ORIGINAL ARTICLES

Rhinitis and Asthma Comorbidity in Spain: The RINAIR Study

José Antonio Castillo Vizuete[a,b] and Joaquim Mullol Miret[b,c,d]

[a]Servei d'Al·lèrgia i Pneumologia, Institut Universitari Dexeus, Barcelona, Spain
[b]Grupo de Trabajo de Rinitis, Área de Asma, SEPAR
[c]Unitat de Rinologia, Servei d'ORL, Hospital Clínic, IDIBAPS, Barcelona, Spain
[d]Centro de Investigación Biomédica en Red (CibeRes) de Enfermedades Respiratorias, Barcelona, Spain

OBJECTIVE: Rhinitis and asthma share an inflammatory mechanism, epidemiological patterns, and symptoms that affect both the nose and the bronchi. The RINAIR study examined the prevalence and characteristics of rhinitis in asthma patients in Spain.

PATIENTS AND METHODS: This prospective epidemiological study was carried out with the participation of 15% of Spanish respiratory medicine specialists sampled randomly from different geographic areas. The study population was composed of 703 asthmatic patients aged over 16 years who were enrolled between February and September 2005. Patient characteristics, prevalence of rhinitis, lung function, allergy test results, and treatment of rhinitis were analyzed.

RESULTS: Seventy-one percent (n=499) of the asthmatic patients had rhinitis. These patients were younger (43.8 years vs 55.4 years; *P*<.0001) and had less severe asthma (forced expiratory volume in 1 second [FEV_1], 85.7% vs 79.7% [*P*<.001]) than asthmatic patients who did not have rhinitis. A correlation was observed between the severity of asthma and the severity of rhinitis (*P*<.001). Atopy was significantly associated with rhinitis (odds ratio, 6.25; 95% confidence interval, 4.3-9.1): 84% of atopic patients and 51% of nonatopic patients had rhinitis. Treatment of rhinitis was associated with an increase in FEV_1 (*P*=.057), irrespective of sex, age, severity of asthma, or smoking.

CONCLUSIONS: Seventy-one percent of asthmatic patients who attended respiratory medicine clinics had rhinitis. These patients were younger and had milder asthma than asthmatics who did not have rhinitis. Furthermore, atopy was correlated with asthma associated with rhinitis. Treatment of rhinitis tended to improve lung function. These findings highlight the need to study and treat the upper and lower respiratory tract as a single airway.

Key words: *Rhinitis. Asthma. Comorbidity. Lung function. Exacerbation. Treatment.*

Comorbilidad de rinitis y asma en España (estudio RINAIR)

OBJETIVO: Rinitis y asma están ligadas por una epidemiología, clínica y mecanismo inflamatorio comunes que interrelacionan nariz y bronquio. El objetivo del estudio RINAIR ha sido estudiar la prevalencia y características de la rinitis en pacientes con asma en España.

PACIENTES Y MÉTODOS: Se ha realizado un estudio epidemiológico de carácter prospectivo con la participación del 15% de los neumólogos españoles, distribuidos aleatoriamente por áreas geográficas. Se incluyó a 703 asmáticos mayores de 16 años entre febrero y septiembre de 2005. Se analizaron datos demográficos, prevalencia de rinitis, función pulmonar, pruebas alérgicas y tratamiento de la rinitis.

RESULTADOS: Un 71% (n = 499) de los asmáticos presentaba rinitis. Éstos eran más jóvenes (43,8 frente a 55,4 años; p < 0,0001) y presentaban un asma menos grave —volumen espiratorio forzado en el primer segundo (FEV_1): un 85,7 frente a un 79,7% (p < 0,001)— que los asmáticos sin rinitis. Se observó una correlación entre la gravedad del asma y la gravedad de la rinitis (p < 0,001). La atopia se asoció significativamente con la presencia de rinitis (*odds ratio* = 6,25; intervalo de confianza del 95%, 4,3-9,1): el 84% de los atópicos y el 51% de los no atópicos tenían rinitis. El tratamiento de la rinitis se asoció (p = 0,057) con un incremento del FEV_1, con independencia del sexo, la edad, la gravedad del asma y el hábito de fumar.

