

Original article

Predictors of bronchial hyperresponsiveness in chronic rhinosinusitis with nasal polyp

Background: Chronic rhinosinusitis with nasal polypoid (CRSNP) and asthma are inflammatory lesions of the respiratory epithelium. This study was conducted to evaluate predictive factors of bronchial hyperresponsiveness (BHR) in patients with CRSNP.

Methods: BHR was evaluated using a methacholine bronchoprovocation test (MBPT) in 122 consecutive patients newly diagnosed with CRSNP at Seoul National University Hospital from January 2004 to June 2006. The following parameters were analyzed and compared between the BHR and non-BHR groups: symptoms, atopic status, current smoking, disease severity of CRSNP based on the Lund–Mackay scoring system of sinus CT, and counts of eosinophils in the serum and nasal tissues.

Results: Thirty-five percent of the patients were found to have BHR, and BHR was found to occur more frequently in patients that were currently suffering from sneezing ($P = 0.007$). In addition, the mean eosinophil counts of the serum and nasal tissues were higher in the BHR group than in the non-BHR group ($P = 0.001$ for the serum, $P = 0.045$ for the nasal tissues), and the eosinophil counts of the serum correlated to those of the nasal tissues ($r = 0.334$, $P = 0.013$). The disease severity, as determined by the Lund–Mackay scoring system, was not different between the two groups ($P > 0.05$). The best cutoff serum eosinophil count for predicting BHR in CRSNP patients was determined to be 300 cells/ μ l (sensitivity 70%, specificity 70%).

Conclusion: Taken together, these results indicate that moderate to severe sneezing and a serum eosinophil count ≥ 300 cells/ μ l may be predictive factors for BHR in patients with CRSNP.

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Many studies have reported a correlation between chronic rhinosinusitis with nasal polyposis (CRSNP) and asthma (1–3). In addition, most severe asthma patients also suffer from nasal and sinus diseases, such as rhinosinusitis (4), and 30% of nasal polyposis patients also have asthmatic symptoms (5). Because coughing is a common symptom of both diseases, evaluation of asthma can easily be overlooked in CRSNP patients.

For patients with bronchial asthma, a thorough evaluation of the risk of anesthesia prior to surgery, as well as careful preparation of the anesthesia is required. In addition, we have to be cautious for patients with asthma because some of these patients are often hypersensitive to aspirin and nonsteroid anti-inflammatory drugs; therefore, administration of these drugs may be fatal. For these reasons, it is necessary for the comorbidity of CRSNP and bronchial asthma to be evaluated.

Bronchial hyperresponsiveness (BHR) is an important characteristic of asthma (6), and asymptomatic BHR is related to the development of asthma (7–9). The meth-

acholine bronchoprovocation test (MBPT) is a well-known test used to determine if a patient is suffering from BHR (10). Earlier studies (11, 12) have focused on the correlation between rhinosinusitis, nasal polyps, allergic rhinitis and BHR; however, these studies did not provide guidelines for the evaluation of BHR prior to conducting surgery on or treating CRSNP patients. In addition, it is impossible to perform lower airway evaluation on all the patients with CRSNP. Therefore, this study was conducted to determine clinical predictors and suggest a clinical guideline for the evaluation of BHR in CRSNP patients.

Methods

From January 2004 to June 2006, 133 consecutive patients were newly diagnosed with CRSNP. A total of 122 (91.7%) of 133 patients, who did not have a history of bronchial asthma, were subjected to evaluation of the lower airway including MBPT.

Eleven patients (8.3%) who had ever been diagnosed as asthma by a doctor were excluded. BHR was defined as a $\geq 20\%$ decrease in the forced expiratory volume in 1 s (FEV_1) after serial administration of methacholine up to a concentration of ≤ 25 mg/ml (2.5, 6.25, 12.5 and 25 mg/ml). Aspirin idiosyncrasy was defined as a $\geq 20\%$ decrease in the FEV_1 after administration of ≤ 360 mg/ml of lysine-aspirin (45, 90, 180 and 360 mg/ml). FEV_1 was measured at 10, 20 and 30 min after inhalation of lysine-aspirin at each concentration. Patients were excluded if they had a history of nasal/sinus surgery, any respiratory disease or had taken any steroid or antihistamine medication within the past 2 weeks. The age of patients ranged from 16 to 73 years (mean: 47 years) and the male to female ratio was 75 : 47. Thirty-five percent of the 122 patients were found to have BHR.

