

Short communication

The link between allergic rhinitis and allergic asthma: A prospective population-based study. The Copenhagen Allergy Study

Background: It has been hypothesized that allergic rhinitis and allergic asthma are manifestations of the same disease entity. We aimed to investigate the relationship between allergic rhinitis and allergic asthma.

Methods: Participants in a population-based study of 15–69-year-olds in 1990 were invited to a follow-up in 1998. A total of 734 subjects were examined on two occasions eight years apart. Allergic rhinitis to pollen was defined as a history of nasal symptoms on exposure to pollens and IgE specific to pollen. Allergic asthma to pollen was defined as a history of lower airway symptoms on exposure to pollens and IgE specific to pollen. Similarly, diagnoses of allergic rhinitis and allergic asthma to animals or mite were defined.

Results: At follow-up, all subjects with allergic asthma to pollen ($n=52$) had in addition allergic rhinitis to pollen. In the longitudinal analysis, there were a total of 28 new (incident) cases of allergic asthma to pollen. They all had allergic rhinitis to pollen at baseline, or had developed allergic rhinitis to pollen at follow-up. Accordingly, allergic rhinitis to animals and mite were ubiquitous in subjects with allergic asthma to animals and mite, respectively.

Conclusions: The results support the hypothesis that allergic rhinitis and allergic asthma are manifestations of the same disease entity.

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We have previously reported a parallel increase in the prevalence of allergic rhinitis symptoms and allergic asthma symptoms during the 1990s among young adults in Copenhagen, Denmark (1). A corresponding increase in the prevalence of IgE antibody positivity and skin prick test reactivity to common inhalant allergens in the same background population supports the notion that the increase in symptoms is real, not merely due to increased recognition of symptoms (2, 3).

Several recent reviews have concluded that a close relationship exists between allergic rhinitis and asthma (4–9). It has even been proposed that allergic rhinitis and allergic asthma are manifestations of the same disease entity and that they represent a continuum of disease. In this way, subjects with less severe disease express only rhinitis, while subjects with more severe disease express both rhinitis and asthma. This concept has been labeled “one airway, one disease” (6), “allergic rhinobronchitis” (8), or “united airways disease” (10). According to this concept, allergic rhinitis should be ubiquitously present in subjects with allergic asthma.

However, epidemiological studies have not been able to demonstrate this convincingly. This may be due to the lack of objective epidemiological definitions of disease. There are two major types of rhinitis: allergic rhinitis and nonallergic rhinitis (11). Allergic rhinitis may be further defined as IgE-mediated rhinitis or non-IgE-mediated rhinitis. In this paper we focus on the IgE-mediated subtype of allergic rhinitis and, accordingly, the IgE-mediated subtype of allergic asthma.

The aim of this prospective population-based study was to investigate the relationship between allergic rhinitis and allergic asthma.

Material and methods

Baseline study

The baseline study was conducted according to a two-stage protocol. In the first stage a screening questionnaire on respiratory symptoms was mailed to a sample of 15–69-years-olds ($n=8000$), living in the western part of Copenhagen, the capital of Denmark. The sample was drawn randomly from the Civil Registration System. A total of

6998, or 87.5%, responded to the screening questionnaire. In the second stage, a random group and a symptom group selected from the respondents were invited to a health examination. The random group was comprised of 793 subjects randomly selected from among the respondents. The symptom group was comprised of 788 subjects selected from among those respondents who had reported upper ("itchy or stuffy nose or sneezing") or lower ("shortness of breath or trouble breathing") respiratory symptoms on exposure to either pollen or furry animals in the screening questionnaire. A total of 146 subjects were included in both groups. Subsequently, 599 (participation rate 75.5%) and 635 (participation rate 80.6%) subjects were examined in the random and the symptom groups, respectively. At total of 122 subjects were included in both groups. Thus, a total of 1112 subjects (overall participation rate 77.5%) were examined. Examinations took place between February 1990 and January 1991. The invitation procedure and characteristics of both participants and nonparticipants have previously been described (12).