CONCLUSIONES: Un 71% de los asmáticos atendidos en las consultas de neumología tiene rinitis. Estos pacientes son más jóvenes y presentan un asma más leve que los asmáticos sin rinitis. Por otro lado, la atopia se relaciona con el asma asociada a rinitis. El tratamiento de la rinitis tiende a mejorar función pulmonar. Estos hallazgos indican la necesidad de estudiar y tratar toda la vía respiratoria de forma integral.

Palabras clave: *Rinitis. Asma. Comorbilidad. Función pulmonar. Exacerbación. Tratamiento.*

Introduction

Rhinitis and asthma share an inflammatory mechanism, epidemiological patterns, and symptoms that affect both the lower and upper airway.[1,2] Rhinitis affects 22% of the Spanish population[3] and asthma 7%.[4] Approximately 70% to 80% of asthmatics have concomitant rhinitis, and recent studies suggest that rhinitis can predispose to subsequent

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Correspondence: Dr J.A. Castillo
Sant Joan, 10
08870 Sitges, Barcelona, Spain
E-mail: 11437jac@comb.es

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development of asthma.[5-18] The same inflammatory cells, mediators,[6,14] and triggers[15] participate in chronic inflammation of the airway mucosa in rhinitis and asthma. Considerable scientific evidence has led to the proposal of a new concept of one airway, one disease linking rhinitis and asthma, whose prevalence is increasing throughout the world.[3,6] This concept has been extended to other diseases involving the nose and lungs.[7,8] Several authors point to a greater risk of asthma exacerbation in patients suffering from untreated rhinitis.[9,10] This can affect health spending,[11] since exacerbations account for 70% of the economic costs of asthma.[12]

The main objective of the RINAIR study was to ascertain the prevalence of rhinitis in asthmatic patients being treated in Spanish respiratory medicine clinics, the characteristics of these patients, and the relationship with the severity of asthma. The study also analyzed lung function and asthma exacerbations according to the presence or absence of rhinitis, in addition to common triggers and the impact of the treatment prescribed by Spanish respiratory medicine specialists.

Patients and Methods

Study Population

This was a prospective epidemiologic study of 742 asthmatic patients aged over 16 years, with the participation of 15% of Spanish respiratory medicine specialists sampled randomly from different geographic areas as follows: North-Coastal (Galicia, Asturias, Cantabria, and the Basque Country), North-Inland (Navarre, Aragon, La Rioja, and Castile and Leon), Center (Castile-La Mancha, Extremadura, and the Community of Madrid), East-Coastal (Catalonia, the Community of Valencia, Murcia, and the Balearic Islands), and South (Andalusia, the Canary Islands, Ceuta, and Melilla). The study population was selected by means of systematic random sampling of all asthma patients who visited a respiratory medicine clinic between February and September 2005, and the 172 participating respiratory medicine specialists were randomly selected, stratified by autonomous community in proportion to the population. As they were each required to select the first 6 asthma patients who attended their clinic, the number of patients expected was 1032, from whom 742 were finally selected (mean 4.3 patients per specialist).

During the visit, a specific questionnaire designed by the Working Group on Rhinitis of the Assembly on Asthma of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) was used to record age, sex, diagnosis of asthma, diagnosis of rhinitis, time since diagnosis of rhinitis and asthma, severity of rhinitis according to the classification proposed by the Allergic Rhinitis and its Impact on Asthma (ARIA) update of 2008,[1] severity of asthma according to the Global Initiative for Asthma (GINA),[6] lung function measured using a bronchodilator test with salbutamol, known triggers (outdoor allergens [pollen], indoor allergens [house dust mites, fungi, and animal dander], and medication), a previous diagnosis of nasal polyposis, smoking, current medication for the treatment of rhinitis and asthma, and asthma exacerbations during the preceding month and preceding 3 months.

Diagnosis of Asthma

Asthma was diagnosed on the basis of a history of dyspnea accompanied or not by cough and/or wheezing, together with reversible airflow limitation. The bronchial obstruction was considered to have reversed if a forced expiratory volume in 1 second (FEV_1) of less than 80% of predicted increased by 15% or more after inhalation of 200 mg of salbutamol. The severity of asthma was classified according to GINA[6] as intermittent, mild persistent, moderate persistent, and severe persistent. An asthma exacerbation was considered to be any worsening of symptoms with an increase in the use of rescue medication (β_2-adrenergic agonists), an unscheduled visit to the respiratory medicine clinic or emergency room, and/or the need for oral corticosteroids.

