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Rhinitis alone or rhinitis plus asthma: what makes the difference?

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Rhinitis alone or rhinitis plus asthma: what makes the difference?. A. Magnan, C. Fourre-Jullian, H. Jullian, M. Badier, A. Lanteaume, D. Vervloet, D. Charpin. ©ERS Journals Ltd 1998.

ABSTRACT: This paper examines the clinical expression of asthma in a group of patients displaying rhinitis according to age, sex, associated symptoms, smoking, familial history of asthma, atopy, type of sensitization to aeroallergens (pollens and/or indoor allergens), total serum immunoglobulin E (IgE), and blood eosinophils.

A total of 117 adults with rhinitis were analysed on the basis of symptoms. Among them, 51 also displayed asthma, defined as a history of recurrent episodes of dyspnoea with a reversible airflow obstruction or a positive methacholine challenge. The logistic regression analysis carried out in a stepwise approach, combining several factors, showed that various parameters affected the risk of having asthma associated with rhinitis. A further analysis was made in 74 rhinitis patients comparing 42 subjects without nonallergic airway hyperresponsiveness (NAAH) to 32 patients with asthma and NAAH.

Atopy, high total serum IgE levels, elevated blood eosinophil count and maternal asthma were associated with asthma. Furthermore, in atopic patients, pollen sensitization was more closely related to rhinitis alone, whereas sensitization to indoor allergens was a major determinant for the association of asthma with the symptoms of rhinitis. The same risk factors as those found in the clinical part of the study discriminated the patients with rhinitis without NAAH from those with rhinitis, asthma and NAAH.

In conclusion, this study gives new insights into the relationships between asthma and rhinitis.

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The prevalence of both rhinitis and asthma has risen over the last decades [1–3]. Of patients with asthma, 40–75% display rhinitis, while asthma symptoms are found in 20–30% of patients with rhinitis [4, 5]. Many studies have investigated the association of asthma or rhinitis with various potential risk factors. This enabled the identification of several risk factors for both diseases. Genetic studies have found chromosomal regions associated with the familial transmission of asthma and/or atopy [3]. Total immunoglobulin E (IgE) levels were shown to be associated with asthma in several surveys [6, 7], irrespective of the patients' atopic status [7]. Blood eosinophilia was also found to be associated with asthma [8], and correlated with the severity of the disease [9]. Other studies have found sensitization to indoor allergens to be a risk factor for asthma, whereas sensitization to pollens increased the risk of rhinitis [10–12]. However, these studies were performed in random samples from the general population or considered asthmatic *versus* normal subjects, without taking rhinitis into account. Therefore, they could not identify specifically the risk factors for asthma in a population of rhinitic subjects. Nevertheless, since the rhinitic population is at risk of asthma, identifying such factors seems of major interest in order to set up preventive strategies. Two further epidemiological studies have considered both diseases together and distinguished risk factors for each of them. Verdiani *et al.* [13] evaluated the nonspecific hyperreactivity of rhinitic subjects according to the seasonal or perennial type of rhinitis. They found that bronchial hyperreactivity was associated with perennial, but not seasonal, rhinitis. More recently, Boulet *et al.* [14] studied, in a large survey of 3,371 patients, the presence of rhinitis and/or asthma and the sensitization to indoor and outdoor allergens. They showed that indoor allergen sensitization was strongly associated with asthma, whereas exclusive sensitization to pollens was associated primarily with rhinitis.

The aim of this study was to go further and identify factors associated with asthma in a population of rhinitic patients, taking into account not only the types of sensitization but also smoking habits, the presence of other symptoms, familial asthma, the level of total serum IgE, the blood eosinophil count and nonallergic airway hyperresponsiveness (NAAH).

Methods

Patients

Data were obtained prospectively from consecutive subjects referred to the asthma and allergy clinic of the Chest Diseases Department of the Sainte Marguerite Hospital,

Marseilles and to the Chest Disease Division of the Martigues Hospital, located in the same area. A single interviewer (C. Fourre-Jullian) collected the data. A total of 117 adults, 58 males and 59 females were included on the basis of rhinitis, alone or associated with asthma.