The following parameters in the BHR and non-BHR groups were then compared: nasal symptoms, serum eosinophil count, eosinophil infiltration ratio in nasal polyp tissues, serum total IgE level, current smoking history, disease severity of CRSNP based on the Lund-Mackay scoring system on sinus CT and the presence of atopy as determined by the multiple allergosorbent test (MAST) or the skin prick test (SPT). Presence of nasal symptoms was documented through a structured interview. Patients were considered to have the nasal symptom if it interfered with daily activities and was considered troublesome during the past 1 year. In addition, the correlation between all of the parameters and BHR was investigated. All nasal polyp tissues were fixed in 4% formaldehyde, dehydrated and then embedded in paraffin. Four serial sections of each specimen were then cut to a 4- μ m thickness, after which hematoxylin and eosin staining was performed. For each section, inflammatory cells under the subepithelial area were counted under a light microscope (original magnification $\times 400$) by four blind investigators. The eosinophil infiltration ratio was then defined by evaluating the eosinophil percentage of all infiltrated inflammatory cells, including eosinophils, lymphocytes, neutrophils and plasma cells. Ninety-eight out of total 122 patients underwent SPT and/or MAST. Skin prick test was performed using 55 common aeroallergens including house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), animal danders (cat epithelia, dog epithelia), molds (*Aspergillus fumigatus*, *Alternaria alternata*), pollens (mugwort, ragweed, alder, hazel, birch, oak) and cockroach (*Blattella germanica*). Histamine and isotonic saline were used as positive and negative controls. A mean wheal diameter greater or equal to that of histamine in the absence of any reaction to the saline was considered as positive response. Atopy was defined as a positive response to one or more allergens on SPT and/or MAST.

Statistical analyses were performed using spss 12.0 (SPSS Inc., Chicago, IL, USA). Data were analyzed using Student's *t*-test, chi-square test and Pearson's correlation test, and *P*-value < 0.05 was considered to be significant.

Results

Forty-three (35.2%) of 122 patients showed BHR. During the same period, 2796 patients (male : female = 1612 : 1184, mean 59 years with an age range from 16 to 88) visited the health care center at our institute, of which, 10.2% were positive for BHR. There was a significant difference in the prevalence of BHR observed in the CRSNP group and the health care population ($P < 0.001$). In addition, aspirin idiosyncrasy was more common in the BHR group (20.9%) than in the non-BHR group (2.5%, $P < 0.001$). Furthermore,

patients with BHR complained of sneezing more frequently than those without BHR (51% vs. 27%, $P = 0.007$, Table 1). However, the sensitization percentage to the common aeroallergens showed no statistical correlation with BHR ($P = 0.319$, Table 1). Additionally, there was no significant difference between the BHR and non-BHR groups when the CT scores, the number of the involved sinuses, the score ratio of ethmoid sinuses to total sinuses, and that of maxillary sinuses to total sinuses were considered.

The mean value of the serum eosinophil counts was higher in the BHR group than in the non-BHR group (430.54 ± 45.19 vs. 243.92 ± 23.64 cells/ μ l, $P = 0.001$). However, the mean level of the total serum IgE of the two groups was not significantly different (170.94 ± 42.86 U/ml in the BHR group vs. 134.88 ± 39.07 U/ml in the non-BHR group, $P > 0.05$, Table 1).

The eosinophil infiltration ratio was higher in the BHR group than in the non-BHR group ($26.08 \pm 3.42\%$ in the BHR group vs. $17.24 \pm 2.61\%$ in the non-BHR group, Student's *t*-test, $P = 0.045$), however, the infiltration ratio of the lymphocytes and neutrophils observed in the two groups was not significantly different ($P > 0.05$). In addition, the serum eosinophil count was significantly correlated with the tissue eosinophil infiltration ratio ($r = 0.334$, $P = 0.013$, Fig. 1). Furthermore, when a cutoff level of 300 cells/ μ l was used, the overall sensitivity and specificity of BHR detection in CRSNP patients using the receiver operating characteristic (ROC) curve was 70% (area under the ROC curve: 0.718, Fig. 2). Moreover, a serum eosinophil count ≥ 300 cells/ μ l and sneezing were found to be predictors of BHR by multivariate logistic regression analysis (Table 2).