Diagnosis of Rhinitis

A diagnosis of rhinitis was based on the presence of symptoms (sneezing, nasal pruritus, nasal obstruction, and/or rhinorrhea). Rhinitis was classified as persistent or intermittent according to the duration of symptoms, and as mild or moderate-severe according to the absence or presence of impaired quality of life (ARIA classification[1]). An exacerbation of rhinitis was considered to be any worsening of symptoms accompanied by increased use of antihistamines and/or nasal corticosteroids.

Allergic Triggers

The triggers of asthma and rhinitis were classified as outdoor (pollen), indoor (house dust mites, fungi, and dog or cat dander), and medication. Asthma or rhinitis triggered by outdoor allergens was diagnosed based on the results of skin prick tests[13] applied to the ventral forearm with 12 allergenic extracts (*Dermatophagoides pteronyssinus; Dermatophagoides farinae; Alternaria, Aspergillus,* and *Cladosporium* species; dog and cat dander; grass weed, *Parietaria* species; and olive, cypress, and plantain pollens). Histamine dihydrochloride (10 mg/mL) was used as a positive control and saline solution, 0.9% as a negative control. The test result was considered positive if, after 15 minutes, the wheal was at least 3 mm in diameter or greater than or equal to the size of that of the positive control.[13]

The medications triggering asthma and rhinitis (acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, and antibiotics) were recorded from the medical history.

Statistical Analysis

Assuming a comorbidity of 70% (based on the relevant international literature), a statistical significance of *P* less than .05, a precision of 5%, and a 95% confidence level (CI), the sample size necessary to estimate the prevalence of the comorbidity of asthma with rhinitis was 557 patients. The RINAIR study eventually included 742 patients. Data were stored using Microsoft Access and the statistical analysis was carried out using SPSS version 12.0 (SPSS, Inc, Chicago, Illinois, USA) and STATA (StataCorp, College Station, Texas, USA). Qualitative variables were compared using a contingency table (χ^2 test). Logistic regression analysis was used to establish the relationships between the different variables and the comorbidity of asthma and rhinitis. The odds ratio, 95% CI, and degree of significance were calculated. Multiple regression was performed to observe the influence of the treatment of rhinitis on the lung function (FEV_1) of patients suffering from both asthma and rhinitis. Statistical significance was set at a *P* value of less than .05. The correlations between ordinal variables were assessed using the Spearman rank correlation coefficient.

Results

Patient Characteristics

Of the initial 742 patients initially included in the study, 39 were excluded (2 for lack of personal details on the

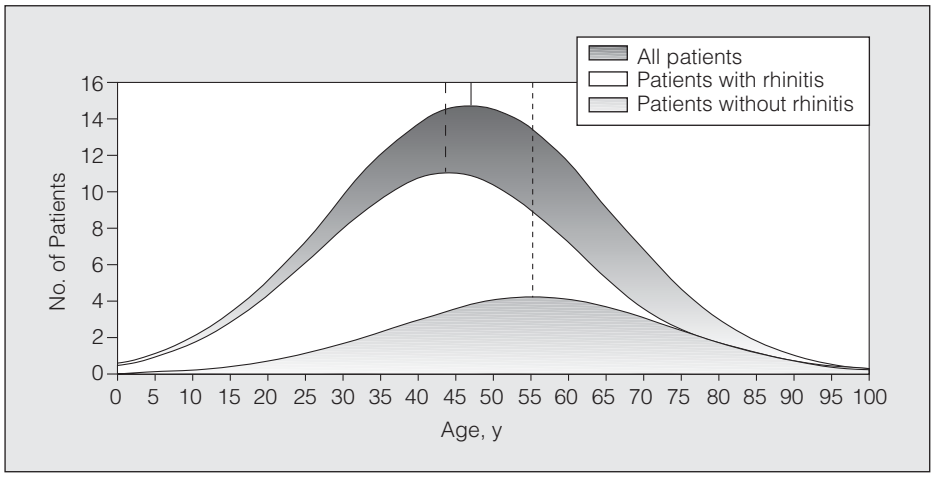

Figure 1. Rhinitis and age groups. Normal distribution of age and mean number of asthmatics with rhinitis. Asthmatics with rhinitis were younger than those without rhinitis.

