

A familial predisposition in bronchial hyperresponsiveness among patients with allergic rhinitis

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Background: Nonasthmatic subjects with allergic rhinitis often have bronchial hyperresponsiveness (BHR). The mechanisms responsible for BHR in asthma include genetic predisposition and airway inflammation, but the causes of BHR in allergic rhinitis are poorly understood.

Objective: The aim of this study was to investigate whether there is a familial predisposition in allergic rhinitis-associated BHR.

Methods: One hundred fifteen children with allergic rhinitis (probands) and their family members underwent methacholine bronchial challenge and skin prick tests with airborne allergens. The probands were divided into 2 groups: BHR(+) (methacholine PC₂₀ <18 mg/mL determined by the dosimeter method; n = 42) and BHR(-) (n = 73).

Results: The overall prevalence of BHR was higher in family members of BHR(+) probands than in those of BHR(-) probands (23.3% [27 of 116] vs 10.5% [21 of 200], $P < .01$). In mothers, this difference was marked (21.4% vs 8.2%, $P < .05$); a similar trend was observed in fathers (16.7% vs 6.8%) and siblings (34.4% vs 18.5%), although the differences did not reach significance ($.05 < P < .1$). The bronchial responsiveness index (BR index), a continuous variable derived from the results of methacholine challenge, was significantly higher among family members of the BHR(+) group than those of the BHR(-) group. Furthermore, even when only family members without BHR were considered, the BR index was significantly higher among those (n = 89) of the BHR(+) group than those (n = 179) of the BHR(-) group. There was no difference in atopic status as assessed by the prevalence of atopy (or atopy index) between family members of the BHR(+) group and the BHR(-) group.

Conclusion: Our results indicated that there is a significant familial predisposition for BHR among patients with allergic rhinitis. Further studies are needed to elucidate whether genetic factors play a role in allergic rhinitis-associated BHR. (*J Allergy Clin Immunol* 1998;102:921-6.)

Key words: Allergic rhinitis, bronchial hyperresponsiveness, bronchial responsiveness index, familial predisposition

Bronchial hyperresponsiveness (BHR) to pharmacologic agonists, such as histamine or methacholine, is a characteristic feature of subjects with asthma.¹ Those with allergic rhinitis but no history of asthma, however, often show heightened bronchial responsiveness.^{2,3} Many studies have suggested that in patients with allergic rhinitis, increased bronchial responsiveness may be a marker for subsequent asthma.^{4,5}

The mechanisms responsible for BHR in asthma include genetic predisposition and the effects of environmental exposures to inflammatory stimuli in the airways of susceptible individuals.⁶ Although asthma and allergic rhinitis appear to be closely associated,⁷ it is poorly understood as to how patients with nonasthmatic allergic rhinitis have BHR. In particular, adequately detailed studies to determine whether increased airway responsiveness is associated with airway inflammation or is linked to another mechanism in subjects with allergic rhinitis, such as one with a genetic basis, have not been undertaken.

Studies of BHR in parents and nuclear families of asthmatic subjects have unanimously agreed that familial, possibly genetic, factors are involved in its genesis.⁸⁻¹⁰ To the best of our knowledge, the question of whether patients with allergic rhinitis are at varying risk of BHR according to whether there is a family history of the condition has never been studied. We therefore decided to investigate whether familial hyperreactivity plays a part in BHR in children with allergic rhinitis. We performed a methacholine challenge test in their families and compared the results with those obtained in the families of children with allergic rhinitis but without BHR.

METHODS

Children with perennial allergic rhinitis (probands) and their families were targeted for this study. In 1996, probands were recruited consecutively from patients between 7 and 16 years of age who were attending the allergy clinic at Seoul National University Children's Hospital and had shown symptoms of sneezing, nasal stuffiness, rhinorrhea, and/or nasal itching throughout the year (lasting for at least 2 years). The clinical records of the subjects, who had responded at the initial visit negatively as to whether they had ever had asthma or whether this disease had ever been diagnosed by a doctor, were reviewed. They were considered as candidates for this study only when the 2 doctors at our clinic agreed that each subject did not have any history of symptoms suggestive of asthma.

