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Prevalence and severity of allergic rhinitis in house dust mite-allergic patients with bronchial asthma or atopic dermatitis

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Summary

Background Allergic rhinitis, asthma and atopic dermatitis are closely associated. Although population-based studies report a high prevalence of rhinitis among asthma patients, less is known of the association between rhinitis and atopic dermatitis and the severity of concomitant rhinitis.

Objectives We aimed to determine the prevalence and severity of allergic rhinitis among asthmatics and patients with atopic dermatitis and assessed whether age and comorbidity influence the severity of rhinitis signs and symptoms.

Methods Three hundred and twenty-five patients recruited for a multicentre trial to study the effect of encasings of mattresses, pillows and duvets on signs and symptoms of allergic rhinitis and/or asthma and/or atopic dermatitis recorded visual analogue scores (VAS) and daily symptom scores and underwent nasal challenge tests with house dust mite (HDM).

Results Based on history and clinical symptoms 92% of the 164 asthmatic patients and 85% of the 86 patients with atopic dermatitis could be diagnosed as having rhinitis. Inclusion of a positive provocation to HDM did not result in a substantial lower prevalence of rhinitis. Subjects reported moderate symptoms, with mean rhinitis VAS scores ranging from 40.0 to 55.0. Presence of atopic dermatitis was associated with lower rhinitis VAS and symptoms scores, whereas in multivariate analysis the presence of asthma was positively associated with nasal responsiveness to HDM.

Conclusion The prevalence of nasal symptoms in patients with bronchial asthma or atopic dermatitis and sensitized to house dust mites is high. Although the majority of patients experience mild to moderate symptoms, the presence of nasal disease needs to be examined in all patients with atopic disorders.

Keywords allergic rhinitis, allergy, atopic dermatitis, bronchial asthma, comorbidity, house dust mite
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Introduction

It has been postulated that allergic rhinitis, asthma and atopic dermatitis are closely associated. Rates of allergic rhinitis among asthmatics vary from 28 to 50% in studies published in the 1970s and 1980s [1–3]. Recently, in a population-based study, the prevalence of rhinitis in patients with asthma was estimated at 78% [4]. However, the association between allergic rhinitis and atopic dermatitis has rarely been studied. Edfors-Lubs showed that the prevalence of rhinitis in patients with dermatitis was 29% [1].

Despite evidence for the high comorbidity in atopic disease, in daily clinical care therapy focuses on the most predominant disease, i.e. asthma, atopic dermatitis or rhinitis.

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Until now, it is not known whether rhinitis as concomitant disease is an important health problem in terms of rhinitis severity. Possibly, symptoms of rhinitis will be overruled by pulmonary and skin problems. In addition, it is possible that – as in many cases rhinitis precedes asthma – the combination of asthma or atopic dermatitis and rhinitis represents a more advanced form of the atopic syndrome characterized by more severe rhinitis.

As treatment of the nose may improve lung function in asthmatics [5] and rhinitis itself has a major impact on quality of life [6], it may be important to screen subjects with asthma or atopic dermatitis on the presence of rhinitis.

As part of DUMAS, the Dutch Mite Avoidance Study – a large population-based multicentre placebo-controlled clinical trial on the efficacy of mattress covers – we conducted a prevalence study using baseline data of the atopic patients aged between 8 and 50 years. We aimed to determine the prevalence and severity of allergic rhinitis among asthmatics and patients with atopic dermatitis and assess whether age and comorbidity influence the severity of rhinitis signs and symptoms.

Materials and methods

Setting

All patients described took part in a multicentre trial to study the effect of encasings of mattresses, pillows and duvets on signs and symptoms of allergic rhinitis and/or asthma and/or atopic dermatitis. Patients were recruited from the Departments of Allergology of the University Hospitals of Rotterdam and Groningen, the Department of Dermatology of the University Medical Center Utrecht and from offices of general practitioners, departments of general and university hospitals and by advertisements and articles in lay magazines.

The study was approved by the medical ethics committees of all three university hospitals and all patients gave written informed consent.