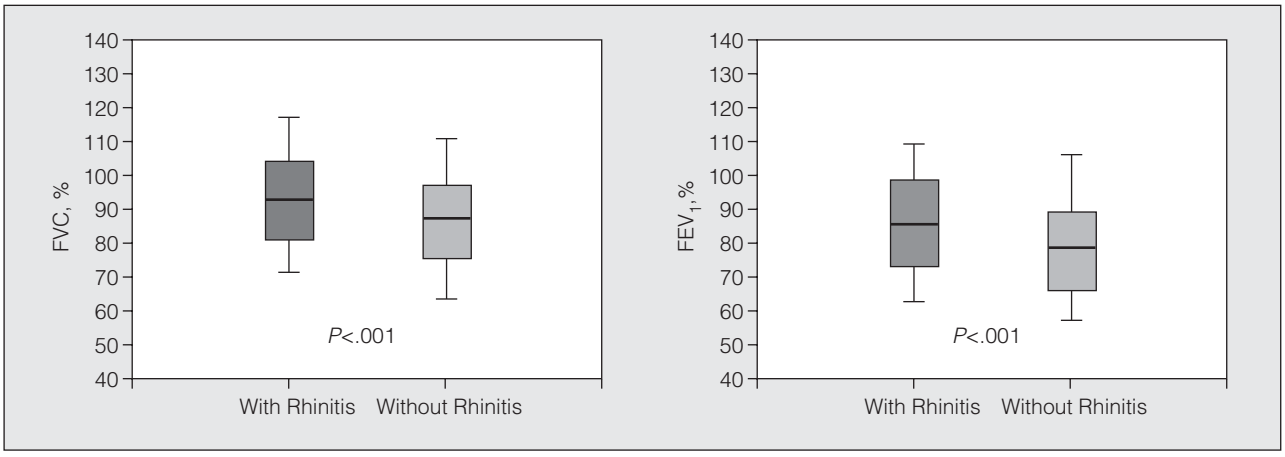

Figure 2. Lung function and rhinitis comorbidity. Asthmatics with rhinitis have a better lung function—forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)—than asthmatics without rhinitis.

case report form, 9 for not fulfilling the inclusion criteria, and 28 for incomplete or unclear data). The characteristics of the 703 eligible patients, all of whom had been diagnosed with asthma for at least 1 year, are presented in Table 1.

Diagnosis of Asthma

The distribution of severity of asthma according to the GINA classification[6] was as follows: intermittent (24.5%), mild persistent (35.4%), moderate persistent (32.7%), and severe persistent (7.4%). Asthma was not controlled in 29% of cases and rhinitis in 44.7% of cases, and these patients had experienced exacerbations during the preceding month.

Diagnosis of Rhinitis

Seventy-one percent of the 703 patients with asthma also had rhinitis. Patients with concomitant asthma and rhinitis were generally younger than those who had asthma only (Figure 1) and their asthma was less severe (Figure 2 and Table 1). There was an inverse relationship between the prevalence of rhinitis and the severity of asthma

TABLE 1
Characteristics of Patients With Asthma

	Asthma With Rhinitis	Asthma Without Rhinitis	*P*
No. of patients,%	496 (71%)	207 (29%)	NS
Age, mean (SD), y	43.8 (17.3)	55.4 (18.3)	<.0001
No. of women,%	288 (62.3%)	115 (61.5%)	NS
FEV_1,%	85.7 (20.9)	79.7 (19.4)	<.001

Abbreviations: FEV_1, forced expiratory volume in 1 second; NS, not significant.