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TABLE I. Clinical characteristics and atopic status of the 2 proband groups

	BHR(+) group	BHR(-) group
No of cases	42	73
Age (y)	11.2 ± 2.6	11.8 ± 2.5
Sex (M/F)	25/17	50/23
Duration of symptoms (y)	3.9 ± 1.1	3.9 ± 1.2
Serum IgE (IU/mL)*	245.5 (107.2-562.3)	229.1 (117.5-446.7)
Atopy index†	3.9 ± 2.2	3.7 ± 1.6
Pattern of positive skin test responses‡	38/16/8/6/12	67/28/10/11/20

*Geometric mean (range of 1 SD).

†Number of allergens to which the subject showed a positive response.

‡Number of cases positive to house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*)/animal dander (cat and dog)/mold (*Aspergillus* and *Alternaria* species)/pollen (oak, alder, rye grass, ragweed, and mugwort)/cockroach.**TABLE II.** Prevalences of BHR and atopy and atopy index in family members belonging to the 2 proband groups

	BHR(+) group	BHR(-) group
Prevalence of BHR (%)		
Father	7/42 (16.7)*	5/73 (6.8)
Mother	9/42 (21.4)†	6/73 (8.2)
Sibling	11/32 (34.4)*	10/54 (18.5)
Male	7/20 (35.0)	5/29 (17.2)
Female	4/12 (33.3)	5/25 (20.0)
Total	27/116 (23.3)‡	21/200 (10.5)
Prevalence of atopy(%); atopy index§		
Father	28/42 (66.7); 3.18 ± 1.47	39/73 (53.4); 2.90 ± 1.23
Mother	27/42 (64.3); 2.88 ± 1.51	36/73 (49.3); 2.58 ± 1.34
Sibling	23/37 (62.2); 2.91 ± 1.28	41/61 (67.2); 2.78 ± 1.26
Male	14/22 (63.6); 2.86 ± 1.46	19/31 (61.3); 2.53 ± 1.22
Female	9/15 (60.0); 3.00 ± 1.00	22/30 (73.3); 3.00 ± 1.27
Total	78/121 (64.5); 2.99 ± 1.42	116/207 (56.0); 2.76 ± 1.27

*.05 < P < .1 compared with that of BHR(-) group.

†P < .05 compared with that of BHR(-) group.

‡P < .01 compared with that of BHR(-) group.

§Number of allergens to which the subject showed a positive response among atopic subjects (mean ± SD).

Abbreviations used

BHR: Bronchial hyperresponsiveness

BR index: Bronchial responsiveness index

Supplementary questions, modified from those by Verdiani et al,¹¹ were asked concerning the presence of the following asthma-related symptoms: (1) attacks of chest tightness, (2) difficulty breathing, (3) occasional or persistent wheeze, (4) breathlessness or cough after exposure to cold air or exercise, (5) chest noises while breathing, (6) chronic cough that persists for more than 3 weeks, and (7) nocturnal symptoms that disturb sleep. The subjects were included in the study only when their parents responded negatively to all the questions. The subjects were excluded from the study if any of the questions were positively answered or their parents could not answer confidently. Physical examination, as well as spirometry, had been normal at each time of the clinic visits. In all subjects the prick method showed an immediate positive skin reaction to extracts of house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) and/or cat or dog dander. Nasal cromolyn sodium had been administered for several months, but it was stopped at least 2 weeks before the study. Exposure to aller-

gens (except for house dust mite) to which immediate skin reactions were elicited was avoided for at least 2 weeks before the study.

Both natural parents and siblings of the probands were asked whether they would participate in the study; only 2 eligible families declined. The ascertainment was done in blinded fashion for knowledge of a family history of atopic disorders. After the ascertainment, information on the history of atopic disorders in family members over 3 years old was obtained; only if diagnosed by a doctor as having asthma, allergic rhinitis, or atopic dermatitis was the history accepted as a positive. Parents gave written informed consent for themselves and children to participate in the study. The study protocol was approved by the Hospital Ethics Committee.