Discussion

The prevalence of BHR in western countries is known to be 12–14% in adults and 53–55% in patients with nasal polyposis (13–15). However, to date, no reports regarding Asian populations have been conducted. According to an epidemiological study conducted on the adult Finnish population, the prevalence of asthma was higher in people with nasal polyposis than in the general population (19.3% vs. 4.4%) (16). In the present study, the prevalence of BHR was found to be higher in CRSNP patients than in the general health care population, which is similar to the findings of studies conducted in western countries (13–15). In addition, a recent report revealed that poor postoperative outcomes often occur after endoscopic sinus surgery in rhinosinusitis patients with asthma (17). Therefore, the evaluation of BHR might be useful for the prediction of surgical outcomes in CRSNP patients. However, it is not feasible to evaluate BHR of all patients, scheduled to undergo surgery; therefore, we

Table 1. Parameters related to bronchial hyperresponsiveness (BHR) between BHR and non-BHR groups

	BHR group, <i>n</i> = 43 (%)	Non-BHR group, <i>n</i> = 79 (%)	Odds ratio (95% CI)	<i>P</i>
Sneezing	22 (51)	21 (27)	2.893 (1.328–6.305)	0.007
Itching sensation	4 (9)	14 (18)	0.469 (0.144–1.526)	0.210
Rhinorrhea	5 (12)	13 (16)	0.668 (0.221–2.019)	0.473
Nasal obstruction	39 (91)	71 (90)	1.099 (0.311–3.882)	0.884
Postnasal drip	21 (49)	43 (54)	0.837 (0.396–1.772)	0.555
Purulent rhinorrhea	19 (44)	27 (34)	1.525 (0.713–3.262)	0.276
Headache	1 (2)	3 (4)	0.603 (0.061–5.982)	0.999
Facial fullness	8 (19)	18 (23)	0.775 (0.312–1.933)	0.590
Atopy	22 (51)	33 (42)	1.460 (0.692–3.081)	0.319
Current smoking	15 (35)	27 (34)	1.032 (0.477–2.237)	0.583
Lund–Mackay score*	17.83 ± 0.92	16.49 ± 0.80	–	0.274
Ethmoid/total score*	0.42 ± 0.03	0.41 ± 0.02	–	0.823
Serum eosinophil count*	430.54 ± 45.19	243.92 ± 23.64	–	0.001
Total IgE*	170.94 ± 42.86	134.88 ± 39.07	–	0.540
Eosinophil infiltration (%)*	26.08 ± 3.42	17.24 ± 2.61	–	0.045
Neutrophil infiltration (%)*	25.33 ± 3.13	32.09 ± 2.71	–	0.108
Lymphocyte infiltration (%)*	37.01 ± 3.55	36.41 ± 3.01	–	0.898
Plasma cell infiltration (%)*	11.58 ± 1.18	14.26 ± 1.72	–	0.208

Chi-square test was used for categorical variables and Student's *t*-test for continuous variables.

*Values are expressed as mean ± SEM.

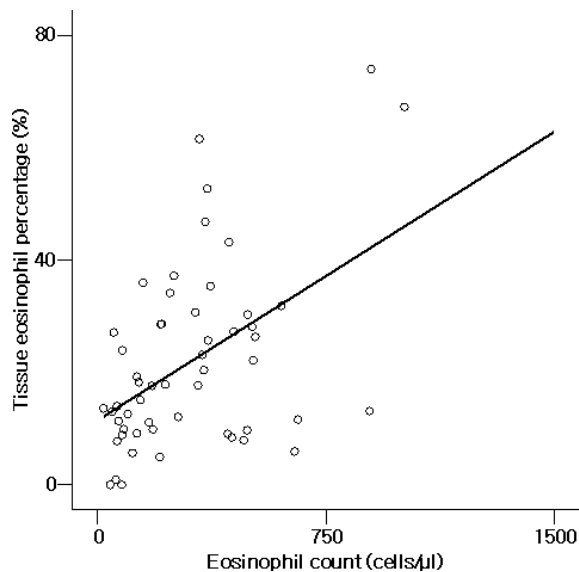


Figure 1. Correlation between the serum eosinophil count and eosinophil infiltration ratio in the nasal polyp. The serum eosinophil count correlates significantly with the tissue eosinophil infiltration ratio ($r = 0.334$, $P = 0.013$).