Diagnosis of rhinitis

Rhinitis was assessed on the basis of the presence of persistent daily rhinorrhoea without any evidence of infection. Most of the patients displayed periods of nasal obstruction alternating with rhinorrhoea. Patients with postnasal drip alone were not included. Based upon the periodicity of symptoms, rhinitis was classified as perennial or seasonal.

Diagnosis of asthma

Asthma was diagnosed on the basis of a history of recurrent episodes of dyspnoea associated with a reversible airway obstruction or a positive methacholine challenge (see below). In the absence of symptoms, subjects were considered as nonasthmatics. The reversible airflow obstruction was defined according to European guidelines [15] by a forced expiratory volume in one second (FEV_1) <80% of the normal value and an increase in FEV_1 Š15% of basal values after inhalation of 200 µg salbutamol.

Diagnosis of atopy

Atopy was defined by at least one positive skin prick test to a common aeroallergen. Antihistamines were excluded for Š1 week in the case of cetirizine and loratadine and for 1 month in the case of astemizole.

The prick test method was used for skin tests. The skin test battery included the following allergens (Laboratoire des Stallergenes, Paris, France): house dust (100 IR, *i.e.* the index of reactivity, which is the concentration (100 IR) that induced a 7 mm weal in a group of sensitized individuals), *Dermatophagoides pteronyssinus* and *D. farinae* (100 IR), feather (1/10 w/v), cat and dog extracts (100 IR), German cockroach (1/10 w/v), alternaria, aspergillus, cladosporium and penicillium (1/10, w/v) were considered indoor allergens; and mixed grass pollen (poa, fescue, timothy, rye, orchard, 100 IR), Bermuda grass (1/20 w/v), parietaria (1/20 w/v), alder (100 IR), birch tree (100 IR), hornbeam, hazel, olive tree, ash, privet, oak, mimosa, poplar, false acacia, lime tree, mulberry, nettle tree (1/20 w/v) and mixed weeds (100 IR), including ragweed mugwort, amarant, goose foot, sorrel and plantain, were considered outdoor allergens. Prick tests were considered positive if the weal diameter 20 min after allergen injection reached at least half that induced by codeine phosphate and more than that induced by 0.9% saline [16].

Diagnosis of rhinitis without nonallergic airway hyperresponsiveness and of asthma with nonallergic airway hyperresponsiveness

Eighty-seven patients underwent a methacholine challenge. Forty-two patients with clinical symptoms of asthma underwent methacholine challenge for the purpose of diagnosis. In 45 nonasthmatic subjects, methacholine challenge was performed to assess the presence of NAAH and to allow a better characterization of the subjects. Prior to methacholine challenge, baseline specific airway resistance (sR_{aw}) measurements were performed on each subject in an 830-L constant-body plethysmograph (Master Lab, Jaeger, Würzburg, Germany), using the method described by DUBOIS *et al.* [17]. A standardized dosimeter technique was used for methacholine inhalation. Methacholine puffs were delivered by a dosimeter (ME-FAR dosimeter, Elletromedically, Brescia, Italy): air driving pressure 1.65 $kg \cdot m^{-2}$, airflow rate 70–75 $L \cdot min^{-1}$, and particle size 0.5–4 µm. A 2 $mg \cdot mL^{-1}$ methacholine solution was used, and 3 mL of this solution were placed in the nebulizer (20 µg metacholine per puff). Cumulative doses of methacholine were administered, and sR_{aw} measurements were made after each dose. NAAH was defined by a 100% increase in sR_{aw} at ð200 µg of methacholine. At the end of the challenge, 200 µg salbutamol was administered when NAAH was present.

From the results of methacholine challenges, the following groups were set up: a group of patients with rhinitis without NAAH, a group with asthma and NAAH, and a group with rhinitis and NAAH but without asthma.

