

Nasal polyps: An independent risk factor for bronchial hyperresponsiveness in patients with allergic rhinitis

Youngjin Ahn, M.D.,¹ Soo-Youn An, M.D.,¹ Tae-Bin Won, M.D.,¹ Jeong-Whun Kim, M.D., Ph.D.,^{1,6} Chul Hee Lee, M.D., Ph.D.,^{1,5,6} Yang-Gi Min, M.D., Ph.D.,^{1,5,6} Sang Heon Cho, M.D., Ph.D.,^{2,5} Heung Woo Park, M.D., Ph.D.,^{2,5} Young Yull Koh, M.D., Ph.D.,³ Sun Sin Kim, M.D., Ph.D.,^{4,5} and Chae-Seo Rhee, M.D., Ph.D.^{1,5,6}

ABSTRACT

Background: Many studies were conducted to figure out the relationship between allergic rhinitis (AR) and lower airway diseases. This study was designed to elucidate the clinical parameters that could predict the coexistence of bronchial hyperresponsiveness (BHR) in AR and suggest a guideline for lower airway evaluation in these patients.

Methods: One hundred seventy-three patients newly diagnosed with AR were evaluated for the lower airway with the methacholine bronchoprovocation test.

Results: BHR was more prevalent in patients with nasal polyps ($p = 0.01$), in patients complaining of moderate to severe symptoms ($p = 0.023$), with higher serum total IgE levels ($p = 0.001$), and with blood eosinophil count ($p = 0.008$). No statistically significant difference was observed between intermittent and persistent AR patients ($p = 0.364$). Blood eosinophil count that could predict BHR was calculated as 320 cells/ μ L ($p = 0.004$).

Conclusion: Instead of a routine lower airway evaluation for all AR patients, we recommend lower airway evaluation for the selected patients with nasal polyps, moderate to severe symptoms, and high blood eosinophil count.

(Am J Rhinol Allergy 24, 359–363, 2010; doi: 10.2500/ajra.2010.24.3502)

Allergic rhinitis (AR) and bronchial asthma (BA) are representative allergic diseases of the upper and lower airways. Furthermore, several studies regarding the comorbidity of AR and asthma have been reported.^{1,2} AR is present in 60–78% of BA patients^{3,4} and 20–40% of AR patients have concomitant BA.^{5,6} Thus, once regarded as two separate disease entities they are thought to be a common disease with different clinical manifestations.

Bronchial hyperresponsiveness (BHR) is a distinct functional characteristic of BA and is greatly associated with an increased risk for developing BA.⁷ Previously reported incidence of BHR in AR patients ranges between 20 and 40%.^{5,6} Factors related to coexistence of BHR in AR patients were reported as sensitization to aeroallergens,^{8,9} higher serum total IgE level,^{8–10} higher blood eosinophil count,⁹ higher nasal eosinophil count,¹⁰ symptoms of nasal obstruction,⁹ persistent AR,¹⁰ or smoking.¹¹ However, previous reports were based on retrospective reviews and were studied for the western population, and the reports on the incidence in oriental populations are scarce.

Selective lower airway evaluation on the patients with persistent symptoms is suggested in the Allergic Rhinitis and Its Impact on Asthma (ARIA) Workshop Report¹² and in its update.¹³ However, Bousquet recently recommended lower airway evaluation for the moderate to severe AR patients.¹⁴ Considering the several factors implicated to be related with BHR, clinical and laboratory factors should be inspected when we decide to evaluate the lower airway. Especially, in the aspect of cost-effectiveness, proper selection of the patients for lower airway evaluation is important. Therefore, inspecting the possible risk factors of BHR in patients with AR and defining the patients for lower airway evaluation on a prospective study would be valuable. In this study, we explain the applicable clinical

and immunologic factors that could predict BHR in AR patients and suggested parameters for evaluation of lower airway hyperreactivity in these patients.

