

The Course of Asthma Parallels that of Allergic Rhinitis: A 23-Year Follow-Up Study of College Students

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ABSTRACT

The purpose of this study is to examine the relationship between the course of asthma and allergic rhinitis among former Brown University students who were diagnosed with these diseases either before or after their freshman year of 1962 or 1963. A total of 738 former students, who were evaluated and underwent skin testing during their freshman year, completed a 23-year follow-up questionnaire inquiring of their history of allergies and asthma and are the focus of this study. The activity of asthma as related to the course of allergic rhinitis (hay fever and/or nonseasonal allergic rhinitis) was examined. Among 44 asthmatic subjects with purely seasonal allergic rhinitis (hay fever and no history of nonseasonal allergic rhinitis), asthma was active in 75% of those with worse hay fever, 70% of those with unchanged hay fever, 50% of those with better (but not symptom-free) hay fever, and 10% of those with symptom-free hay fever. The resolution of asthma symptoms correlated significantly with improvement in hay fever ($p = 0.0053$). Among 70 asthmatics with any form of allergic rhinitis (hay fever and/or nonseasonal allergic rhinitis), asthma was active

in 75.0% of those with worse allergic rhinitis, 66.7% of those with unchanged allergic rhinitis, 53.3% of those with better (but not symptom-free) allergic rhinitis, and 20.0% of those with symptom-free allergic rhinitis. The resolution of asthma symptoms correlated significantly with improvement in allergic rhinitis ($p = 0.0052$). The activity of allergic rhinitis as related to the course of asthma was also examined. Among 44 asthmatic subjects with purely seasonal allergic rhinitis (hay fever and no history of nonseasonal allergic rhinitis), hay fever was active in 100% of those with worse asthma, 100% of those with unchanged asthma, 90.9% of those with better (but not symptom-free) asthma, and 60.9% of those with symptom-free asthma. The resolution of hay fever symptoms correlated significantly with improvement in asthma ($p = 0.0109$). Among 71 asthmatic subjects with any form of allergic rhinitis (hay fever and/or nonseasonal allergic rhinitis), allergic rhinitis was active in 91.9% of those with active asthma and 64.7% of those with symptom-free asthma. The resolution of allergic rhinitis symptoms correlated significantly with improvement in asthma ($p = 0.0078$). In summary, among individuals with asthma and allergic rhinitis, improvement of allergic rhinitis was associated with a resolution of asthma symptoms, whereas a worsening of allergic rhinitis was associated with the persistence of asthma symptoms. Likewise, among asthmatic subjects with allergic rhinitis, improvement of asthma was associated with a resolution of allergic rhinitis symptoms, whereas a worsening of asthma was associated with the persistence of allergic rhinitis symptoms. (Allergy and Asthma Proc 21:371–376, 2000)

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Asthma, hay fever, and nonseasonal allergic rhinitis were thoroughly evaluated in 1836 Brown University freshmen, 99.2% of the freshmen classes, in the initial study during 1962–1963.¹ This group of former Brown University

freshmen was subsequently studied 3 years, 7 years, and 23 years later.²⁻⁷

In the first part of this 23-year follow-up study, 1601 individuals were contacted and asked to complete a questionnaire, and 1021 (64%) returned them.⁴ Previously, 738 (72%) of these individuals had been skin tested. The mean age of these 738 participants at the time of the 23-year follow-up was 40 years with an age range of 38–64 years, 97% being between the ages of 40 and 42 years. This group was composed of 69% males and 31% females, which was essentially the same ratio of 70% males and 30% females in the original study.^{1,4} At the time of the follow-up study, 30 (4%) of these 738 individuals lived outside of the continental United States.⁵

The cumulative prevalences of asthma, hay fever, and nonseasonal allergic rhinitis were previously reported in this 23-year follow-up study.⁴⁻⁷ Cumulative prevalence was defined as the percentage of individuals with either a past or present history of a particular disease. The cumulative prevalence of asthma was 11.4%, hay fever was 41.5%, and nonseasonal allergic rhinitis was 14.0%. The cumulative prevalence of allergic rhinitis (hay fever and/or nonseasonal allergic rhinitis) was 45.8%.