Total serum immunoglobulin E measurements

Serum IgE was assayed in the sera of the patients using the PRIST technique (Pharmacia, Uppsala, Sweden). Values were expressed in $IU \cdot mL^{-1}$ and were transformed as log values so that a normal distribution of the data could be assumed.

Blood eosinophils

Blood eosinophils were counted after staining with 2% eosin. Absolute $counts \cdot mm^{-3}$ were transformed as log values so that a normal distribution of the data could be assumed.

Evaluation

The following parameters were considered for analysis: age; sex; clinical diagnosis (asthma, perennial rhinitis, seasonal rhinitis, conjunctivitis); active smoking; exsmoking; asthma in parents, siblings and offspring; presence of atopy; sensitization to pollens and/or indoor allergens; level of total serum IgE; blood eosinophil count; and NAAH.

Data analysis

Analysis of variance was used to compare quantitative variables such as age, total IgE, and eosinophil count. Contingence analysis was used for qualitative variables (tobacco, atopy, family asthma). Principal factor analysis and logistic regression analysis were performed to analyse all variables.

Logistic regression analysis was used to rate the effect of covariates on risk of rhinitis or asthma. The model included quantitative variables: age, total IgE levels, eosinophil count and familial history of asthma. We performed a backward stepwise analysis with a variable number of iterations, leading to an estimate of the odds ratio, together with its confidence interval and degree of significance. SPSS 6.1 for the Power Macintosh (SPSS, Chicago, IL, USA) was used as software.

Results

Classification of patients

Among the 117 patients included in the study, 66 subjects displayed rhinitis alone and 51 (43%) displayed an associated clinical asthma.

In 87 patients, a methacholine challenge was performed and enabled the comparison of better characterized subjects. Three groups were considered: the first group included 42 patients with a diagnosis of rhinitis without NAAH, the second group included 32 patients with a diagnosis of rhinitis associated with asthma and NAAH, and a third group of 13 patients with rhinitis and NAAH but without clinical asthma, which was characterized, but was too small to be included for statistical analysis.

Comparison of variables between patients with rhinitis versus *patients with rhinitis and asthma*

In this analysis, the presence of NAAH was not considered, and all 117 patients were included. There was no significant difference in both groups in age, sex, percentage of active smokers, exsmokers, presence of conjunctivitis, periodicity of the rhinitis (seasonal or perennial) and asthma history in father, siblings or offspring. As shown in table 1, maternal asthma, history of asthma in at least one member of the family, atopy and sensitization to indoor allergens were significantly more frequent in asthmatic subjects. In these patients, the log total serum IgE and log eosinophil count were higher. Sensitization to outdoor allergens (pollens) was as frequent in both groups.

Table 1. – Comparison of variables between patients with rhinitis and patients with rhinitis and asthma

	Rhinitis	Rhinitis with asthma	p-value
All patients			
Subjects n	66	51	
Age yrs	36±12	34±15	NS
Males	30 (45)	28 (55)	NS
Females	36 (55)	23 (45)	NS
Current smokers	11 (17)	13 (25)	NS
Exsmokers	9 (14)	9 (18)	NS
Conjunctivitis	33 (50)	28 (55)	NS
Seasonal rhinitis	16 (24)	15 (29)	NS
Perennial rhinitis	50 (76)	36 (71)	NS
Asthmatic father	3 (5)	4 (8)	NS
Asthmatic siblings	7 (11)	7 (14)	NS
Asthmatic children	4 (6)	4 (8)	NS
Sensitization to pollens	36 (54)	30 (59)	NS
Asthmatic mother	2 (3)	9 (18)	0.007
Atopy	40 (61)	42 (82)	0.01
Sensitization to indoor allergens	22 (33)	32 (63)	0.016
Log total IgE	4.50±1.6	5.39±1.4	0.02
Log eosinophils count	2.22±0.3	2.44±0.4	0.019
Atopic patients			
Subjects n	40	42	
Sensitization to pollens	1 (2)	9 (21)	0.008
Sensitization to indoor allergens	36 (90)	30 (71)	0.04
	22 (55)	32 (76)	0.04
Log eosinophils count	2.26±0.3	2.46±0.4	0.01

In the atopic patients, only significant data are shown. Values are presented as number of subjects and mean±SD with percentages shown in parentheses. NS: nonsignificant; IgE: immunoglobulin E.