Follow-up study

At the time of follow-up, 28 subjects had died, 8 had emigrated, and 12 could not be located. Thus, a total of 1064 of the participants from the baseline study were invited to a re-examination; 734 subjects were examined (participation rate 69.0%). Baseline characteristics of both participants and nonparticipants to the follow-up study have previously been described (13). Thus, male sex and a high educational level at baseline were significantly associated with participation in the follow-up study. No other significant differences in baseline characteristics between participants and nonparticipants were observed. We invited the eligible subjects in the same month as they had been examined in the baseline study to avoid potential seasonal differences. Hence, a total of 63.9% (469/734) of the participants in the follow-up study was examined on a date within two months (62 days) of the date of examination in the baseline study. The median follow-up time was 7 years 10 months (range 6 years 10 months–8 years 8 months). The mean age of the participants was 46.8 years (382 women and 352 men). The participants were examined between October 1997 and November 1998. The ethics committee of Copenhagen County approved the study.

Measurement of IgE antibodies

In both the baseline and the follow-up study, venous blood was taken on the day of examination and the blood samples were left to coagulate for 2 h. The serum was then separated by centrifugation at 3000 r.p.m. for 10 min and frozen immediately afterward. The serum samples used for the analysis of IgE antibodies were kept at -20°C without thawing until the analysis in 1999. Serum samples were available for analysis from 98.7% (1098/1112) and 99.5% (730/734) of the subjects examined at baseline and follow-up, respectively. The serum samples were analyzed for IgE specific to birch, grass (timothy), mugwort, dog, cat and mite (*Dermatophagoides pteronyssinus*) with the ADVIA Centaur IgE antibody assay system (Bayer Corporation) (13). The stability of IgE antibodies in serum samples stored at -20°C has previously been confirmed (2). The analysis for IgE antibodies was judged to be positive if the measurement was in excess of 0.35 kU/l.

Diagnoses of allergic rhinitis and allergic asthma

Allergic rhinitis to pollen was defined as an affirmative answer to the question "Have you within the last 12 months had an itchy or stuffy nose or have you been sneezing when near grass, trees, or flowers?" and a positive test for IgE antibodies to at least one of birch, grass, or mugwort.

Allergic asthma to pollen was defined as an affirmative answer to the question "Within the last 12 months have you experienced

shortness of breath or trouble breathing following exposure to grass, trees, or flowers?" and a positive test for IgE antibodies to at least one of birch, grass, or mugwort.

Allergic rhinitis to animals was defined as an affirmative answer to the question "Have you within the last 12 months had an itchy or stuffy nose or have you been sneezing following exposure to furry animals, e.g. horse, dog, cat, rabbit, guinea pig, or hamster?" and a positive test for IgE antibodies to at least one of dog or cat.

Allergic asthma to animals was defined as an affirmative answer to the question "Within the last 12 months have you experienced shortness of breath or trouble breathing following exposure to furry animals, e.g. horse, dog, cat, rabbit, guinea pig, or hamster?" and a positive test for IgE antibodies to at least one of dog or cat.

Allergic rhinitis to mite was defined as an affirmative answer to the question "Have you within the last 12 months had an itchy or stuffy nose or have you been sneezing following exposure to dust when cleaning rooms or making beds, or when in bed?" and a positive test for IgE antibodies to mite.

Allergic asthma to mite was defined as an affirmative answer to the question "Within the last 12 months have you experienced shortness of breath or trouble breathing following exposure to dust when cleaning rooms or making beds, or when in bed?" and a positive test for IgE antibodies to mite.

Answers to the above questions were obtained in a questionnaire, which was completed at home and collected on the day of the examination. Identical questions were used in the two studies. A validation of these questions against IgE antibody positivity to inhalant allergens in a random sample of our background population has previously been presented. Hence, both allergic rhinitis symptoms and allergic asthma symptoms were significantly associated with IgE antibody positivity (1, 2).

Statistical analysis

Only subjects with complete information on relevant variables at both examinations were included in the analyses. Statistical associations were expressed by odds ratios (OR) and 95% confidence intervals (CI). Odds ratios were sex and age adjusted in a logistic regression model. All data were analyzed with SPSS for WINDOWS (RELEASE 10.0).