Subjects

Patients aged 8 to 50 years were eligible if either a ratio of allergen and histamine weal diameter was ≥ 0.7 using intradermal skin tests [7] or RAST class was 2 or more. Clinically, allergic rhinitis was defined by clinical features and classical history of rhinitis (nasal obstruction, sneezing, watery discharge) for at least 1 year. This physician based diagnosis meets the criteria of the guidelines of the International Consensus on Rhinitis [8]. However, to ensure that all patients included in the intervention study did have allergic rhinitis based on house dust mite allergy, a positive nasal challenge test to HDM was required in combination with the clinical diagnosis at entrance (test diagnosis).

The presence of asthma was defined by a 1-year history of asthma, physician-based diagnosis or use of inhalation steroids, reversibility of 9% or more, or PC_{20} methacholine of 9.8 μg or less.

The presence of atopic dermatitis was defined by the criteria of Hanifin and Rajka (a consensus base scoring system of clinical characteristics) [9]. To ensure that patients with active disease were enrolled for the purpose of the trial, the severity of the disease was assessed with the Leicester sign score, a scoring system for disease activity [10]. Using this system the extent of more than 1% and 6 points or more was required to enter the trial.

Some additional inclusion and exclusion criteria were required for admittance to the randomized trial. Patients had to be exposed to house dust mites (i.e. ≥ 200 μg Der P1 or Der F1 in a dust sample). Moreover, patients sensitized to pets with those pets at home were excluded. Also, anatomical disorders of the nose, pregnancy or lactation, daily use of inhalation steroids ≥ 1600 μg/day (adults) or ≥ 800 μg/day (children), oral steroids, cyclosporin, regular use of antibiotics for upper or lower airway infection or regular use of oral steroids for exacerbation of asthma were considered as exclusion criteria.

Data collection

Anamnestic data such as gender, age, smoking habits, data for the diagnosis of rhinitis, asthma or atopic dermatitis (history, physical examination, lung function tests), skin test results for the diagnosis of house dust mite allergy and measurements of Der P1 exposure were obtained.

All study patients underwent several additional tests to assess the severity of potential rhinitis, asthma or dermatitis. These measurements were performed in the period of September to November, ensuring that assessments were done in a period of relative high exposure to house dust mites in the Netherlands [11].

Assessment of rhinitis

Severity of rhinitis assessed by visual analogue scales To score the severity of the disease during the past 14 days as experienced by the patients we used visual analogue scales (VAS) [12]. The patient was asked to evaluate his or her complaints on a continuous horizontal line of 100 mm, where 0 mm represents no complaints and 100 mm very serious complaints. Blom *et al*. showed that the rhinitis VAS in case of complaints of rhinitis has a good performance.

Severity of rhinitis assessed by a daily nasal symptom card Daily nasal symptoms were recorded during 14 days. Nasal obstruction, nasal discharge and sneezing were recorded on a 0–3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Scores were summed and the average of 14 days was reported as daily nasal score. Nasal medication was stopped according to the protocol [1] and replaced by Acrivastine 8 mg capsules, taken as needed with a maximum of three capsules daily. To obtain unbiased symptom scores, use of acrivastine was discouraged. Patients with a daily symptom score filled in during 11 days or less were excluded from analysis.

Nasal provocation The procedure for nasal provocation has been described elsewhere [13]. Before nasal provocation each patient had to acclimatize for 30 min in the room where nasal provocation took place. After this period, a composite symptom score according to Lebel et al. [14], comprising the number of sneezes during those 30 min, nasal stuffiness, itching of the nose, eyes, palate and ears, rhinorrhea and post-nasal drip was obtained. Patients received one puff of PBS in both nostrils by means of a nasal spray with a fixed dose of 0125 mL/puff. At 10-min intervals the four items were scored just before challenge with the next dose (100, 1000 and 10 000 BU/mL). Challenge tests were performed after the 14-day period of scoring daily symptoms, thereby ensuring that no medication was used before the tests.

We considered a nasal provocation to be positive when the symptom score after nasal inhalation of either 100, 1000 or 10000 BU/mL HSM increased by at least three points with respect to nasal inhalation of PBS.