Among atopic subjects, maternal asthma was again more frequent in asthmatics, as was sensitization to indoor allergens. In atopic subjects, the presence of asthma was studied according to the number of positive skin tests. In both groups the number of paucisensitized patients (less than four positive skin tests) and that of polysensitized patients (more than four positive skin tests) was equivalent. It was thus the nature, rather than the number, of sensitizations that discriminated asthmatic from nonasthmatic atopics subjects. The total eosinophil count was still significantly higher in the group of atopic asthmatics. In contrast, sensitization to pollens was higher in the rhinitic nonasthmatics, and IgE levels were no longer significantly different between the two atopic subgroups (table 1).

The relative risk of developing clinical asthma for a patient with clinical rhinitis was evaluated. As shown in table 2, the presence of atopy, a high eosinophil count and a familial history of asthma significantly increased the risk of developing asthma in patients with rhinitis. In the subgroups of atopic patients, indoor allergen sensitization and familial history of asthma increased the risk of having asthma five and 10 fold, respectively.

The discriminant analysis, computed in a stepwise manner and combining all variables studied, showed that the best predictive variables separating the group with rhinitis alone from that with rhinitis and asthma were maternal asthma, sensitization to indoor allergens and blood eosinophilia. The probability of correctly classifying the patients in each group by using these three parameters alone was 70.1%.

In the atopic subpopulation, the best discriminating variables were, in decreasing order, maternal asthma, blood eosinophilia and sensitization to pollen. The probability of correctly classifying the patients in each group by using these three parameters alone was 69.5%.

Comparison of variables between patients with rhinitis without nonallergic airway hyperresponsiveness and patients with rhinitis, asthma and nonallergic airway hyperresponsiveness.

As in the first analysis, which did not consider NAAH, history of maternal asthma, atopy, sensitization to indoor allergens, total serum IgE and blood eosinophil counts proved to be factors discriminating asthmatic rhinitic subjects with NAAH from subjects with rhinitis alone, without

Table 2. – Logistic regression analysis: clinical rhinitis compared to clinical asthma with rhinitis

	Odds ratio	95% CI	p-value
All patients			
Atopy	4.5	1.83–11.5	0.001
Log eosinophils count increase by 1 log unit	3.7	1.10–12.53	0.03
Asthma in family	4	1.36–11.77	0.01
Atopic patients			
Sensitization to indoor allergens	4.6	1.17–18.51	0.02
Asthma in family	9.8	2.19–44.58	0.002

CI: confidence interval.

Table 3. – Comparison of variables between patients with rhinitis without nonallergic airway hyperresponsiveness (NAAH) and patients with rhinitis, asthma and NAAH

	Rhinitis without NAAH	Rhinitis, asthma and NAAH	p-value
All patients			
Subjects n	32	42	
Age yrs	34±12	31±15	NS
Males	22 (52)	18 (56)	NS
Females	20 (48)	14 (44)	NS
Current smokers	6 (14)	7 (22)	NS
Exsmokers	4 (9)	5 (16)	NS
Conjunctivitis	17 (40)	16 (50)	NS
Seasonal rhinitis	9 (20)	7 (22)	NS
Perennial rhinitis	33 (79)	25 (78)	NS
Asthmatic father	3 (7)	1 (3)	NS
Asthmatic siblings	6 (14)	4 (12)	NS
Asthmatic children	2 (5)	2 (6)	NS
Sensitization to pollens	21 (50)	18 (56)	NS
Asthmatic mother	1 (2)	6 (19)	0.01
Atopy	24 (57)	28 (88)	0.004
Sensitization to indoor allergens	13 (31)	23 (72)	0.0004
Log total IgE	1.97±0.7	2.52±0.6	0.0006
Log eosinophils count	2.17±0.3	2.44±0.4	0.0004
Atopic patients			
Subjects n	24	28	
Asthmatic mother	0 (2)	6 (21)	0.02
Sensitization to pollens	21 (87)	18 (64)	0.05
Sensitization to indoor allergens	13 (54)	23 (82)	0.03
Log eosinophils count	2.22±0.3	2.45±0.5	0.02

In the atopic patients, only significant data are shown. Values are presented as number of subjects and mean±SD with percentages shown in parentheses. NS: nonsignificant; IgE: immunoglobulin E.