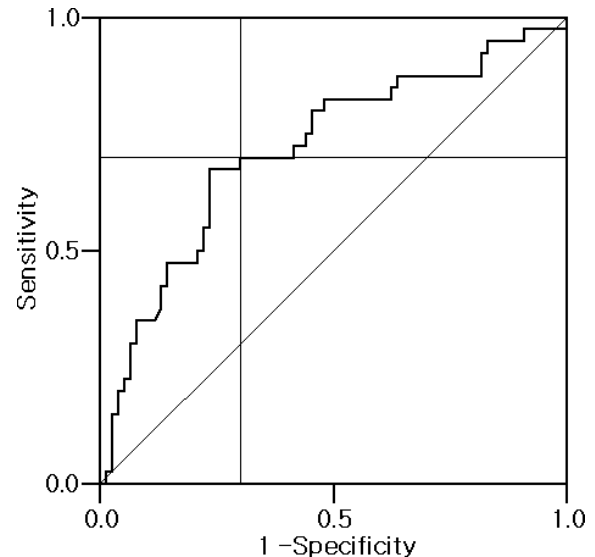


Figure 2. The receiver operating characteristic (ROC) curve for the serum eosinophil count. At the cutoff level of 300 eosinophils/ μ l, the sensitivity and specificity was 70% (area under the ROC curve: 0.718).

attempted to identify clinical predictors that could be used as a guideline for determining whether CRSNP patients should be evaluated for BHR.

Interestingly, the nasal symptom of sneezing is a useful predictor of BHR. Generally, several nasal symptoms overlap in patients with CRSNP. Among these symptoms, sneezing is regarded as a symptom of neurogenic

inflammation that could reflect lower airway inflammation. However, BHR did not differ with regard to the sensitization to allergens, which indicates that nonallergic inflammation, as well as allergic inflammation, could be attributable to BHR in CRSNP patients.

It has been reported that smoking is associated with increased BHR (18, 19), which is unclear in the present study. Total Lund–Mackay scores and the ratios of the

Table 2. Multivariate logistic regression analysis of the predicting factors for bronchial hyperresponsiveness*

Predicting factors	P	Odds ratio	95% CI
Eosinophil count (≥ 300 cells/ μ L)	<0.001	7.095	2.831–17.783
Sneezing	0.024	2.827	1.143–6.990

*Other variables in the regression model included age, sex, other nasal symptoms, presence of atopy, current smoking, Lund–Mackay score and total IgE level, none of which were significant.

separate sinus scores to the total scores were not different between the two groups evaluated in this study, which is inconsistent with the findings of another study (20) that found the ethmoid sinus to be the preferred site of CRS in patients with coexisting asthma. However, this discrepancy in findings might have been caused by the difference of the study population: BHR in the CRSNP patients vs. CRS in the asthma patients.

As in allergic rhinitis, serum total IgE could not be used to predict BHR in our study (11, 12). However, eosinophils infiltrate into most nasal polyps in patients with CRSNP (21), and in our study, eosinophil infiltration ratio, as well as the serum eosinophil counts, were found to be predictors of BHR in patients with CRSNP, just like serum eosinophilia as a predictor of allergic rhinitis (11, 12). In the present study, the mean values of

the serum eosinophil counts and the ratio of eosinophils in the tissue were found to be higher in the BHR group than in the non-BHR group. Additionally, serum eosinophil counts and eosinophil infiltration ratio showed significant correlation, which may have been due to eosinophil infiltration from the blood into the target organ. This correlation between the nasal polyposis and BHR has previously been explained by oxidative stress (22) and eosinophilic inflammation of the airway (5).

Because a blood test is a more feasible tool than a tissue biopsy, we conducted an ROC curve analysis of the serum eosinophil count. To achieve a higher sensitivity, in this study, the cutoff value was decreased to 210 cells/ μ L (sensitivity 83%, specificity 52%), however, it can be adjusted up to 377 cells/ μ L to obtain a higher specificity (sensitivity 48%, specificity 82%). In addition, multivariate analysis showed that the serum eosinophil count and sneezing were useful predictors of BHR in patients with CRSNP.

In conclusion, an elevated serum eosinophil count could be a useful predictor for BHR in CRSNP patients. Therefore, preoperative evaluation of BHR may be recommended in CRSNP patients that present moderate to severe sneezing symptom and high serum eosinophil count. However, further large population-based prospective studies of CRSNP patients based on our suggestive guidelines are necessary.

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