In patients aged ≥ 18 years nasal lavage was carried out before each nasal challenge step.

Statistical analysis

Data were stored in Microsoft Access® 97 for Windows (Microsoft Corporation, Seattle, USA) and analysed using SPSS, version 9.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics including percentages for categorical variables and means (SD) or median (P25, P75) for continuous variables were used. Univariate analysis to estimate differences and 95% confidence intervals (95% CI) between comparison groups included Pearson chi-square tests for categorical and Student's *t*-test or Mann–Whitney *U*-test for continuous variables. Finally, multivariate regression modelling was applied to assess the association of age and diagnosis on outcome

variables such as rhinitis VAS, daily symptom score and HDM provocation, independent of potential confounding variables. In these analyses, only those variables that were associated with the outcome at a *P*-level < 0.10 and that materially altered the parameter estimate of the main explanatory variable (age or diagnosis), were kept in the model. To check the assumptions and to enhance the accuracy of the applied regression model, we used the following regression diagnostics: visual verification of the normality assumption using normal probability plots and a plot of the adjusted standardized residuals, evaluating outliers by calculating the Mahalanobis distance for each patient, and the presence of multicollinearity was evaluated by calculating the variance inflation factor (VIF). Adjusted regression coefficients, their 95% CI and corresponding two-sided *P*-values are given.

Results

In all, 325 eligible atopic patients (mean age 27.2 ± 11.6) were included in the randomized clinical trial. Asthma was present in 164 patients (50%), atopic dermatitis in 86 patients (26%) and 111 patients (34%) were diagnosed with rhinitis only. Baseline characteristics of the study population are given in Table 1.

It appeared that 92% of the asthmatic patients and 85% of the patients with atopic dermatitis did have a history of nasal symptoms lasting more than 1 year (physician-based diagnosis). Inclusion of a positive provocation to HDM (test diagnosis) did not result in a substantial lower prevalence of rhinitis (Table 2).

The proportion of a physician-based and test diagnosis of rhinitis in asthmatic subjects < 18 years amounted to 89% and 85%. Subjects with atopic dermatitis younger than 18 did have a prevalence of 77% for both physician-based and test diagnosis of rhinitis. Differences across age-categories were not significant ($P > 0.05$). As shown in Table 2, patients with atopic dermatitis did have a lower prevalence of nasal symptoms and definite rhinitis than patients without skin disease.

It was shown that patients scored moderately using the rhinitis VAS, with mean scores ranging from 40.0 to 55.0 (Table 3). Acrivastine escape medication was infrequently used. In a 14-day time interval total median number of capsules amounted 0 (25% percentile = 0; 75% percentile = 7). With univariate analysis it was shown that patients with atopic dermatitis did have lower rhinitis VAS scores than subjects without skin disease. Assessment with daily symptom scores generated low scores on

Table 1. General characteristics

	Asthma ($n = 164$)	Atopic dermatitis ($n = 86$)	Rhinitis only ($n = 111$)
Age (x; SD)	26.0 ± 11.9	25.7 ± 10.3	29.1 ± 11.2
Male percentage	41	37	41
Adult (≥ 18 year) %	68	74	76
Intradermal skin tests HDM			
30 BU/mL (skin index)	1.0 ± 0.7	1.1 ± 0.6	1.0 ± 0.5
Eosinophils (10^6/L)	451 ± 355	489 ± 389	273 ± 199
Baseline FEV_1 of predicted	92% ± 18		
PC_{20} methacholine (μg/mL)	4.29 ± 17.71		
LSS severity		20, 1 ± 13	
LSS extent percentage		29.9 (2–88)	

Table 2. Prevalence of rhinitis in asthmatics and patients with atopic dermatitis

Diagnosis of rhinitis	Asthma			Atopic dermatitis		
	Present ($n = 164$)	Absent ($n = 161$)	*P*	Present ($n = 86$)	Absent ($n = 239$)	*P*
Physician based	92.1*	87.6	0.38	84.9	96.2	< **0.001**
Positive nasal challenge	92.1	90.1	0.53	88.4	92.1	0.31
Test diagnosis	84.1	87.6	0.38	79.1	88.3	**0.04**

*Proportion (%).