NAAH (table 3). In the atopic population, maternal asthma and indoor-allergen sensitization were more frequent, and blood eosinophils counts were higher in the subgroup with rhinitis, asthma and NAAH. In contrast, the prevalence of pollen sensitization was higher in the pure rhinitis group, without NAAH (table 3). In the nonatopic subgroup, only total blood serum IgE was higher in the rhinitis with asthma and NAAH group (log total IgE 2.31 *versus* 1.56, p=0.02).

When we evaluated the relative risk of developing asthma and NAAH in patients with rhinitis without NAAH, atopy and blood eosinophil count were again found to be risk factors (table 4). In this analysis, total serum IgE levels were also a risk factor. In the atopic subgroup, sensitization to indoor allergens increased the risk of developing asthma and NAAH in patients displaying rhinitis by a factor of 18.

The most important discriminating factors for having asthma and NAAH associated with rhinitis were, in decreasing order, maternal asthma, indoor-allergen sensitization and high blood eosinophilia. The probability of a correct diagnosis using these three factors alone was 71.6%. In atopic subjects the same discriminating variables were found. The probability of classifying the patients correctly in each group by using these three parameters alone was 71.2%.

Table 4. – Logistic regression analysis: rhinitis, asthma and nonallergic airway hyperresponsiveness (NAAH) compared to rhinitis without NAAH

	Odds ratio	95% CI	p-value
All patients			
Atopy	1.7	1.08–3	0.04
Log eosinophils IgE increase by 1 log unit	2.6	1.03–6.8	0.04
Log eosinophils count increase by 1 log unit	4.6	1.14–18.03	0.02
Atopic patients			
Sensitization to indoor allergens	18.6	1.61–2.16	0.01
Log eosinophils count increase by 1 log unit	18.07	1.55–2.11	0.01

CI: confidence interval; IgE: immunoglobulin E.

Discussion

This study shows that, in subjects with rhinitis, the occurrence of asthma is related to atopy, sensitization to indoor allergens, total serum IgE levels, blood eosinophilia and maternal asthma. These parameters are all known to be associated with asthma in epidemiological studies, but have never been evaluated together in a rhinitic population. In addition, the logistic regression analysis allowed the relative importance of these risk factors to be weighed up, with eosinophil counts representing a greater risk for developing asthma than IgE levels, which represented a greater risk than atopy. In atopic patients, the presence of blood eosinophils and sensitization to indoor allergens were equivalent to an 18-fold increase in risk for a rhinitic subject to display asthma. Taking the bronchial hyperreactivity into account, the same factors were found to be associated with asthma. Except for maternal asthma, a higher degree of significance was found, despite a smaller number of subjects in both groups. This suggests that in the intermediate subgroup with rhinitis and bronchial hyperreactivity but without clinical asthma, the same factors were involved but with a lower expression. However, this group was too small to permit analysis (not shown).