TABLE 2
Prevalence of Rhinitis According to the Severity of Asthma: The More Severe the Asthma, the Lower the Prevalence of Comorbidity With Rhinitis

Severity of Asthma	Prevalence of Rhinitis, %
Intermittent asthma	88
Mild persistent asthma	80
Moderate persistent asthma	62
Severe persistent asthma	54

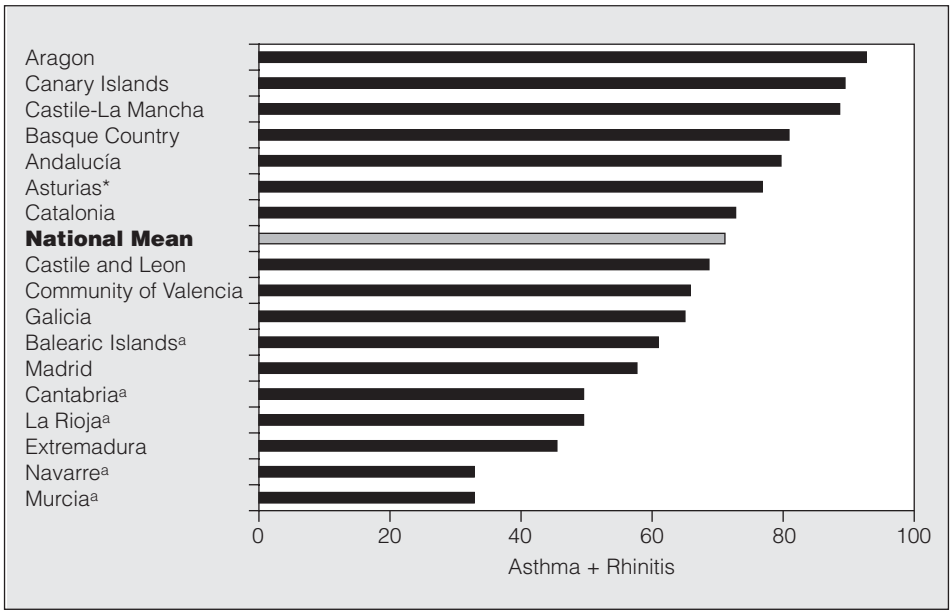

Figure 3. Prevalence of rhinitis by Spanish autonomous community and mean prevalence in all of Spain. [a]Autonomous communities where fewer than 20 cases were recorded.

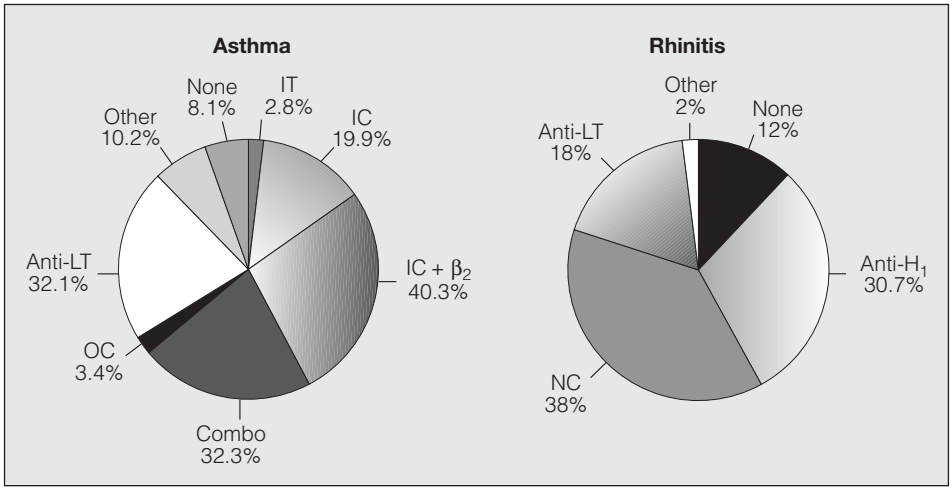

Figure 4. Treatment of asthma and rhinitis in patients from the RINAIR study. The same patient may have been taking several drugs. As for treatment of asthma, 72% of patients received a combination of inhaled corticosteroids (IC) plus long-acting β_2-adrenergic agonists. Other treatments were antileukotrienes (anti-LT, 32.1%), IC in monotherapy (19.9%), oral corticosteroids (OC, 3.4%), and immunotherapy (IT, 2.8%). No treatment was prescribed in 8% of the cases. Rhinitis was treated with intranasal corticosteroids (NC, 38%), antihistamines (anti-H_1, 30.7%), and anti-LT (18%). No treatment was prescribed in 12% of the asthmatics. Combo indicates the combination of IC and long-acting β_2-adrenergic agonists in the inhaler.