Asthmatic subjects often have allergic rhinitis. In this 23-year follow-up study, asthmatic subjects were approximately twice as likely to have a history of allergic rhinitis than nonasthmatic subjects (85.7% versus 40.7%).⁵ In a study by Kapsali and colleagues, 98.9% of allergic asthmatic subjects had rhinitis.⁸ Gaga and colleagues reported that elements of inflammation exist even in the nasal mucosa of nonrhinitic asthmatic subjects.⁹

Individuals with allergic rhinitis often have asthma. In our study, asthma occurred over seven times more often in individuals with a history of allergic rhinitis than in participants without a history of allergic rhinitis (21.3% versus 3.0%).⁵ Mullarkey and colleagues reported that 58% of the patients diagnosed as having allergic rhinitis on the basis of histories correlating with positive skin tests and markedly elevated total serum IgE levels had histories or findings consistent with asthma.¹⁰ Even among patients with allergic rhinitis and no clinical evidence of asthma, nonspecific bronchial hyper-responsiveness has often been demonstrated.¹¹⁻¹⁴

Participants in our study with a history of allergic rhinitis had approximately three times the risk of developing new asthma when compared with controls (10.5% versus 3.6%) ($p < 0.002$).⁴ In addition, students with positive allergy skin tests had more than three times the risk of developing new asthma over a 23-year period than did skin-test negative students (10.6% versus 3.2%) ($p < 0.001$). Also, allergy skin test positive students had more than twice the risk of developing new hay fever over this same period than skin test negative students (42.9% versus 18.8%) ($p < 0.0001$). In our study, hay fever developed before or at the same time as asthma in 65.5% of those individuals with a cumulative prevalence of both diseases.⁵ Likewise, nonseasonal allergic rhinitis occurred before or at the same time as asthma in

69.3% of those participants with a history of both diseases. Other studies have demonstrated a similar temporal relationship between allergic rhinitis and asthma.¹⁵⁻¹⁷

Little is known from long term studies as to whether the long term course of asthma parallels that of allergic rhinitis. The purpose of this study is to examine the relationship between the course of asthma and allergic rhinitis in our 23-year follow-up group. The activity of a particular disease was classified as either active or symptom-free. A disease was considered active if the symptoms were better (but not symptom free), unchanged, or worsened, at the time of the 23-year follow-up study as compared to several years previously. Individuals were classified as symptom-free if they had no symptoms for at least the previous 2 years.

MATERIALS AND METHODS

Initial Study of College Students

During the first week of college (1962 and 1963), each freshman, with assistance from allergy-trained medical personnel, completed a questionnaire that documented any personal history of allergy.¹ The specific type or types of allergies as well as onset age, duration, symptoms, time of year affected, and therapy were noted. Family history of allergic disease was reported if known. The information was corroborated through correspondence with their parents. Additional information on histories was obtained by personal interview of freshmen at the time of skin tests.

Skin tests were done by the scratch technique. The glycerinated extracts included tree, grass, and ragweed pollen, mold, animal, and selected foods as previously described.¹ House dust mite extracts were not available at that time and were therefore not used for testing. Saline was used as a negative control. The students were instructed not to take any antihistamines for 24 hours prior to testing. Reactions were considered positive if they were definitely larger than the negative control. Of the 1836 Brown University freshmen studied, 1243 (68%) were skin tested. Physical examination and chest X ray, required of freshmen at that time, were also evaluated.

An individual diagnosis was established by evaluating the answers given on the original questionnaire and at the time of skin testing and additional information supplied by parents. Skin scratch test results were not used to classify individuals as affected with a particular diagnosis. The diagnosis of asthma was based on a history of recurrent, reversible episodes of wheezing and dyspnea (at least three separate episodes) not caused by any other diseases. Hay fever or seasonal allergic rhinitis was defined as a history of watery, itchy eyes, rhinorrhea, and sneezing occurring during the same seasonal period for at least 2 consecutive years. The diagnosis of nonseasonal allergic rhinitis was based on a history of similar symptoms as hay fever, but occurring nonseasonally and associated with exposure to particular antigens, e.g., animal danders. The term allergic rhinitis, when not preceded by either seasonal or nonseasonal, was

used to describe hay fever and nonseasonal allergic rhinitis occurring either singly or in combination.

23-Year Follow-up Study

The same information and criteria established in our initial report were used in our follow-up studies performed 3, 7, and 23 years after the initial information was obtained from freshmen.⁴⁻⁷ Repeated efforts were made to contact all former students who had participated in the initial study. Names and addresses of these individuals were obtained from Brown University Alumni Office, which has a current address file.

Each of these former students was asked to complete a detailed three-page follow-up questionnaire of their history of asthma, hay fever, and nonseasonal allergic rhinitis. Each person was asked to provide information concerning any past or new type of allergy or problem related to an allergy that had developed; the season, if any, of occurrence; the symptoms manifested; the year of onset and duration of symptoms; the causes of symptoms if they were known; and new family history of allergy that may have developed. A recurrence of a previous asthma or allergic rhinitis was not classified as a new disease. Skin tests were not repeated in

the follow-up studies because most of the graduates were no longer in the Brown University geographic area.

Statistical probability was determined by using either the chi-squared test for trend or Fisher's exact test as appropriate.

