

Perennial rhinitis: An independent risk factor for asthma in nonatopic subjects

Results from the European Community Respiratory Health Survey

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Background: Although clinical and experimental studies suggest that upper respiratory tract dysfunction may affect the lower airways, rhinitis is usually not studied as a potential risk factor for asthma. This is because both diseases share key elements of pathogenesis and are usually considered as different manifestations of the same underlying "atopic" state.

Objective: We sought to assess whether asthma is associated with rhinitis in the absence of immunologic disorders in a population study.

Methods: Data from 34 centers participating in the European Community Respiratory Health Survey were analyzed. Random samples of 20- to 44-year-old subjects were invited to complete a detailed questionnaire and undergo total and specific IgE measurements, skin prick tests to 9 allergens, and bronchoprovocation challenges with methacholine.

Results: Subjects with perennial rhinitis ($n = 1412$) were more

likely than control subjects ($n = 5198$) to have current asthma. After adjustment for sex, age, smoking habit, family history of asthma, geographic area, and season at the time of examination, asthma was strongly associated with rhinitis among atopic subjects (odds ratio [OR] = 8.1; 95% confidence interval [CI] = 5.4–12.1) but also among nonatopic subjects (OR = 11.6; 95% CI = 6.2–21.9). Moreover, the association remained very strong when the analysis was restricted to nonatopic subjects with IgE levels of 80 kIU/L or less (OR = 13.3; 95% CI = 6.7–26.5). In nonasthmatic subjects bronchial hyperresponsiveness was also more frequent in subjects with rhinitis than in those without rhinitis (OR = 1.7; 95% CI = 1.2–2.6 in nonatopic subjects with IgE levels of ≤ 80 kIU/L).

Conclusion: The strong association between perennial rhinitis and asthma in nonatopic subjects with normal IgE levels is consistent with the hypothesis that rhinitis is an independent risk factor for asthma. (*J Allergy Clin Immunol* 1999;104:301–4.)

Key words: Rhinitis, asthma, bronchial hyperresponsiveness, atopy, population study

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There is strong evidence that perennial rhinitis and asthma frequently occur together in the same patients,^{1–3} but the nature of the association is not well known.

The 2 conditions share etiologic factors. Atopy, which is the predisposition for the development of an IgE-mediated response to common environmental allergens, is an important determinant of an individual's susceptibility to both allergic rhinitis and asthma.⁴ Rhinitis and asthma may therefore both be clinical manifestations of an underlying predisposing immunologic state.

Burrows et al⁵ showed that asthma was strongly associated with serum IgE levels independently of sensitivity to specific allergens (assessed by skin prick tests), whereas allergic rhinitis was mainly associated with skin test reactivity. More recently, an analysis of the Spanish data from the European Community Respiratory Health Survey (ECRHS) confirmed that asthma was associated with total serum IgE independently of specific IgE levels.⁶ In a longitudinal study of first-year college students, Settiple et al⁷ found that positive allergy skin test responses on the one hand and allergic rhinitis on the other were significant risk factors for the development of new asthma. However, the relative importance of these factors has not been analyzed, and the possibility that rhinitis may itself be a risk factor for asthma in the absence of atopy and increased total IgE levels has not been investigated.

Abbreviations used

BHR: Bronchial hyperresponsiveness

CI: Confidence interval

ECRHS: European Community Respiratory Health Survey

OR: Odds ratio

Inflammatory cells have been found to be present in the lower airways of nonasthmatic patients with allergic rhinitis,^{1,2} and clinical studies have shown that intranasal steroids can decrease the nonspecific or allergen-specific bronchial response.^{3,8} Such findings suggest a more direct link between upper and lower respiratory disorders.

Studying the relationship in nonatopic subjects between perennial rhinitis and asthma and between perennial rhinitis and bronchial hyperresponsiveness (BHR), which is a major feature of asthma, would make it possible to test whether rhinitis is a risk factor for asthma in the absence of immune disorders.