Table 3. Severity of nasal symptoms and signs in asthmatics and patients with atopic dermatitis according to age-category

Rhinitis outcome measure	Asthma			Atopic dermatitis		
	Present	Absent	*P*§	Present	Absent	*P*
Visual analogue scale	45.9 (37.0–54.7)*	55.0 (44.1–65.9)	0.189	53.4 (38.5–68.4)	48.6 (40.8–56.4)	0.553
	48.3 (42.9–53.9)†	49.8 (44.4–55.1)	0.720	40.0 (32.9–47.0)	52.6 (48.1–57.1)	**0.003**
	47.5 (42.9–52.2)‡	51.0 (46.2–55.8)	0.307	43.3 (36.9–49.7)	51.4 (47.5–55.2)	**0.035**
Daily symptoms	1.9 (1.5–2.3)*	2.0 (1.6–2.5)	0.736	1.6 (1.0–2.1)	2.1 (1.8–2.5)	0.130
	2.0 (1.7–2.0)†	2.3 (2.0–2.6)	0.191	2.0 (1.6–2.4)	2.2 (2.0–2.5)	0.325
	2.0 (1.8–2.2)‡	2.2 (2.0–2.50)	0.162	1.9 (1.6–2.2)	2.2 (2.0–2.4)	0.115
Nasal response to HDM	18.3 (16.6–20.1)*	15.3 (13.4–17.1)	0.200	16.8 (14.0–19.7)	17.1 (15.6–18.6)	0.854
	18.2 (16.8–19.5)†	17.2 (16.1–18.4)	0.283	17.0 (15.2–19.0)	17.9 (16.9–18.3)	0.392
	18.2 (17.2–19.3)‡	16.7 (15.8–17.7)	0.460	17.0 (15.5–18.5)	17.7 (16.8–18.5)	0.416

Mean and 95% confidence interval. *Children < 18 years. †Adults[3] 18 years. ‡Total group. §*P*: significance level (two-sided).

Table 4. The independent association between atopic comorbidity and severity of rhinitis: rhinitis VAS

Explanatory	Children $n=91$ Model: $F=2.59$, d.f. $=3$, $P=0.057$				Adults $n=231$ Model: $F=5.10$, d.f. $=3$, $P=0.002$			
	ß*	95 CI†	*t*‡	*P*§	b	95 CI	*t*	*P*
Asthma (0 = no, 1 = yes)	−0.10	−0.30–0.11	−0.90	0.37	0	−0.13–0.13	0	0.99
Atopic dermatitis (0 = no, 1 = yes)	0.10	−0.11–0.31	0.90	0.37	−0.17	−0.30–0.05	−2.71	**<0.01**
Rhinitis (0 = no, 1 = yes)	0.26	0.05–0.46	2.41	0.02	0.16	0.04–0.29	2.53	0.01

Three persons had one or more missing values and were excluded from the final model b. Daily nasal symptoms. *ß = standardized regression coefficient. †95 CI = 95% confidence interval. ‡*t* = *t*-statistic. §*P* = significance level, two-sided.

Table 5. The independent association between atopic comorbidity and severity of rhinitis: daily nasal symptoms