RESULTS

The activity of asthma as related to the course of allergic rhinitis was examined in our 23-year follow-up study group (Tables I and II). Among 44 asthmatic subjects with hay fever and no history of nonseasonal allergic rhinitis, asthma was active in 75.0% of those with worse hay fever, 70.0% of those with unchanged hay fever, 50.0% of those with better (but not symptom-free) hay fever, and 10.0% of those with symptom-free hay fever (Table I). One asthmatic patient with an unknown course of hay fever was not included. The resolution of asthma symptoms correlated significantly with improvement in hay fever ($p = 0.0053$).

Among nine asthmatic subjects with nonseasonal allergic rhinitis and no history of hay fever, asthma was active in 80.0% of those individuals whose nonseasonal allergic rhinitis was unchanged, and 50.0% of those whose nonseasonal allergic rhinitis was symptom-free. None of these

TABLE I

Activity of Asthma as Related to the Course of Hay Fever

Hay Fever*		Asthma		<i>p</i> Value for Trend
Symptoms	Number	Active No. (%)	Symptom-Free No. (%)	
Worse	4	3 (75.0)	1 (25.0)	0.0053
Unchanged	10	7 (70.0)	3 (30.0)	
Better†	20	10 (50.0)	10 (50.0)	
Symptom-free	10	1 (10.0)	9 (90.0)	
Total	44	21	23	

*And no history of nonseasonal allergic rhinitis.

†But not symptom-free.

TABLE II

Activity of Asthma as Related to the Course of Allergic Rhinitis

Allergic Rhinitis*		Asthma		<i>p</i> Value for Trend
Symptoms	Number	Active No. (%)	Symptom-Free No. (%)	
Worse	4	3 (75.0)	1 (25.0)	0.0052
Unchanged	21	14 (66.7)	7 (33.3)	
Better†	30	16 (53.3)	14 (46.7)	
Symptom-free	15	3 (20.0)	12 (80.0)	
Total	70	36	34	

*History of hay fever and/or nonseasonal allergic rhinitis.

†But not symptom-free.

TABLE III

Activity of Hay Fever as Related to the Course of Asthma

Asthma		Hay Fever*		<i>p</i> Value for Trend
Symptoms	Number	Active No. (%)	Symptom-Free No. (%)	
Worse	3	3 (100.0)	0 (0.0)	0.0109
Unchanged	7	7 (100.0)	0 (0.0)	
Better†	11	10 (90.9)	1 (9.1)	
Symptom-free	23	14 (60.9)	9 (39.1)	
Total	44	34	10	

*And no history of nonseasonal allergic rhinitis.

†But not symptom-free.

TABLE IV

Activity of Allergic Rhinitis as Related to the Activity of Asthma

Asthma		Allergic Rhinitis*		<i>p</i> Value
Symptoms	Number	Active No. (%)	Symptom-Free No. (%)	
Active	37	34 (91.9)	3 (8.1)	0.0078
Symptom-free	34	22 (64.7)	12 (35.3)	
Total	71	56	15	

*History of hay fever and/or nonseasonal allergic rhinitis.

asthmatic subjects reported that their nonseasonal allergic rhinitis was worse or better (but not symptom free). The resolution of asthma symptoms trended in association with improvement in nonseasonal allergic rhinitis, although the trend was not statistically significant ($p = 0.5238$).

Among 70 asthmatic subjects with allergic rhinitis, asthma was active in 75.0% of those with worse allergic rhinitis, 66.7% of those with unchanged allergic rhinitis, 53.3% of those with better (but not symptom-free) allergic rhinitis, and 20.0% of those with symptom-free allergic rhinitis (Table II). One individual with active asthma had unchanged hay fever and better (but not symptom-free) nonseasonal allergic rhinitis and was not included. The resolution of asthma symptoms correlated significantly with improvement in allergic rhinitis ($p = 0.0052$).

The activity of allergic rhinitis as a function of asthma symptoms was examined (Tables III and IV). Among 44 asthmatic subjects with purely seasonal allergic rhinitis, hay fever was active in 100% of those with worse asthma, 100% of those with unchanged asthma, 90.9% of those with better (but not symptom-free) asthma, and 60.9% of those with symptom-free asthma (Table III). One asthmatic patient with an unknown course of hay fever was not included. The resolution of hay fever symptoms correlated significantly with improvement in asthma ($p = 0.0109$).

Among nine asthmatic subjects with nonseasonal allergic rhinitis and no history of hay fever, nonseasonal allergic

rhinitis was active in 66.7% of individuals with active asthma and 33.3% of those whose asthma was symptom-free. The resolution of nonseasonal allergic rhinitis trended in association with improvement in asthma, although the trend was not statistically significant ($p = 0.5238$).