Data from a large population-based study were used to assess whether the relationships between perennial rhinitis and asthma and between perennial rhinitis and BHR exist in nonatopic subjects, as well as in atopic subjects.

METHODS

Data were collected as part of the ECRHS (methods described elsewhere⁹). Briefly, participants at 48 study centers randomly selected samples of 20- to 44-year-old subjects who completed a short postal questionnaire about asthma and asthma-like symptoms. In 34 centers, randomly selected subsamples from the initial respondent samples were then invited to attend for further tests, including an extended interviewer-administered questionnaire, respiratory function testing with methacholine challenge, skin prick tests (Phazets) for 9 common allergens (*Dermatophagoides pteronyssinus*, cat, *Cladosporium* spp, *Alternaria alternata*, timothy grass, olive, birch, *Parietaria* spp, and common ragweed), specific serum IgE measurements to 5 allergens (*D pteronyssinus*, cat, *Cladosporium* spp, and timothy grass for all centers, plus birch for Northern Europe, *Parietaria* spp for Southern Europe, and ragweed for North America, New Zealand, and Australia), and total IgE measurement.¹⁰ Subjects were defined as having current asthma if they had at least 1 asthma attack or had taken asthma medication in the previous 12 months. Perennial rhinitis was defined as affirmative answers to both of the following questions for the reported diagnosis of allergic rhinitis and symptoms of perennial rhinitis, respectively: "Do you have any nasal allergies, including hay fever?" and "When you are near animals, such as cats, dogs, or horses; near feathers, including pillows, quilts, or duvets; or in a dusty part of the house, do you ever get a runny or stuffy nose or start to sneeze?" Subjects with negative answers to both questions were considered as control subjects. BHR was defined as a 20% or greater decline in FEV₁ after inhalation of 1 mg of methacholine or less. Atopy was defined as at least 1 positive specific IgE measurement (≥ 0.35 kIU/L) or 1 positive skin test response (wheal mean diameter ≥ 3 mm larger than that produced by the negative control).

Univariate analyses were carried out to test the association between rhinitis and asthma and between rhinitis and BHR and to identify possible confounding factors. Contingency tables were analyzed by using chi-square tests. Continuous variables were analyzed by using *t* tests. Multivariate logistic regressions with asthma or

BHR as independent variables were used to test the association between these outcomes and rhinitis and to estimate odds ratios (ORs), taking confounding factors into account (SAS statistical package).

RESULTS

Data were analyzed for 1412 subjects with perennial rhinitis and 5198 control subjects with complete information on asthma, BHR, atopy, and family history of asthma. Compared with control subjects, subjects with rhinitis were slightly younger (32.8 years vs 33.5 years; $P = .001$), the proportion of men was lower (47.0% vs 53.0%; $P = .001$), and the proportion of smokers (current or past smoker, 48.4% vs 59.5%), as well as the proportion of current heavy smokers (at least 20 cigarettes/day; 8.2% vs 15.6%; $P = .001$), was lower.

The frequency of current asthma was 16.2% among individuals with rhinitis versus 1.0% among control subjects (OR = 19.9; 95% confidence interval [CI] = 14.6-27.2). Among nonasthmatic subjects, the frequency of BHR was 22.5% in subjects with rhinitis versus 7.5% in control subjects (OR = 3.6; 95% CI = 3.0-4.3).

Atopy was present in 74.7% of subjects with rhinitis and 25.6% of control subjects. Asthma was much more frequent among atopic than among nonatopic subjects (9.7% vs 1.1%; $P = .001$). However, among nonatopic subjects, the proportion of subjects with asthma remained significantly higher for subjects with rhinitis than for control subjects (7.8% vs 0.5%; $P = .001$), as was the case among atopic subjects (19.1% vs 2.3%; $P = .001$; ORs are shown Table I). Similarly among nonasthmatic subjects, the relationship between rhinitis and BHR was observed for both atopic and nonatopic subjects. The frequency of BHR in subjects with rhinitis and in control subjects was as follows: 11.6% and 6.6%, respectively, among nonatopic subjects ($P = .001$) and 26.7% and 10.0%, respectively, among atopic subjects ($P = .001$).