Results

Table 1 and Table 2 show the cross-sectional relationship between allergic rhinitis and allergic asthma in the baseline and the follow-up study, respectively. It shows that allergic rhinitis was ubiquitous in subjects with allergic asthma. At follow-up, 100% (52/52) of subjects with allergic asthma to pollen had allergic rhinitis to pollen, 89% (31/35) of subjects with allergic asthma to animals had allergic rhinitis to animals, and 95% (19/20) of subjects with allergic asthma to mite had allergic rhinitis to mites (Table 2). Thus, at follow-up, a total of 4 subjects had allergic asthma to animals without allergic rhinitis to animals. Nevertheless, two of these 4 subjects had allergic rhinitis to animals at baseline; and one of the remaining two subjects had allergic rhinitis to mite at follow-up. At follow-up, one subject had allergic asthma to mite without allergic rhinitis to mite (Table 2); and this subject had allergic rhinitis to mite at baseline. Thus, only one subject with allergic asthma at follow-up did not have allergic rhinitis at follow-up or at baseline.

Table 1. The cross-sectional relationship between allergic rhinitis and allergic asthma at baseline in 1990

Allergic rhinitis		Allergic asthma			
		To pollen	No	To animal	To mite
		Yes	No	Yes	No
To pollen	Yes	45	128		
	No	1	543		
To animal	Yes			37	25
	No			2	657
To mite	Yes				19
	No				1

Approximately one-quarter of subjects with allergic rhinitis to pollen had in addition allergic asthma to pollen (26.0% and 28.4% in 1990 and 1998, respectively) (Tables 1 and 2). This proportion appeared considerably higher for animal and mite allergy. Thus, approximately half of subjects with allergic rhinitis to animals (59.7% and 52.5% in 1990 and 1998, respectively) and allergic rhinitis to mite (50.0% and 52.8% in 1990 and 1998, respectively) had in addition allergic asthma to animals and allergic asthma to mite, respectively.

Table 3 shows the number of subjects who developed allergic asthma (incident cases of allergic asthma) during the follow-up period. Among the 28 incident cases of allergic asthma to pollen, a total of 18 subjects had allergic rhinitis to pollen at baseline, and the remaining 10 subjects had developed allergic rhinitis to pollen during the follow-up period. Among the 10 incident cases of allergic asthma to animals, a total of 4 subjects had allergic rhinitis to animals at baseline, and 5 subjects developed allergic rhinitis to animals during the follow-up period. Among the 10 incident cases of allergic asthma to mite, a total of 5 subjects had allergic rhinitis to mite at baseline, and the remaining 5 subjects developed allergic rhinitis to mite during the follow-up period.

A total of 39% ($n=67$) of subjects with allergic rhinitis to pollen at baseline were monosensitized to birch, grass, or mugwort, while a total of 29% ($n=11$) of subjects with allergic rhinitis to mite at baseline were monosensitized to mite. In contrast, only 5% ($n=7$) of subjects with allergic rhinitis to animals at baseline were monosensitized to dog or cat. Among subjects with a

diagnosis of allergic rhinitis, multisensitized subjects were not significantly more likely to have or to develop the corresponding diagnosis of allergic asthma (data not shown).

Discussion

We found that at follow-up allergic rhinitis to pollen was present among all incident cases and among all prevalent cases of allergic asthma to pollen. Also, allergic rhinitis to animals or mite was ubiquitous among incident and prevalent cases of allergic asthma to animals or mite, respectively.

Only one of the subjects with allergic asthma at follow-up did not have allergic rhinitis at follow-up or at baseline. Thus, allergic rhinitis appeared to be present among nearly all subjects with allergic asthma. In the longitudinal analysis, all incident cases of allergic asthma to pollen had allergic rhinitis to pollen at baseline or had developed allergic rhinitis to pollen at follow-up. Similarly, all incident cases of allergic asthma to mite had allergic rhinitis to mite at baseline or had developed allergic rhinitis to mite at follow-up. However, one incident case of allergic asthma to animals did not have allergic rhinitis to animals at baseline. Nor had this case developed allergic rhinitis to animals at follow-up. It should be noted that some degree of misclassification is inevitable when assessing symptoms of respiratory allergy by self-completed questionnaire. Therefore, the very few subjects with allergic asthma without allergic rhinitis might be explained by misclassification.