Among 71 asthmatic subjects with allergic rhinitis, allergic rhinitis was active in 91.9% of those with active asthma, and 64.7% of those with symptom-free asthma (Table IV). The resolution of allergic rhinitis symptoms correlated significantly with improvement in asthma ($p = 0.0078$).

DISCUSSION

The former Brown University students who were previously skin tested as college freshman and who responded to the 23-year follow-up questionnaire were the focus of this study. This group was specifically considered because the results of prior allergy skin tests were of importance in Part I of this study.⁴ The fact that the total population of college freshmen when compared to those who volunteered for allergy testing (68%) was very similar in composition as determined by sex ratio and history of allergy supported the decision to focus on skin tested students.¹

The relationship between the activities of asthma and allergic rhinitis was the focus of this part of the 23-year follow-up study. Among asthmatics with allergic rhinitis,

resolution of asthma symptoms correlated with improvement in allergic rhinitis. In a study by Huse and colleagues using a database of 1261 asthmatic subjects, those with significant nasal allergy were compared to patients with mild or no symptoms of nasal disease.¹⁸ Consistent with our own observations, those individuals with more severe rhinitis were more likely than those with less severe nasal disease to have moderate to severe asthma (19.6% versus 11.8%), nocturnal awakening due to asthma (60.2% versus 51.2%), and loss of work as a result of asthma difficulties (24.1% versus 21.1%).

A number of possible mechanisms have been proposed through which allergic rhinitis may affect asthma including a nasobronchial reflex, pulmonary aspiration of nasal contents, and mouth breathing caused by nasal obstruction. In a study by Yan and Salome involving patients with allergic rhinitis and asthma, histamine was applied to the nose.¹⁹ A fall in FEV1 was observed in half of the patients. Corren and colleagues, in a similar study, applied allergen to the nose in patients with allergic rhinitis and asthma. An increase in bronchial hyperresponsiveness was observed, both immediately and during the late phase reaction.²⁰ The studies by Yan and Corren support the theory that asthma exacerbation by rhinitis is a result of upper airway and bronchial reflexes.

Postnasal drainage of inflammatory cells into the lower airways may play an important role in increasing bronchial responsiveness. Induction of nasal inflammation in an animal model of rhinosinusitis resulted in increased bronchial responsiveness without causing airflow limitation.²¹ Blockage of nasal secretions draining into the lungs prevented this increase in lower airway reactivity.

Mouth breathing caused by nasal obstruction secondary to allergic rhinitis has been proposed as another mechanism by which allergic rhinitis affects asthma. Shturman-Ellstein and colleagues demonstrated that mouth breathing associated with nasal obstruction resulted in worsening of exercise-induced asthma and that exclusive nasal breathing significantly reduced bronchospasm after exercise.²² Warming and humidification of inspired air before it reaches the lower airways may be the explanation for this observation.²³ Also aeroallergens and pollutants are more likely to enter the lungs during mouth breathing when the nose is obstructed, resulting in increased bronchial reactivity.²⁴

From a therapeutic standpoint, there also appears to be a relationship between allergic rhinitis and asthma. Intranasal corticosteroids can prevent an increase in nonspecific bronchial reactivity and asthma symptoms associated with seasonal and perennial allergen exposure.²⁵⁻²⁸ Studies have shown that antihistamines not only decrease nasal allergy symptoms, but also may reduce asthma symptoms, and improve pulmonary function among patients with both diseases.²⁸

Few studies have looked at how the treatment of asthma may affect coexisting nasal disease. In our study, asthmatic subjects who were now symptom-free were more likely than

those individuals with active asthma to have resolution of allergic rhinitis symptoms. Greiff and colleagues demonstrated that treating subclinical asthma with an orally inhaled glucocorticoid improved allergic rhinitis.²⁹ In their placebo-controlled, double-blind, parallel-group seven-week study during the birch pollen season, patients with allergic rhinitis and bronchial hyperresponsiveness to methacholine but without clinical asthma were treated with orally inhaled budesonide. In addition to preventing seasonal development of increased bronchoconstrictor responsiveness to methacholine, nasal symptoms were also reduced as well as nasal and peripheral blood eosinophilia and nasal lavage fluid eosinophilic cationic protein.

In conclusion, this long-term study of college students suggests that the course of asthma occurs in parallel to that of allergic rhinitis. Among individuals with asthma and allergic rhinitis, improvement of allergic rhinitis was associated with a resolution of asthma symptoms, whereas a worsening of allergic rhinitis was associated with the persistence of asthma symptoms. Likewise, among asthmatic subjects with allergic rhinitis, improvement of asthma was associated with a resolution of allergic rhinitis symptoms, whereas a worsening of asthma was associated with the persistence of allergic rhinitis symptoms.

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