The probands and their families underwent bronchial challenge with methacholine and skin prick tests with airborne allergens. For the former test, subjects were required to be older than 7 years and to have an FEV₁ of at least 70% of the predicted normal value.^{12,13} For skin prick testing, siblings were required to be older than 3 years. The study was performed between November 1996 and February 1997, except for the probands' skin tests. This period corresponds to pollen-free winter season when the levels of house dust mites have been found to be the lowest and least changing in our country.¹⁴ At the time of study, all subjects had been free of acute respiratory tract infection for 4 weeks. Family members who were taking medication

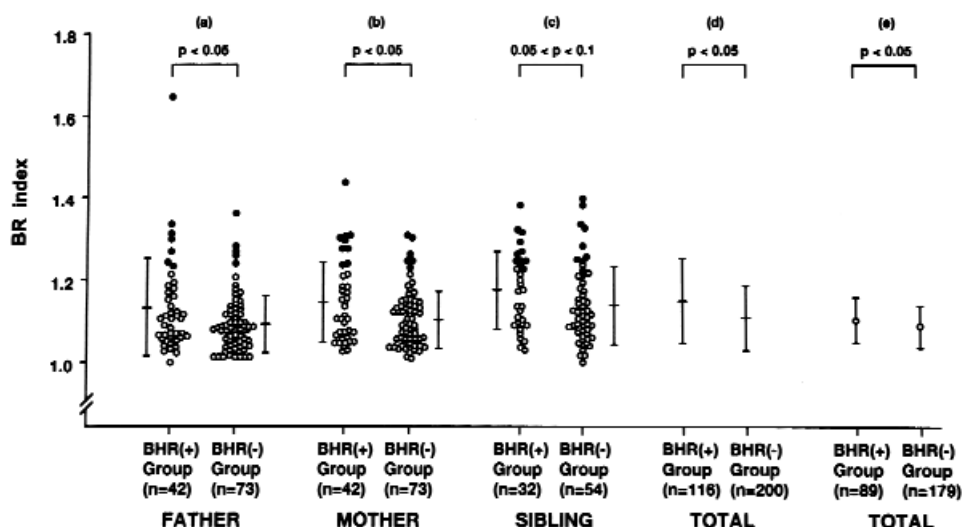


FIG 1. Comparison of BR index in each constituent grouping (a, b, c), total members (d), and members without BHR (e) in families belonging to the 2 proband groups. Filled circles, Subject with BHR; open circles, subjects without BHR. Mean and 1 SD are indicated with horizontal bars (bars, subjects with and without BHR combined; bars with circles, only subjects without BHR).

for their atopic disorders were required to stop using topical corticosteroid or cromolyn for 3 days and bronchodilator or other miscellaneous medications for 7 days before the study.

Methacholine bronchial challenges were carried out by a modification of the method described by Chai et al.¹⁵ By dilution in buffered saline (pH 7.4), methacholine (Sigma Chemical, St Louis, Mo) at concentrations of 0.075, 0.15, 0.3, 0.625, 1.25, 2.5, 5, 10, and 25 mg/mL was prepared. A Rosenthal-French dosimeter (Laboratory for Applied Immunology, Baltimore, Md), triggered by a solenoid valve set to remain open for 0.6 seconds, was used to deliver the aerosol generated from a DeVilbiss 646 nebulizer with pressurized air at 20 psi. Each subject inhaled 5 inspiratory capacity breaths of buffered saline and increasing concentrations of methacholine until FEV₁ fell by more than 20% of its postsaline value or the highest concentration was reached. FEV₁ was measured with a computerized spirometer (Microspiro-HI 298, Chest), and the largest value of triplicate FEV₁ at 1.5 minutes after each inhalation was adopted for analysis. The PC₂₀ was obtained from the log concentration-percentage fall in FEV₁ curve by linear interpolation of the last 2 points. Subjects were considered to have BHR if they showed a decline in FEV₁ of 20% or more at a concentration of methacholine less than 18 mg/mL (ie, a PC₂₀ < 18).¹⁶ To calculate a continuous index of methacholine responsiveness, the log of the slope of the percentage decline from baseline FEV₁ after the last dose of methacholine per unit concentration of methacholine (bronchial responsiveness index [BR index]) was calculated as described by Burrows et al.¹⁷