METHODS

From January 2005 through June 2006, 173 patients newly diagnosed with AR in an otorhinolaryngology clinic were enrolled in the study. The diagnoses were made by one senior otorhinolaryngologist according to the ARIA guideline. All patients were investigated for the lower airway with methacholine bronchoprovocation test (MBPT). During the same study period, 2799 subjects who had performed MBPT as part of a routine health screening examination in the health care center of the same hospital were designated as the general population group.

Patients with current or previous chronic rhinosinusitis, previous history of nasal surgery, who had recently taken oral and nasal antihistamines or corticosteroids (2 weeks), and with a previous history of asthma or other pulmonary diseases were excluded. Mean age was 30 years old (5–77 years) and male-to-female ratio was 114:61. Symptom duration and severity of AR were classified according to the newly proposed ARIA classification.¹²

The presence of BHR was determined by MBPT. Methacholine challenge tests were performed using a modification of the method described by Springer *et al.*¹⁵ Determination of BHR was performed in two manners. For adult patients, BHR was defined as $\geq 20\%$ fall of forced expiratory volume in 1 second (FEV_1) after administration of methacholine in a concentration of >8 mg/dL. For children, BHR was measured by the following method. After the end of each inhalation, the trachea and the two zones of both lungs (upper front and lower back) were auscultated repeatedly during quiet breathing for ~ 3 minutes. Each observer evaluated wheezing independently, and wheezing was considered to occur only when the observer (Y.Y.K, a senior pediatrician) confirmed it. Arterial oxygen saturation was monitored continuously during and after each inhalation. The procedure was continued until either an end point or maximal concentration was reached. The end point was defined as the concentration of methacholine resulting in audible wheezing and/or a fall in oxygen saturation of at least 5% from baseline (desaturation).

Clinical parameters including classification of AR according to the

From the Departments of ¹Otorhinolaryngology, ²Internal Medicine, ³Pediatrics, ⁴Health Care System Gangnam Center, Seoul National University Hospital, Seoul, ⁵Institute of Allergy and Clinical Immunology and ⁶Center for Sensory Organ, Seoul National University Medical Research Center, Seoul, Korea

Disclaimer/Acknowledgement: None

Address correspondence and reprint requests to Chae-Seo Rhee, M.D., Department of Otorhinolaryngology, Seoul National University Hospital, 101 Daehangno, Jongno-gu, Seoul 110-744, Korea

E-mail address: csrhee@snu.ac.kr

Copyright © 2010, OceanSide Publications, Inc., U.S.A.

Table 1 Clinical findings related to bronchial hyperresponsiveness (BHR)

	BHR(+)	BHR(–)	OR	95% CI		<i>p</i> Value
				Lower	Upper	
Demographic factors						
Age						
Child	8	24	0.991	0.408	2.404	0.983
Adult	35	106				
Total	43	130				
Sex						
Male	30	83	0.765	0.364	1.608	0.479
Female	13	47				
ARIA classification						
Allergy duration						
Intermittent	8	31	1.502	0.622	3.623	0.364
Persistent	31	80				
Allergy severity						
Mild	7	42	2.783	1.128	6.867	0.023
Moderate severe	32	69				
Physical examination						
Nasal polyps						
Present	12	11	4.188	1.688	10.389	0.001
Absent	31	119				
Deviated nasal septum						
Present	19	65	0.792	0.396	1.583	0.508
Absent	24	65				

ARIA = Allergic Rhinitis and Its Impact on Asthma; OR = odds ratio.

ARIA, nasal symptoms such as sneezing, itching, rhinorrhea, nasal obstruction, nasal endoscopic findings, symptoms and signs associated with asthma, and immunologic laboratory parameters including blood eosinophil count, serum total IgE, and status of allergen sensitization using multiple radioallergosorbent test or skin-prick test were evaluated. Asthma was diagnosed by the physicians using the criteria proposed by the American Thoracic Society.¹⁶ The criteria included reversible airway hyperreactivity; at least two symptoms of cough, wheezing, chest tightness and nocturnal dyspnea; and >20% fall of FEV₁ after administration of methacholine.