(Table 2). There were no differences in gender or smoking. For a large number of patients asthma was not controlled, and they had experienced exacerbations of asthma (29%) and/or rhinitis (44.7%) during the preceding month. The relationship between comorbidity and the number of exacerbations during the preceding month was not statistically significant.

According to the ARIA classification,[1] the severity of rhinitis was mild intermittent in 9.2% of cases, moderate-severe intermittent in 47.4%, mild persistent in 16.3%, and moderate-severe persistent in 27.1%. There was a positive correlation (Spearman rank correlation coefficient, 0.33; $P<.0001$) between severity of asthma and severity of rhinitis. The prevalence of rhinitis in asthmatics by autonomous community and geographic area is shown in Figure 3 and Table 3.

The treatments used for asthma and rhinitis are shown in Figure 4. The lung function of asthmatics with treated concomitant rhinitis (antihistamines, antileukotrienes, or nasal corticosteroids) was better, although not significantly so (FEV_1 [SD], 89.2% [22.1%]), than that of patients who received no treatment for rhinitis (85.2% [20.7%]).

TABLE 3
Comorbidity of Asthma With Rhinitis by Geographic Area

	Comorbidity		
	Yes	**No**	**Total**
North-Coastal, n (%)	68 (70.8%)	28 (29.2%)	96
North-Interior, n (%)	61 (75.3%)	20 (24.7%)	81
Center, n (%)	91 (62.3%)	55 (37.7%)	146
East-Coastal, n (%)	154 (68.8%)	70 (31.2%)	224
South, n (%)	122 (83.0%)	25 (17.0%)	147
Total, n (%)	496 (71.5%)	198 (28.5%)	694[a]

[a]Data on the patient's Spanish autonomous community of residence were not available in 9 cases.

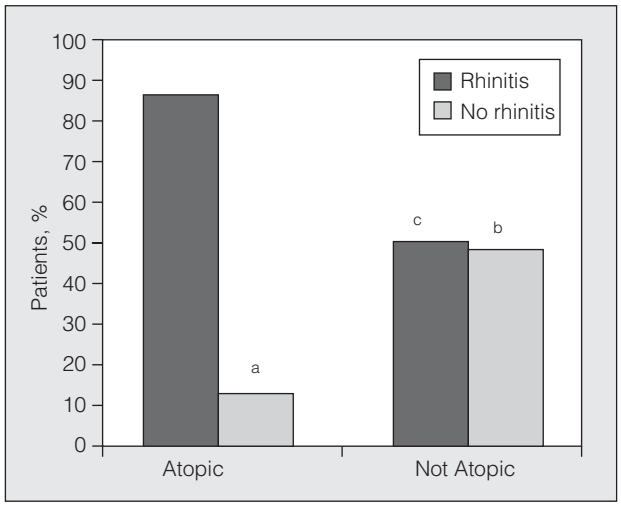

Figure 5. Relationship between rhinitis and atopy in asthma patients. There was a clear relationship between asthma-rhinitis comorbidity and the presence of atopy. Concomitant rhinitis affected 84.7% of atopic asthmatics. There was also a significant difference between atopic and nonatopic asthmatics.
[a]*P*<.05 vs patients with both rhinitis and atopy.
[b]P<.01 vs patients with both rhinitis and atopy.
[c]*P*<.01 vs atopic patients without rhinitis.

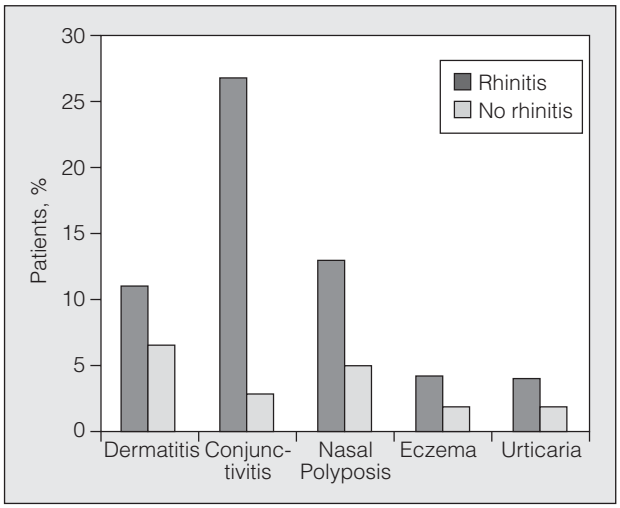

Figure 6. Associated diseases in asthmatics with rhinitis. Patients with asthma and rhinitis had a significantly greater prevalence of associated conditions than patients with asthma and no rhinitis (*P*<.05). These associated conditions were conjunctivitis (26.9% vs 2.6%), nasal polyposis (13.7% vs 5%), and atopic dermatitis (11.2% vs 7%). No significant differences were observed for eczema or urticaria.