Rhinitis, asthma, BHR, and atopy all correlated with sex, age, smoking status, family history of asthma, and geographic area. We therefore carried out multiple logistic regression analyses including all these factors and the season at the time of the examination.

The probability of having asthma was strongly associated with perennial rhinitis, independent of the possible confounders tested, for both atopic and nonatopic subjects, with ORs greater than 9 (Table I).

To assess whether these associations were still observed in subjects with normal IgE levels, the analysis was eventually restricted to subjects with total IgE levels of 80 kIU/L or less. After adjustment for the possible confounders listed above, asthma remained significantly associated with perennial rhinitis in the 1180 atopic subjects with normal IgE levels but also among the 3654 nonatopic subjects with normal IgE levels (OR = 9.8 [$P = .001$] and OR = 13.3 [$P = .001$], respectively; Table I).

The relationship between rhinitis and BHR in nonasthmatic subjects was not as strong as that between the presence of rhinitis and asthma, but BHR was also indepen-

TABLE I. ORs and 95% CIs for the association between perennial rhinitis and asthma and between perennial rhinitis and BHR for atopic and nonatopic subjects

	Asthma				BHR in nonasthmatic subjects			
	Atopic		Nonatopic		Atopic		Nonatopic	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
All subjects, no adjustment	9.9	6.7–14.5	17.2	9.5–31.2	3.3	2.6–4.1	1.8	1.3–2.6
All subjects, adjusted*	8.1	5.4–12.1	11.6	6.2–21.9	3.3	2.6–4.2	1.5	1.0–2.2
Subjects with IgE ≤80 kIU/L, adjusted*	9.8	5.0–19.2	13.3	6.7–26.5	3.2	2.2–4.8	1.7	1.2–2.6

*Logistic regression adjusted for sex, age, smoking status, family history of asthma, geographic area, and season at the time of examination.

dently associated with rhinitis in all groups, including nonatopic subjects with normal IgE levels (OR, 1.7; $P = .007$).

Finally, the analysis was rerun with an extremely sensitive definition of atopic status: at least 1 positive specific IgE measurement or at least 1 skin test wheal of greater than 0 mm¹¹ (ie, 1 mm or more), so that the subjects with very small wheals were not considered as nonatopic. The results were practically unchanged. Particularly for nonatopic subjects with IgE levels of 80 kIU/L or less, rhinitis was still strongly associated with asthma (OR = 13.0; 95% CI = 6.4–26.5) and with BHR in nonasthmatic subjects (OR = 1.6; 95% CI = 1.0–2.4).

DISCUSSION

Our results from a large population study show that the relationships between perennial rhinitis and asthma and between perennial rhinitis and BHR exist even in nonatopic subjects with total IgE measurements in the normal range.

As in all large population studies, data were collected by means of questionnaires, which is a potential limitation. An additional difficulty was related to the international design of this study. However, a high degree of standardization was obtained by the use of questions from previously validated questionnaires and by strict procedures of translations and back translations. Moreover, the consistency of the results in the different countries was previously checked, and geographic area was accounted for in the analysis as a possible confounding factor.