At the end of the challenge, family members of the probands underwent skin testing by the prick method with a panel of 12 allergens commonly found in Korea. The panel included house dust mites (*D pteronyssinus*, and *D farinae*), animal dander (cat and dog), molds (*Aspergillus* and *Alternaria* species), pollens (oak, alder, rye grass, ragweed, and mugwort), and cockroach. A positive control of histamine (1 mg/mL) along with a negative diluent control were included in all tests. A subject who showed at least 1 positive response to the allergens tested (mean wheal diameter of 3 mm or more)¹⁸ was considered atopic, and his or her atopy index (the total number of allergens to which response had been positive)¹⁹ was calculated.

Statistical analysis

Results were expressed as mean $\pm$ SD unless otherwise indicated. BR index was calculated as the log of the percent decline in FEV₁/log final methacholine concentration in milligrams/deciliters after adding 10 to eliminate negative values.¹⁷ Values or prevalences between the 2 groups of probands or their family members were compared with Student's *t* test or the chi-square test. In the comparison between the 2 groups of family members, the probands themselves were excluded. In each case, a *P* value less than .05 was considered statistically significant.

RESULTS

One hundred twenty-one probands and their families participated in the study. Six probands (2 with BHR and 4 without) and their families dropped out because some member or members of these families could not perform the applicable tests. Complete data were therefore available for 115 probands and their families.

The probands were divided into 2 groups according to whether BHR was present, and Table I summarizes the clinical characteristics of their members; with regard to mean age, sex ratio, and duration of symptoms, the BHR(+) and BHR(-) groups did not differ. Atopic status, assessed by total serum IgE, atopy index, and the pattern of positive skin test responses, was not different between the 2 groups.

Families of the BHR(+) group consisted of 42 fathers (mean age, 40.5 $\pm$ 3.8 years), 42 mothers (38.6 $\pm$ 3.5 years), and 39 siblings (9.9 $\pm$ 3.8 years; 23 males and 16 females) of whom 32 were older than 7 years and 2 were younger than 3 years. Families of the BHR(-) group consisted of 73 fathers (41.6 $\pm$ 4.1 years), 73 mothers (39.0 $\pm$ 4.0 years), and 64 siblings (11.1 $\pm$ 3.8 years; 32 males and 32 females) of whom 54 were older than 7 years and 3 were younger than 3 years. The age of each constituent

family grouping and the sex ratio of siblings were not statistically different between the 2 groups. With regard to a history of atopic disorders in family members aged over 3 years, asthma was more common among those of the BHR(+) group than those of the BHR(−) group (13.2% [16 of 121] vs 6.3% [13 of 207], $P = .033$), but the prevalence of allergic rhinitis (21.5% [26 of 121] vs 19.8% [41 of 207]) or atopic dermatitis (10.7% [13 of 121] vs 12.6% [26 of 207]) was similar between the 2 family groups (data not shown). Overall, BHR(+) probands had a positive family history (at least 1 member with atopic disorder) in 52.4% (22 of 42) of cases compared with 46.6% (34 of 73) of BHR(−) probands (not significant).

The prevalence of BHR and atopic status in the families of each proband group are shown in Table II. The overall prevalence of BHR was higher among family members of the BHR(+) group than those of the BHR(−) group (23.3% [27 of 116] vs 10.5% [21 of 200], $P = .002$); this figure was marked for mothers (21.4% vs 8.2%, $P = .043$), and a similar trend was observed among fathers (16.7% vs 6.8%, $P = .097$) and siblings (34.4% vs 18.5%, $P = .098$), although the differences did not reach significance. When the data for male and female siblings were analyzed separately, there was no significant difference in either sex.