Atopy, defined by at least one positive skin prick test to a common aeroallergen, is by itself a significant risk factor for a subject with rhinitis to display asthma. In agreement with this result, SEARS *et al.* [10] evaluated the risk of asthma in relation to sensitization to 11 common allergens in a group of 714 13-yr-old New Zealand school children and found that the cumulative prevalence of asthma symptoms increased almost linearly with the number of positive skin tests. In addition, the type of sensitization influences the type of allergic disease. Indeed, the prevalence of sensitization to indoor allergens was significantly higher in patients with asthma than in patients with rhinitis alone in the present study. Thereby, previous data obtained in patients with asthma and/or rhinitis are confirmed in a rhinitic population. In the study of SEARS *et al.* [10], sensitization to house dust mite (HDM) and to cat danders were independent risk factors for asthma, whereas grass sensitization was not. In a study of 419 Japanese schoolchildren [11], asthma was associated with high levels of IgE specific for HDM but not for grass pollen. In contrast, seasonal allergic rhinitis correlated with high levels of IgE specific for grass pollen. In a group of 143 young subjects,

COOKSON *et al*. [12] evaluated the relationship between skin-prick-test reactivity to common allergens and bronchial responsiveness. The risk of bronchial hyperresponsiveness was greater in subjects sensitized to house dust and mould than in those reactive to grass. VERDIANI *et al*. [13] showed a higher bronchial responsiveness in patients with perennial as compared to seasonal rhinitis. More recently, BOULET *et al.* [14] showed, in 3,371 consecutive patients, that in subjects with respiratory allergic symptoms, indoor- allergen sensitization was strongly associated with asthma, whereas exclusive sensitization to pollens was associated primarily with rhinitis.

Atopy is frequently associated with a high IgE level. However, it was shown that total blood IgE was associated with asthma, independent of the presence of atopy [6, 7], whereas allergic rhinitis was found to be highly correlated with positive skin tests. A close relationship between asthma and total IgE, independent of specific responses, was confirmed in a Spanish survey [18]. These results are in agreement with the present study, in which the levels of total serum IgE were significantly higher in the group of rhinitis plus asthma subjects than in the group, subjects with rhinitis alone. This difference was also found, although to a lesser extent, in nonatopic patients. This suggests that the elevated total IgE levels in rhinitis associated with asthma are, on the one hand, the result of the higher percentage of atopic patients in this group and, on the other hand, the consequence of the genetic linkage between NAAH and total IgE [6].

Although high IgE levels are associated with asthma, the influence of IgE on the asthmatic process is unknown. In contrast, eosinophils are responsible for the epithelial injury [19]. Indeed, the presence of eosinophils in the bronchial mucosa is considered as specific to asthma [20], and there is a strong correlation between the number of eosinophils infiltrating the bronchi and the severity of asthma [9]. Peripheral blood eosinophilia is widely recognized as a feature of asthma [8, 21, 22]. Recently [23], peripheral blood eosinophilia was proposed as a marker for asthma activity. Eosinophils are also involved in allergic rhinitis, as shown by various studies of the nasal mucosa in this disease [24]. However, blood eosinophilia in pure rhinitis has not been studied specifically. Indeed, peripheral blood eosinophilia has been found to be elevated in rhinitis, but the asthmatic or bronchial hyperreactive subjects included could account for this increase [25, 26]. In the present study, a high blood eosinophil count is a discriminating factor for having asthma associated with rhinitis, both in the total population and in the atopic subgroup. This result confirms the strong relationships between eosinophils and asthma, and suggests that, in pure rhinitis, eosinophilia is limited to the nose.

With regard to familial asthma, only maternal asthma was discriminant for the presence of asthma in rhinitic subjects. Although some studies [27, 28] reported that the association between childhood and parental asthma did not depend on the sex of the parents, COOKSON *et al*. [29] found a genetic transmission of atopy only through the maternal line, and MARTINEZ *et al*. [30] reported an association between maternal asthma and persistent wheezing in children. Recently, BERGMANN *et al*. [31] also found a clear relationship between maternal, but not paternal, asthma and recurrent wheezing in the first 2 yrs of life.

In conclusion, this study gives new insights into the relationships between asthma and rhinitis, showing the tight association in rhinitic patients of asthma and the presence of atopy, high serum immunoglobulin E levels, blood eosinophilia, and maternal asthma. In atopic rhinitic subjects, asthma is strongly associated with sensitization to indoor allergens. We suggest that, in rhinitic subjects, these parameters should be taken into account to best manage underlying asthma.

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