Explanatory variables	Asthma absent ($n=148$) Model: $F=5.07$, d.f. $=3$, $P=0.002$				Asthma present ($n=146$) Model: $F=2.19$, d.f. $=3$, $P=0.09$			
	ß*	95 CI†	*t*‡	*P*§	β	95 CI	*t*	*P*
Atopic dermatitis (0 = no, 1 = yes)	−0.22	−0.38– 0.05	−2.63	**0.01**	0.08	−0.08–0.24	0.95	0.35
Rhinitis (0 = no, 1 = yes)	0.17	0–0.33	2.00	**0.05**	0.19	0.03–0.35	2.34	**0.02**
Child = 0/Adult = 1	0.08	0.04–0.29	0.96	0.34	0.03	−0.14–0.19	0.31	0.76
	Atopic dermatitis absent $n=221$ Model: $F=3.96$, d.f. $=3$, $P=0.009$				Atopic dermatitis present $n=73$ Model: $F=3.87$, d.f. $=3$, $P=0.013$			
	ß*	95 CI†	*t*‡	*P*§	β	95 CI	*t*	*P*
Asthma (0 = no, 1 = yes)	−0.15	−0.28–– 0.02	−2.21	**0.03**	0.21	−0.08–0.24	1.86	**0.07**
Rhinitis 0 = no, 1 = yes	0.15	0.02–0.28	2.21	**0.03**	0.26	0.03–0.35	2.31	**0.02**
(Child = 0/Adult = 1)	0.03	−0.10–0.16	0.43	0.67	0.13	−0.14–0.19	1.12	0.27

31 persons had one or more missing values and were excluded from the final model. *ß = standardized regression coefficient. †95 CI = 95% confidence interval. ‡*t* = *t*-statistic. §*P* = significance level, two-sided.

a 0–9 scale in all groups. The presence of asthma or atopic dermatitis did not influence daily nasal symptoms or nasal reactivity to HDM.

With multivariate analysis the independent effect of disease (asthma, atopic dermatitis and rhinitis) and age on rhinitis severity in terms of rhinitis VAS, daily symptoms or nasal responsiveness to HDM was evaluated. In case of rhinitis VAS, age and diagnosis of atopic dermatitis yielded a significant interaction effect. Therefore the association between diagnosis and rhinitis VAS is presented in different models according to age category (Table 4). It appeared that in adults the presence of atopic dermatitis was negatively associated with the outcome of the rhinitis VAS. In case of daily nasal symptoms, diagnosis of asthma and atopic dermatitis yielded a significant interaction effect. In separate models it was shown that atopic dermatitis was inversely related with daily nasal symptoms in non-asthmatic subjects, whereas asthma was inversely related with daily nasal symptoms in subjects without atopic dermatitis (Table 5). In contrast, asthma was positively and significantly associated with the outcome of the nasal challenge test (Table 6). As expected, rhinitis VAS and daily nasal symptoms were significantly associated with the diagnosis of rhinitis. By definition, nasal challenge results were associated with rhinitis.

Table 6. The independent association between atopic comorbidity and severity of rhinitis: nasal response to HDM

Explanatory variables	Nasal response to HDM ($n=325$) Model: $F=13.03$, d.f. $=4$, $P=<0.001$			
	ß*	95 CI†	*t*‡	*P*§
Asthma (0 = no, 1 = yes)	0.14	0.03–0.24	2.59	**0.01**
Atopic dermatitis (0 = no, 1 = yes)	−0.01	−0.11–0.09	−0.19	0.85
Rhinitis (0 = no, 1 = yes)	0.35	0.25–0.45	6.75	**<0.001**
Child = 0/Adult = 1	0.07	−0.03–0.17	1.34	0.18

Daily nasal symptoms. *ß= standardized regression coefficient. †95 CI = 95% confidence interval. ‡*t* = *t*-statistic. §*P* = significance level, two-sided.

Discussion

This is the first large study to show that not only asthma but also atopic dermatitis is highly associated with allergic rhinitis. Although self-reported severity of rhinitis signs and symptoms in these patients seemed to be moderate, screening on nasal disease and subsequent treatment might further enhance the quality of life of these patients.

Before we can accept these findings, some potential limitations need to be addressed. The cross-sectional design of the study does not allow for causal inference. We can therefore not be sure whether rhinitis precedes or follows the onset of asthma or dermatitis. Several prospective cohort studies, however, suggest that rhinitis may precede and is a risk factor for asthma [15, 16], whereas dermatitis may be one of the first manifestations of the atopic syndrome.