We could carry out this analysis because the study population was large, and the number of nonatopic subjects who reported having allergic rhinitis and symptoms of perennial rhinitis was sufficient. This situation (ie, “allergic” rhinitis without atopy) might seem somewhat surprising, but it is not unusual. Droste et al¹² analyzed the Dutch part of the ECRHS, which also included the age range of 45 to 70 years, and considered subjects with nasal symptoms regardless of their responses to the question concerning nasal allergies. Among those with symptoms of perennial rhinitis, the proportion of subjects with 1 or more positive skin prick test responses or specific IgE was 53%. Our definition of rhinitis included both a diagnosis of nasal allergies and the presence of current nasal symptoms. However, in spite of this more specific defini-

tion, 25% of the subjects with rhinitis were not atopic. Given the number and the choice of the allergens tested, it is unlikely that a large proportion of subjects classified as nonatopic were allergic to allergens that were not tested. In the preparation of this survey, considerable time was spent discussing the appropriate allergens to use. In addition to the common panel of 9 allergens, centers were allowed to add 2 “local” allergens that were particularly frequent in the region. The proportion of the population designated as atopic in any center varied very little when these tests were considered in addition to the common panel of allergens (overall difference, <1%). To avoid misclassification of atopic subjects as nonatopic, we considered subjects to be atopic if they had either at least 1 specific IgE measurement or 1 positive skin prick test response. Moreover, the results were very similar when we used an even more sensitive definition of atopy by considering a skin prick test response as positive if the mean wheal diameter was at least 1 mm. Although there is no definite agreement about the level of serum IgE that exceeds the normal limit, the level of 100 kIU/L is commonly used to separate subjects with normal and elevated IgE levels. We chose a lower threshold (80 kIU/L) so as to reduce the risk of classifying subjects with immune disorders as subjects with normal IgE levels.

A possible explanation for the presence of nonatopic subjects with “allergic” rhinitis is that these subjects reported having nasal allergies because they had symptoms similar to those of perennial allergic rhinitis but actually had some other nasal disorders. These disorders may include nonallergic, noninfectious perennial rhinitis (also referred to as *vasomotor rhinitis*) or nonallergic rhinitis with eosinophilia syndrome, which is a recently characterized condition with symptoms similar to those of perennial allergic rhinitis that has been shown to be associated with BHR and bronchial inflammation.¹³

Whatever the nature of such nonatopic rhinitis, our results show that the relationships between rhinitis and asthma and between rhinitis and BHR may exist when there is no evidence of an immunologic disorder that might predispose the patients to both upper and lower airways disease.

In the study of Burrows et al,⁵ there were no asthmatic subjects among subjects with extremely low IgE levels. The authors concluded that asthma almost always has an allergic basis and challenged the concept of non-allergic (“intrinsic”) and allergic (“extrinsic”) asthma as

2 distinct forms. In our study, although asthma was much more frequent in atopic subjects and in subjects with elevated IgE levels, there were a number of asthmatic subjects among the nonatopic subjects with normal IgE levels, and among these subjects the risk of asthma was associated with rhinitis. Asthma related to nonallergic perennial rhinitis might therefore explain some cases of so-called "intrinsic asthma."

There are several possible mechanisms linking upper and lower airway dysfunction. They include nasal-bronchial reflex, mouth breathing because of nasal obstruction, or pulmonary aspiration of nasal contents.^{2,3} Our finding that the association between rhinitis and asthma is not explained by impaired immunologic status, and the biologic plausibility that upper dysfunction may affect lower airways, are consistent with the view that nasal disease can directly cause lower airway disorders.

This hypothesis should be tested in longitudinal surveys, taking atopic status into account. A recent report of a 23-year follow-up study showed that asthma was 7 times more likely to occur in individuals with allergic rhinitis than in individuals without allergic rhinitis. However, it was not investigated whether this could be the result of atopic subjects being more likely to have both rhinitis and asthma, and treatment of rhinitis was not considered.¹⁴ Given the beneficial effects of the treatment of rhinitis on concomitant asthma and BHR reported in short-term clinical studies, long-term studies of nonasthmatic subjects with perennial or otherwise chronic rhinitis should also determine whether rhinitis therapy can prevent the development of asthma. The next stage of the ECRHS, in which all subjects who participated in the last survey should be reexamined (ie, 8 to 10 years after the first examination), will enable us to address these issues.

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