The association between allergic rhinitis and allergic

Table 2. The cross-sectional relationship between allergic rhinitis and allergic asthma at follow-up in 1998

Allergic rhinitis		Allergic asthma			
		To pollen	No	To animal	To mite
		Yes	No	Yes	No
To pollen	Yes	52	131		
	No	0	534		
To animal	Yes			31	28
	No			4	658
To mite	Yes				19
	No				1

Table 3. Incidence of allergic asthma among subjects with or without allergic rhinitis at baseline (subjects with allergic asthma at baseline are excluded from the analysis)

Allergic rhinitis at baseline		Incidence of allergic asthma			Odds ratio (95% CI)†
		To pollen	To animal	To mite	
To pollen	Yes	1.8% (10/544)			1 (reference)
	No	14.1% (18/128)			8.2 (3.6–18.5)
To animal	No		0.9% (6/657)		1 (reference)
	Yes		16.0% (4/25)		18.9 (4.8–73.9)
To mite	No			0.7% (5/682)	1 (reference)
	Yes			26.3% (5/19)	46.5 (10.8–199.9)

† Sex and age adjusted.

asthma appears to be stronger than has been reported by other authors (5, 7, 8). A possible explanation could be that the definitions of allergic rhinitis and allergic asthma used in the present study were very specific. Kapsali et al., however, reported a similar high prevalence of 98.9% (360/364) of allergic rhinitis in patients with allergic asthma (14), whereas Greisner et al. reported that allergic rhinitis was present in 85.7% (72/84) of asthmatics in a follow-up study of college students (15). Although the definition of asthma was specifically related to inhalant allergy, it was strongly associated with reported wheezing within the last 12 months. Thus, at baseline 73% of subjects with at least one of the diagnoses of pollen, animal, or mite allergic asthma had also experienced wheezing within the last 12 months (sex and age adjusted OR 13.4, 95% CI, 7.6–23.6).

Among the incident cases of allergic asthma that developed allergic rhinitis during the follow-up period, it was not possible to determine which of the two came first. However, the results strongly support the interpretation that allergic rhinitis precedes, or develops concurrently with, the development of allergic asthma. This has also been indicated by cross-sectional (16, 17) and prospective (15, 18) studies.

The relationship between rhinitis and asthma symptoms was stronger for animal and mite allergy than for pollen allergy. Thus, approximately one-quarter of subjects with allergic rhinitis to pollen had in addition allergic asthma to pollen, while approximately one-half of subjects with allergic rhinitis to animals (or mite) had in addition allergic asthma to animals (or mite). Moreover, the risk of developing allergic asthma appeared to be higher for allergic rhinitis related to perennial allergens than allergic rhinitis related to seasonal allergens (Table 3). The reason for this is not clear. One explanation could be that the period of exposure to pollens in Denmark is from April to August, while exposure to mite and animals is likely to be perennial. Another explanation could be that pollens are relatively large and less respiratable.

Current knowledge suggests that the most important link between rhinitis and asthma is the presence of inflammation of the nasal and bronchial mucosae (19). The present study has demonstrated a remarkably

strong epidemiologic association between rhinitis and asthma when both relate to inhalant allergy, a finding that suggests that allergen driven IgE-mediated inflammation of the airways may represent the pathophysiologic link between these manifestations. On the other hand, a strong association between nonallergic rhinitis and nonallergic asthma has also been demonstrated (20).

Allergic rhinitis and allergic asthma may also be linked from a therapeutic point of view. Thus, it is of interest that pharmacological treatment of the nose tends to improve coexisting asthma (7, 8, 10, 21, 22). Furthermore, studies of allergen specific immunotherapy in patients with allergic rhinitis due to pollen allergy have found improvements of coexisting asthma (23, 24). Other authors have hypothesized that allergen-specific immunotherapy prevents the development of asthma in children with allergic rhinitis due to pollen allergy (25) and in adolescents with allergic rhinitis due to mite allergy (26). The above evidence suggests a holistic therapeutic approach for allergic rhinitis and allergic asthma.

In conclusion, the results support the concept that allergic rhinitis and allergic asthma are manifestations of one disease entity. This concept and its clinical implications have recently been the subject of an exhaustive review (27). Thus, physicians should be aware that patients with allergic rhinitis often experience asthmatic symptoms, that they are at increased risk of developing allergic asthma, and that a diagnosis of allergic rhinitis should be considered in all patients with allergic asthma. These patients may benefit from treatment of their allergic rhinitis that may improve coexisting asthma or reduce the risk of developing asthma.

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