Statistical analysis was performed using a computer software package, SPSS Version 12.0 (SPSS, Inc., Chicago, IL). Student *t*-test and chi-square analysis were used and odda ratio (OR) was calculated. Differences were considered significant when the value of *p* > 0.05.

RESULTS

Among the 173 AR patients, 43 patients (24.9%) showed BHR according to the MBPT. Among the patients who had BHR, 65.1% (28/43) were subsequently diagnosed with BA and are receiving additional medical treatment. In the general population group, 287 of 2799 patients (10.3%) showed BHR. BHR rate in patients with AR did not differ between adults (24.8%, 35/141) and children (25%, 8/32) or between the sexes (Table 1).

BHR rate was significantly higher in patients with moderate to severe AR (32/101; OR = 2.783; *p* = 0.023). There was a trend of higher BHR rate among the persistent AR group, but it was not statistically significant (*p* = 0.364). BHR rate was also significantly higher in patients with nasal polyps (12/23; OR = 4.188; *p* = 0.01). However, the presence of septal deviation did not affect BHR.

No significant difference was found in the presence of nasal symptoms such as sneezing, itching, rhinorrhea, and nasal obstruction (Table 2). Patients who had wheezing showed a higher rate of BHR, (16/38; OR = 2.909; *p* = 0.05). Other symptoms related to asthma such as dyspnea or cough were not positively related (Table 2).

Sensitivity for individual allergens (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and house dust) showed no statistical differ-

ence between BHR and non-BHR groups. The number and type (indoor versus outdoor) of sensitized allergen also did not show any difference between the groups (Table 3).

Mean serum eosinophil count was significantly different between the BHR and non-BHR groups (406.38 cells/ μ L versus 298.85 cells/ μ L; *p* = 0.008). Mean total IgE was 519.74 U/mL in the BHR group and 286.4 U/mL in the non-BHR group, and this was also statistically significant (*p* < 0.001; Table 4). Using the receiver operating characteristic curve, we calculated the cutoff value for serum eosinophil count and total IgE level (Fig. 1). A statistically significant cutoff value for eosinophil count was obtained at 320 cells/ μ L, but not for total IgE level.

Logistic regression analysis was performed to find out the relationship between these clinical factors and BHR (Table 5). Presence of nasal polyps (OR = 4.188; *p* = 0.002) was considered the single most powerful predictor for BHR. Blood eosinophil count of >320 cells/ μ L (OR = 2.79; *p* = 0.005) and moderate to severe symptoms of AR (according to ARIA classification; OR = 2.783; *p* = 0.026) could also be considered as predictors for BHR. However, serum total IgE level and wheezing were not considered as a predictor for BHR.

DISCUSSION

Epidemiologic and pathophysiological data indicated that AR and asthma are manifestations of one syndrome. Therefore, in examining and treating AR, the parallel relationship between rhinitis and asthma should be considered simultaneously.

Although asymptomatic BHR was also reported from 19 to 62%,¹⁷ BHR measured by MBPT is still considered as the pathognomonic finding of BA.⁷ In our study, 28 of 43 patients (65.1%) with BHR were diagnosed with BA and received medical treatment. On the other hand, 8 of 132 patients (6.1%) without BHR were diagnosed with mild asthma. The MBPT of these patients showed a mean decrease of FEV₁ by 15.4% (12–19%). Our study showed a strong correlation between BHR and BA (OR = 28.9; *p* < 0.001), which supports the performance of lower airway evaluation in patients at risk of BHR.