Secondly, the observed prevalence of rhinitis was rather high. Comparison with other studies is hampered by the differences in definition of rhinitis. We therefore used both a symptom-based and test-based definition and results appeared surprisingly similar. Comparing our results with earlier studies we observed a higher prevalence of rhinitis in asthma than in early questionnaire-based studies [1–3]. Our results are more in line with the recent observation of 78% prevalence in asthmatic subjects [4]. By analogy with our observations Malo reported that 92% of subjects with occupational asthma to high molecular weight allergens experience rhinitis symptoms [17]. Another explanation for this high prevalence might be that we measured signs and symptoms at the physicians' office instead of by self-administered questionnaires.

Thirdly, our study population might not be applicable to the allergic asthma and atopic dermatitis patient population. We only included those patients allergic for house dust mite in our study. How these results may apply to patients allergic for other allergens is not known. Atopic dermatitis may be present even in the absence of an IgE response to specific allergens; it is possible that in this particular subgroup the proportion of coexistent rhinitis differs from our study group.

Various recruitment strategies were used to enhance generalization of the results. Patients were recruited from university centres, general hospitals, general practice and by advertisements.

The high prevalence of rhinitis in subjects with asthma and atopic dermatitis is a reflection of the concept that rhinitis, asthma and atopic dermatitis are part of the same atopic syndrome. Atopy – the personal or familial tendency to produce IgE antibodies to low dose antigens and to develop typical symptoms such as asthma, rhinoconjunctivitis and eczema/dermatitis [18] – forms the basis of the close connection between these disorders. Development of allergic sensitization and diseases are partly under common genetic control. Evidence for linkage between candidate loci for allergic disease and total IgE concentrations is found in the same regions for which reasonable evidence for linkage to asthma has been reported [19]. Linkage between atopy, including total and specific IgE, and allergic rhinitis or atopic dermatitis is, however, less well established. The coexistence of all three atopic disorders gives further evidence for the concept of common genetic control.

Probably, the nose is the organ in which allergy comes most constantly to clinical expression.

It appears that the presence of asthma leads to increased mucosal sensitivity to HDM in the nose. This might be an illustration of the tight connection between upper and lower airways, which has been illustrated by the observation that allergic rhinitis may have an unfavourable effect on asthma. Allergen challenge of the nose may increase bronchial hyperresponsiveness [20], treatment with nasal steroids may have a beneficial effect on lower airway function [5]. Very recently, it has been shown that segmental bronchial challenge leads to inflammatory events in the nasal mucosa [21].

The findings of this study suggest that rhinitis is not appreciated as a major problem in these patients. It is possible that patients consider their nasal symptoms as less important because of a predominance of the other atopic disorders, which might explain the negative association between atopic dermatitis and the rhinitis VAS and the daily symptom score. Also, the negative association between asthma and daily nasal symptoms is in line with this assumption. However, the latter finding does not fit in with the observed increase in nasal responsiveness to HDM in this subgroup. Perhaps the masking effect of asthma on rhinitis symptoms overshadows the clinical effects of increased responsiveness to HDM.

Although age ranged from 8 to 50 years, age-effects on rhinitis severity were not important.

Alternatively, we have to reject the hypothesis that rhinitis symptoms in combination with asthma or atopic dermatitis are more severe, thereby representing an advanced stage of the atopic syndrome.

The findings of this study may have some practical implications. First, it supports the notion that all patients with asthma or atopic dermatitis should be examined for the presence of nasal disease. Even if rhinitis is mild to moderate in a large proportion of subjects, assessment of the history of nasal complaints and examination of the nose may be valuable to select patients with more severe disease. This is particularly important as allergic rhinitis may have a substantial impact on health-related quality of life [6]. Secondly, although the study was not designed to establish the most accurate method of diagnosing allergic rhinitis, one may argue that inclusion of a nasal challenge test is somewhat redundant, as addition of a nasal challenge test does not affect the proportion of patients with rhinitis very much. These observations fit in with the recent consensus statement that nasal allergen provocation is required only if discrepancies between history and other tests are present [22].

In conclusion, we demonstrated that the prevalence of nasal symptoms in patients with bronchial asthma or atopic dermatitis and sensitized to house dust mites is high. Although the majority of patients experience mild to moderate symptoms, the presence of nasal disease needs to be examined in all patients with atopic disorders.

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