In the multivariate analysis, where FEV_1 was considered a dependent variable and treatment of rhinitis an independent variable—with age, sex, smoking, and severity of asthma as potential confounders—this improvement in FEV_1 approached significance independently of the severity of asthma, sex, age, or smoking (Table 4).

Atopy and Triggers

The most common triggers were outdoor aeroallergens (pollen, 48%) and indoor aeroallergens (house dust mites, fungi, and animal dander, 30%), exercise (25%), and to a much lesser extent, medication (4.5%), and food (2%). Of the asthmatics analyzed (n=420), 59.7% had a positive skin prick test result for an aeroallergen. Atopy, that is, the presence of positive allergy tests, was significantly related to the presence of associated rhinitis (Figure 5) (odds ratio, 6.25; 95% CI, 4.35-9.10). The distribution of outdoor aeroallergens (pollen) and indoor aeroallergens (house dust mites and pet dander) was similar throughout the country, with a predominance of outdoor allergens (pollen) in all geographic areas except North-Coastal (Galicia, Asturias, Cantabria, and the Basque Country), where there was a predominance of indoor allergens (house dust mites and pet dander).

Other Comorbid Conditions

In addition to rhinitis, the asthmatic patients analyzed had conjunctivitis (26.9%), chronic rhinosinusitis or nasal polyposis (13.7%), atopic dermatitis (11.2%), eczema (3.8%), and urticaria (3.7%). The association between comorbidity and more severe asthma was not statistically significant in this study. Nevertheless, patients with asthma and rhinitis also had a greater prevalence of associated conditions than patients with asthma and no rhinitis (Figure 6).

Discussion

This study reflects the caseload of respiratory medicine practices in Spain in terms of the diagnosis and management of rhinitis in patients suffering from asthma. The results are important because of the paucity of published data on the management of rhinitis by respiratory medicine specialists and because the participating specialists from throughout the country were randomly distributed in proportion to the population. The prevalence of asthma with concomitant rhinitis is very high in Spain—71% of the asthmatics who visited the respiratory medicine clinic

TABLE 4
Multivariate Analysis of the Influence of Treatment of Rhinitis on Lung Function (FEV_1) in Patients With Rhinitis and Asthma (Adjusted for All the Variables in the Table)

	Coefficient	*P*	95% CI
Age, increments of 1 year	–0.170	.005	–0.29 to –0.054
Sex, female	0.31	NS	–3.63 to 4.25
Severity			
Mild intermittent	1	–	–
Mild persistent	–2.79	NS	–7.65 to 2.05
Moderate persistent	–13.55	.0001	–18.96 to –8.14
Severe persistent	–28.30	.0001	–37.19 to –19.4
Current smoker	–1.90	NS	–7.51 to 3.70
Treated rhinitis	5.78	.057	–0.18 to 11.7

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 second; NS, not significant.

also suffered from rhinitis. These patients are usually younger and have milder asthma than asthmatics who do not have rhinitis, which is much more common among atopic patients, who make up almost two-thirds of all the asthma patients attended at these clinics. The severity of asthma and the severity of rhinitis are correlated, and treatment of rhinitis tends to improve lung function in asthmatic patients, although not significantly. These results reinforce the main message of the ARIA guidelines,[1] which recommend systematic investigation of the presence of rhinitis in patients with asthma.

Asthma and rhinitis are highly prevalent conditions that coexist or precede one another,[14] and rhinitis is currently considered a risk factor for the onset of asthma.[15] These conditions share the pathophysiologic mechanisms that characterize chronic inflammation of the airway mucosa, in which the same inflammatory cells and mediators participate.[16] Nasal challenge and segmental bronchial challenge in nonasthmatic patients with seasonal rhinitis induce eosinophilic inflammation in both nasal and bronchial mucosa, with respiratory symptoms.[17] Therefore, it seems reasonable that treatment of one section of the airway can affect the other and that studying the effect of treating rhinitis on the outcome of asthma could prove useful.