The prevalence of atopy was not significantly different between each constituent family grouping or total family members of the BHR(+) and BHR(−) groups. Neither was atopy index among the atopic subjects significantly different between the two family groups (Table II).

Fig 1 shows the BR index of each constituent family grouping and total family members of the 2 proband groups; the BR index was significantly higher among fathers (1.135 ± 0.116 vs 1.094 ± 0.070 , $P = .040$; Fig 1, a) and mothers (1.147 ± 0.096 vs 1.104 ± 0.069 , $P = .015$; Fig 1, b) of the BHR(+) group than those of the BHR(−) group, and a similar trend was found among siblings (1.175 ± 0.094 vs 1.138 ± 0.093 ; Fig 1, c), although the difference did not reach significance ($P = .083$). In consequence, the index was higher among total family members of the BHR(+) group than those of the BHR(−) group (1.149 ± 0.103 vs 1.110 ± 0.078 , $P = .049$; Fig 1, d). This may be attributable to the higher frequency of BHR, and hence the higher BR index, among family members of the BHR(+) group. When only family members without BHR were considered, however, those of the BHR(+) group still had a higher BR index than those of the BHR(−) group (1.105 ± 0.055 vs 1.089 ± 0.051 , $P = .032$; Fig 1, e).

DISCUSSION

There have been several investigations of bronchial responsiveness to pharmacologic stimuli such as histamine or methacholine in patients with allergic rhinitis.^{3,5,20} In this study the prevalence of BHR was 36.5% (42 of 115), a figure similar to that seen in other studies when differences in challenge methods³ and criteria for BHR⁵ are taken into account. In fact, there is a continuous unimodal distribution of bronchial responsiveness in

the general population,²¹ and a cut-off point of 18 mg/mL separating normal from increased bronchial responsiveness may appear arbitrary. We have previously found that a PC_{20} greater than 18 mg/mL virtually rules out current symptomatic asthma, and for this reason, this concentration has been chosen as the criteria for BHR. Over half (25 of 42) of our hyperresponsive subjects were in the "asthmatic" range ($PC_{20} < 8$ mg/mL),²² although to eliminate hidden asthma from our study, our patients were carefully screened for vague lower respiratory symptoms. This suggests that the difference in BHR between subjects with rhinitis and those with asthma is not merely quantitative. Between the BHR(+) and BHR(−) group in this study there was no difference in total serum IgE levels or the number or pattern of positive skin test responses to aeroallergen. Although atopy has been found in population studies to be associated with an increase in bronchial responsiveness²³ and can heighten BHR when this is already present,²⁴ the above observation suggests that the presence or absence of BHR in subjects with allergic rhinitis might not depend on atopic status or the allergens to which they become sensitized.²⁵

Studies in both humans and animals have demonstrated a genetic predisposition to BHR,^{9,26} such as greater concordance for this trait among monozygotic than dizygotic twins.²⁷ Family studies have shown that there is a higher prevalence of BHR among the relatives of asthmatic subjects than among those of nonasthmatic subjects.^{8,28} To our knowledge, this is the first study in which bronchial responsiveness has been assessed in the families of patients with allergic rhinitis. Because of the heterogeneous age of the population studied, it is difficult to compare the overall prevalence of BHR in families with that in the general population, but this seems to be higher in the former because the prevalence among parents (11.7%, 27 of 230) was higher than that among the adult population (7.0%, 37 of 526) of Korea.²⁹ Our results have shown that the prevalence of BHR in families in the BHR(+) group is significantly higher than that in families in the BHR(−) group, which suggests that in allergic rhinitis there is a familial component of BHR. This difference may be responsible for the higher prevalence of asthma among families in the BHR(+) group because all the asthmatic subjects have concomitant BHR. In addition to examining bronchial responsiveness in terms of PC_{20} , we have calculated an index of FEV_1 decline during methacholine challenge. This method of expressing responsiveness, the BR index,¹⁷ provides a continuous variable for bronchial responsiveness even in subjects who are not responsive enough to have a measurable PC_{20} . On the basis of PC_{20} criteria ($PC_{20} > 25$ mg/mL), most of the family members we studied are in fact regarded as not reactive. A statistically significant difference in the BR index was found between families in the BHR(+) group and those in the BHR(−) group; although small in absolute terms, this difference remains significant, even when only family members without BHR were considered. Our finding suggests that family members in the BHR(+) group