ARIA guidelines suggested repetitive evaluation of lower airways

Table 2 Clinical symptoms related to bronchial hyperresponsiveness (BHR)

	BHR(+)	BHR(−)	OR	95% CI		<i>p</i> Value
				Lower	Upper	
Nasal symptoms						
Sneezing						
Present	31	90	1.148	0.535	2.463	0.723
Absent	12	40				
Itching sense						
Present	11	34	0.971	0.441	2.136	0.941
Absent	32	96				
Rhinorrhea						
Present	34	104	0.944	0.403	2.212	0.895
Absent	9	26				
Nasal obstruction						
Present	27	95	0.622	0.3	1.29	0.200
Absent	16	35				
Asthmatic symptoms and signs						
Cough						
Present	15	40	1.205	0.581	2.5	0.615
Absent	28	90				
Dyspnea						
Present	8	23	0.969	0.486	1.932	0.923
Absent	24	72				
Wheezing						
Present	16	22	2.909	1.347	6.282	0.05
Absent	27	108				

OR = odds ratio.

Table 3 Allergens related to bronchial hyperresponsiveness (BHR)

	BHR(+)	BHR(−)	OR	95% CI		<i>p</i> Value
				Lower	Upper	
Sensitized allergen						
House dust						
Present	13	48	0.860	0.397	1.859	0.701
Absent	23	73				
<i>Dermatophagoides pteronyssinus</i>						
Present	23	64	1.576	0.731	3.397	0.165
Absent	13	57				
<i>Dermatophagoides farinae</i>						
Present	26	72	1.769	0.784	3.996	0.167
Absent	10	49				
Single vs multiple sensitization						
Single	6	37	2.202	0.845	5.741	0.1
Multiple	30	84				
Indoor vs Outdoor allergen						
Indoor	6	16	0.777	0.279	2.16	0.627
Outdoor	30	103				

OR = odds ratio.

in an effort toward early detection of symptoms and signs of lower airway involvement.¹² However, in the actual clinical setting, it is neither always possible nor necessary to have every patient with AR undergo evaluation for BHR. In view of this cost-effectiveness issue, searching for clinical parameters that render primary care physicians to refer AR patients for lower airway evaluation is valuable. To our knowledge, there have been no previous studies proposing a practical guideline for evaluating BHR in patients with AR.

Previous studies inspecting BHR in AR patients have focused mainly on finding the factors associated with BHR and fall short of providing a guideline for the evaluation of BHR. In this study, we

Table 4 Laboratory parameters related to bronchial hyperresponsiveness (BHR)

	Mean	Standard Deviation	<i>t</i>	<i>p</i> Value
Eosinophil (cells/ μ L)				
BHR(+), <i>n</i> = 41	406.38	33.95	–2.748	0.008
BHR(–), <i>n</i> = 127	298.85	19.466		
Total IgE(U/mL)				
BHR(+), <i>n</i> = 34	519.74	124.646	–2.515	0.001
BHR(–), <i>n</i> = 117	286.4	34.72		

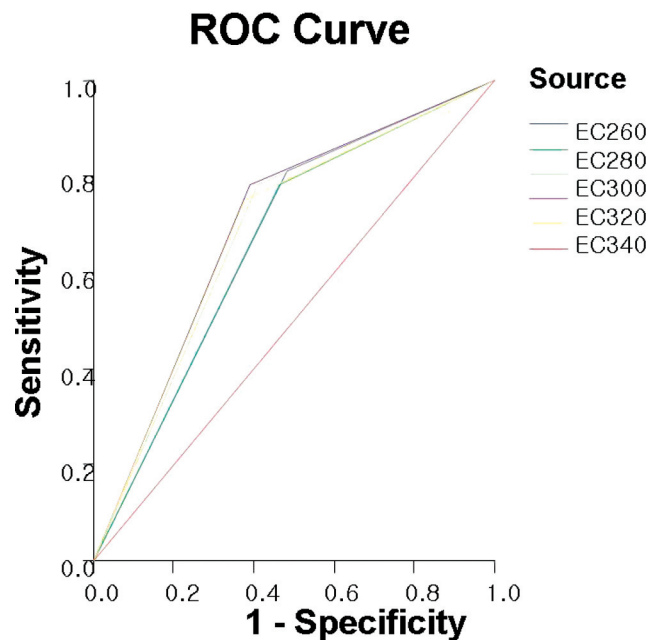


Figure 1. Determination of the cutoff value for eosinophil count. Cutoff value, 320; sensitivity, 66%; specificity, 62%; $p = 0.004$.