RINAIR is one of the first prospective and randomized studies to evaluate the prevalence of rhinitis in patients with asthma, as well as the influence of rhinitis treatment on lung function. In Spain, as in other European countries,[18,19] the prevalence of asthma with concomitant rhinitis is very high. Other recent Spanish studies on the comorbidity of rhinitis and asthma[20-22] have provided data that are completely consistent with the results for prevalence in rhinitis in the present study. Furthermore, the lower prevalence of rhinitis in the older age group supports the observation in some studies that rhinitis remits with age.[23] The association between atopy and rhinitis is clear in our study, as published elsewhere,[18] although we did not find the same association in nonatopic asthmatics as did other authors,[19] probably because of the greater age range of the patients included in our study.

Despite the fact that the new ARIA guidelines[1] highlight the need for integrated treatment of the airway and systematic investigation of rhinitis in asthmatics, our respiratory medicine clinics are perceived as paying little attention to comorbid rhinitis, its treatment, and its influence on asthma. More asthma exacerbations have been observed among patients with concomitant rhinitis. Some authors studied small samples, finding no relationship between exacerbation and comorbid rhinitis,[24] whereas others looked at large yet retrospective samples[25] and found a significant correlation between the comorbidity of asthma and rhinitis and a greater number of exacerbations, visits to the emergency room, admissions to hospital, and increased use of health care resources. We did not find a statistically significant correlation between concomitant rhinitis and asthma exacerbations, probably because the total number of patients was very low for this type of statistical analysis; however, we did detect a tendency toward a better lung function in asthmatics whose rhinitis had been treated.

Several recent studies reveal a difference between asthma with treated rhinitis and asthma with untreated rhinitis, demonstrating a lower risk of asthma exacerbation.[9,10] In contrast, a recent Cochrane Airways review[26] did not find evidence of significant improvement in asthma symptoms, lung function, or bronchial hyperreactivity to methacholine among patients treated with nasal corticosteroids compared with those who were not. The authors attribute this lack of improvement to the poor sensitivity of lung function tests for the measurement of airway inflammation. In order to resolve this apparent contradiction with the recommendations of the ARIA guidelines,[1] it would be necessary to carry out new studies to analyze the influence of rhinitis therapy on the control of asthma using techniques that are more sensitive to airway inflammation (eosinophil counts in induced sputum or measurement of the fraction of exhaled nitric oxide),

The ARIA guidelines,[1] which state that the optimum treatment of rhinitis can improve asthma, specify the need for combined treatment of asthma and rhinitis covering the upper and lower airway. Designing harmonized treatment strategies is also advisable in the light of studies showing that combining montelukast and inhaled budesonide in patients with associated allergic rhinitis is significantly more effective at reducing bronchial obstruction than doubling the dose of budesonide (the COMPACT trial[27]) or that introducing montelukast in the treatment of chronic asthma and concomitant rhinitis improves asthma control and reduces consumption of health care resources (the PRACTICAL trial[29]). Taking this new evidence into account will enable us to reduce the cost of treating these patients, since inappropriate therapy of rhinitis in asthmatics can lead to poorer control of asthma, with more exacerbations and poorer lung function.

A possible limitation of the present study is the seasonal nature of the data collected from patients who visited between February and September 2005—this could have affected the recording of exacerbations because we did not have a complete annual register. Furthermore, atopy was only considered to be present when the result of skin prick testing with an aeroallergen was positive. Another important limitation is that, in the multivariate analysis of the influence of rhinitis treatment on lung function (FEV_1), the type of drug used was not taken into consideration, and rhinitis was considered treated when any drug (antihistamines, nasal corticosteroids, montelukast) or a combination of drugs was prescribed.

The high prevalence of rhinitis in asthmatic patients in Spain makes it essential for respiratory medicine specialists to recognize and treat this disease, which is so closely linked to asthma. The results of this study show that the severity of asthma and the severity of rhinitis are correlated, and that treating rhinitis tends to improve lung function. These findings support the principal message of the ARIA guidelines,[1] that the upper and lower airway should be studied and treated as one.

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