ROC curves are constructed from sensitivity and specificity of a diagnostic test.²⁰ Sensitivity and specificity measures require a positivity threshold for classifying the test results as either positive or negative. An ROC curve is a plot of a one specificity (false positive result of a test) versus its sensitivity and provides information about the test performance.²⁰ The accuracy of the test depends on how well the test discriminates the group being tested into those with and without the disease. Accuracy is measured by the area under the ROC curve. An area of 1.0 represents a perfect test performance. Our result showed an area of 0.80 under ROC curve, which was considered a good test performance (Fig. 1). Having eosinophil percentage above cutoff value (68%) was ~2.5 times as likely to occur in a patient with BHR as in a patient without BHR. Although the test is not strong at confirming BHR (ppv is 40%), it will, however, pick up 100% of all BHR⁺ patients (sensitivity). The most striking evidence in this study is that nasal eosinophil percentage below cutoff value is a very good indication that a patient does not have BHR (npv = 100%). Nonallergic rhinitis with eosinophilia syndrome (NARES) has been known for ~30 years, a clinical syndrome comprising symptoms consistent with AR in which an absence of atopy has been confirmed by allergen skin testing, and nasal cytology analysis shows >20% eosinophils.²¹ Leone *et al.* reported that patients with NARES but without histories of respiratory symptoms have a measurable bronchial responsiveness.²² However, they reported that there is no relationship between nasal inflammation and bronchial responsiveness. BHR was detected in 4 of 11 NARES patients among nonatopic rhinitis in the present study. Our findings also showed that patients with persistent rhinitis who had BHR revealed decreased nasal flow. Previously, a significant negative relationship was shown between eosinophilic infiltration and nasal airflow and a significant positive relationship was shown between nasal airflow and FEV₁ in patients with PAR and asthma.²³ Our findings constitute evidence of a relationship between nasal airflow and BHR in patients with persistent rhinitis regardless of being atopic. Nasal breathing is protective for lower airways by humidifying, warming, and filtering the inspired air and by dissolving soluble gases on the moist mucosa. A decrease in nasal airflow causes mouth breathing in which the protective effects of nasal breathing are lost. In asthmatic patients, oral breathing has been shown to cause a decrease of lung function and initiate asthma symptoms.²⁴ It was speculated that those patients with mouth breathing expose environmental allergens and irritants that could lead to the development of BHR in a genetically predisposed individual.²² Whether this is certain is still not known. It could be speculated that the clinical severity of rhinitis affected BHR in the airways; however, we could not find any statistically significant difference in nasal symptom scores between those patients with and without BHR. The major limitation of the study was decreased power that was found as 55% because of the lack of the number of patients with asymptomatic BHR. The present study is not an actual valid study but a preliminary study on this subject. Sale *et al.*¹⁹ reported an association between nasal eosinophilia and the degree of BHR similar to our result. The scraping method to obtain nasal cells was considered a cheap, simple, and safe method and it has been used in previous studies.²⁵

Coexistence of asthma and AR is a well-known entity. Previous studies suggested that AR, particularly perennial rhinitis, is a risk factor for subsequent asthma development.^{9,26} BHR, a characteris-

tic feature of asthma, describes the ability of the airways to narrow after exposure to constrictor agonists. Although asymptomatic BHR is found in rhinitis patients, whether subsequent asthma develops in those rhinitis patients with BHR in the following years is not known.

The results of the present study suggested that the low percentage of nasal eosinophils might be helpful to rule out the presence of BHR in patients with perennial persistent rhinitis, regardless of being atopic. Although the present findings indicate that nasal eosinophilia is associated with BHR in persistent rhinitis, it is difficult to establish whether these subjects might be at increased risk of developing asthma over time. Considering the results of the present study and previous epidemiological and immunologic evidence between rhinitis and asthma, it could be thought that asthma starts in the nasal mucosa, particularly in those patients with higher nasal eosinophils. Follow-up studies should be performed to clarify the possible correlation in persistent rhinitis patients.

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