Table 5 Logistic regression analysis for factors affecting bronchial hyperresponsiveness

	<i>p</i> Value	OR	95% CI
AR severity	0.026	2.783	1.128–6.867
Nasal polyps	0.002	4.188	1.688–10.389
Eosinophil count (≥ 320 cells/ μ L)	0.005	2.79	1.368–5.690

AR = allergic rhinitis; OR = odds ratio.

investigated the clinical and immunologic parameters that could predict BHR in patients with AR and could suggest a guideline for lower airway evaluation in these patients.

Presence of nasal polyp(s) on physical examination was the most powerful predictor for BHR in patients with AR (OR = 4.188; $p = 0.002$, on logistic regression analysis). This result implies that careful nasal cavity examination for patients with AR is too important to be emphasized.

It is postulated that a common underlying mechanism is responsible for both peripheral blood eosinophilia and BHR. Eosinophils residing in peripheral airways, as has been observed in asthma, might create a local environment that easily permits the eventual development and persistence of symptoms.¹⁷ Previous study with rhinitis patients⁹ and another with the general population¹⁰ support our findings that blood eosinophils are elevated in the BHR group. In these reports eosinophilia ($>5\%$ of eosinophils among WBCs or >275 cells/ μ L) was used for determining increased eosinophil levels. On the contrary, in our study we compared the absolute eosinophil count between each group and tried to determine the possible cutoff value that could predict BHR. Although this value differs from the current definition of eosinophilia, we think that it may reflect a more accurate prediction of BHR. A statistically significant cutoff value for blood eosinophil count was calculated as 320 cells/ μ L, with 66% of sensitivity and 62% of specificity. Positive predictive value was 42.9%; however, these values are relatively low for clinical application.

Serum total IgE level was implied to be related to BHR in many studies,^{8–10} and this relationship was also proved in our study

(519.74 in the BHR group and 286.4 in the non-BHR group; $p = 0.001$). However, we failed to calculate a statistically significant cutoff value for serum total IgE level and logistic regression analysis also revealed no significant relationship between BHR and serum total IgE level.

BHR was reported to be higher in patients with perennial AR compared with patients with seasonal AR. ARIA update in 2007¹³ also recommend that in all patients with persistent rhinitis, asthma should be routinely investigated by history and, if needed, using pulmonary function tests assessing the reversibility of airflow obstruction under inhaled short-acting β_2 -agonists. However, duration of symptoms was not a significant predictor in our study group. Instead, BHR was significantly higher in the moderate to severe group (OR = 6.87; $p = 0.023$). Ethnic difference and different allergen sensitization could have caused this discrepancy. Because most of the patients with AR in Korea had been sensitized to dust mite, a perennial allergen, AR patients with intermittent symptoms were relatively uncommon. However, considering that studies using the ARIA guideline are scarce, and considering the changing guideline,¹⁴ further studies regarding this issue are required.

BHR was also reported to be higher in subjects sensitized to aeroallergens and with multiple allergen sensitizations.¹⁸ However, these relationships were not evident in our study. In our study, allergen sensitization to *D. pteronyssinus* and *D. farinae* was 86.5% (90/104) and 84.6% (88/104), respectively, which is higher than in a previously performed study on a Korean population¹⁹ showing 52.5 and 44.5% sensitization. This high rate of aeroallergen sensitization could have confounded the difference between BHR and non-BHR groups.