whose bronchial responsiveness (on the basis of PC₂₀ criteria) appears to be normal show greater responsiveness than those in the BHR(–) group. Together with the higher prevalence of BHR among families in the BHR(+) group, these observations on the BR index provide further evidence that in BHR among patients with allergic rhinitis there is a significant familial predisposition.

The demonstration of familial aggregation provides an important piece of evidence that genetic factors play a role in allergic rhinitis–associated BHR, although it does not imply that there is always a genetic basis. Familial aggregation can be caused by common environmental factors or by an interaction of environmental and genetic factors that can influence the perceived pattern of inheritance. BHR in asthma is caused by the interaction between baseline bronchial responsiveness and airway changes caused by the inflammatory process³⁰; a number of arguments suggest that genetic factors might control this baseline hyperresponsiveness.^{8,31} However, the largest part of BHR in asthma is probably acquired and related to airway inflammation,³² which is also a common feature of allergic rhinitis.³³ There is, in addition, convincing evidence that BHR in patients with allergic rhinitis could be induced by repeated allergic reaction. Patients with perennial rhinitis are at much higher risk of having BHR than those with seasonal rhinitis.¹¹ Bronchial responsiveness in subjects with allergic rhinitis is known to increase either after nasal allergen challenge³⁴ or after natural exposure.³⁵ These findings suggest that BHR may be an acquired abnormality, perhaps as a consequence of chronic low-grade exposure to allergens. It is not clear, however, whether BHR in allergic rhinitis is caused by nasal inflammation resulting from postnasal mediator drip, which directly alters bronchial smooth muscle contractility,³⁶ or airway inflammation itself.³⁷ Besides this allergic inflammation, many environmental factors, such as viral respiratory infection³⁸ and exposure to pollutants,³⁹ may be involved. BHR in subjects with allergic rhinitis therefore appears to be of multifactorial origin and influenced by genetic susceptibility and environmental factors. Nonetheless, an investigation of the underlying genetic mechanisms responsible for susceptibility to BHR will improve our understanding of the factors that lead to the development and progression of allergic rhinitis–associated BHR.

Although our study was directed toward BHR rather than atopy, there was no difference in atopic status, as assessed by the prevalence of positive skin test responses, or in the atopy index, between families in the BHR(+) group and BHR(–) group. The prevalence of atopy among parents of the 2 groups combined (56.5%, 130 of 230) was higher than that (40.8%, 172 of 422) among the adult population of Korea.⁴⁰ Our finding suggests that an inherited tendency for atopy to develop is no more an important factor for determining BHR in children with allergic rhinitis than is the atopic status of these children, and it is compatible with that of a previous study⁴¹ suggesting that bronchial hyperreactivity and atopy may be

under separate genetic control. Some studies^{42,43} that have investigated familial aggregation in BHR have been hampered by lack of control of the atopic status of family members. In this respect families of patients with allergic rhinitis may be a good subject for the study of genetic factors responsible for BHR.

In conclusion, our results indicated that in BHR among patients with allergic rhinitis there is a significant familial predisposition. Although this finding may provide a piece of evidence for the involvement of genetic influence in allergic rhinitis–associated BHR, further studies, including environmental factors such as mite and pet exposure, are needed to further elucidate that conclusion.

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