In conclusion, factors indicating BHR were presence of nasal polyps (OR = 4.2), moderate to severe AR according to the ARIA classification (OR = 2.8), and elevated blood eosinophil count (>320 cells/ μ L; OR = 2.8). These parameters can easily be assessed at the clinic by physical examination, history taking, and a simple blood test. Therefore, we suggest that any newly diagnosed AR patient with one or more of these factors should be assigned to the high risk group for BHR and a lower airway evaluation can be recommended. This selective evaluation would be helpful to increase the cost-effectiveness of the test.

REFERENCES

- Pederson PA, and Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy* 38:25–29, 1983.
- Beasley R. ISAAC-Phase I results: Global comparison. *Eur Respir J* 17:212, 1997.
- Nayak AS. The asthma and allergic rhinitis link. *Allergy Asthma Proc* 24:395–402, 2003.
- De Marco R, Locatelli F, Cazzoletti L, et al. Incidence of asthma and mortality in a cohort of young adults: A 7-year prospective study. *Respir Res* 16:95, 2005.
- Townley RG, Ryo UY, Kolotkin B, et al. Bronchial sensitivity to methacholine in current and former asthmatics and allergic rhinitis and control subjects. *J Allergy Clin Immunol* 56:429–442, 1975.
- Braman SS, Barrows AA, DeCotiis BA, et al. Airway hyperresponsiveness in allergic rhinitis: A risk factor for asthma. *Chest* 91:671–674, 1987.
- Katlaris CH. Allergic rhinitis and asthma: Epidemiological evidence for the link. *Clin Exp Allergy Rev* 3:5–8, 2003.
- Campos A, Reyes J, Blanquer A, et al. Total serum IgE: Adult reference values in Valencia (1981–2004). Usefulness in the diagnosis of allergic asthma and rhinitis. *Allergol Immunopathol (Madr)* 33:303–306, 2005.
- Di Lorenzo G, Pacor ML, Mansueto P, et al. Determinants of BHR in subjects with rhinitis. *Int J Immunopathol Pharmacol* 18:715–722, 2005.
- Jansen DF, Rijcken B, Schouten JP, et al. The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. *Am J Respir Crit Care Med* 159:924–931, 1999.

11. Jensen EJ, Dahl R, and Steffensen F. Bronchial reactivity to cigarette smoke: Relation to lung function, respiratory symptoms, serum-immunoglobulin E and blood eosinophil and leukocyte counts. *Respir Med*. 94:119–127, 2000.
12. Bachert C, van Cauwenberge P, and Khaltaev N. Allergic rhinitis and its impact on asthma. In collaboration with the World Health Organization. Executive summary of the workshop report. 7–10 December 1999, Geneva, Switzerland. *Allergy* 57:841–855, 2002.
13. Bousquet J, Khaltev N, Craz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) Update 2008.
14. Bousquet J. Allergic rhinitis management pocket reference. *Allergy* 63:991–996, 2008.
15. Springer C, Godfrey S, Picard E, et al. Efficacy and safety of methacholine bronchial challenge performed by auscultation in young asthmatic children. *Am J Respir Crit Care Med* 162:857–860, 2000.
16. American Thoracic Society. Lung function testing: Selection of reference values and interpretive strategies. *Am Rev Respir Dis* 144:1202–1218, 1991.
17. Jansen DF, Timens W, Kraan J, et al. Asymptomatic bronchial hyperresponsiveness and asthma. *Respir Med* 91:121–3420, 1997.
18. Valdesoiro L, Bosque M, Marco MT, et al. Allergic rhinitis and bronchial hyperresponsiveness. *Allergol Immunopathol (Madr)* 32:340–343, 2004.
19. Ko YH, Park SY, Lee JH, et al. A clinical statistics on the offending allergens of allergic rhinitis. *Korean J Otolaryngol* 41:44:42–47, 1998. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.