ORIGINAL CONTRIBUTION

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Prevalence and characteristics of rhinitis in asthmatic patients attending primary care in Spain (the RINOASMAIR study)*

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SUMMARY

Introduction: *Rhinitis and asthma share epidemiological, pathophysiological, and clinical features. The aim of the RINOASMAIR study was to examine the prevalence and characteristics of rhinitis in asthmatics in a Primary Care setting in Spain.*

Methods: *A prospective epidemiological study was conducted with the participation of 1,027 Primary Care Physicians (PCP). A total of 4,174 asthmatics were included and demographic data, rhinitis prevalence, lung function, atopy, and rhinitis treatment were analysed.*

Results: *71% of asthmatics suffered from rhinitis, these being younger (42.8 vs 50.2 yr; $p < 0.0001$) and having milder asthma ($FEV_1 = 80.2\%$ vs 76.1%, $p < 0.002$) than those without rhinitis. A significant correlation ($Rho = 0.35$, $p < 0.0001$) between asthma and rhinitis severities was found. Atopy was associated to rhinitis, 77.8% of atopic compared to 47.6% of non atopic having rhinitis.*

Conclusions: *Most asthmatics (71%) visited by Spanish PCP suffer from rhinitis, and these patients are younger and have milder asthma than asthmatics without rhinitis.*

Key words: rhinitis, asthma, comorbidity, lung function, exacerbation, treatment

INTRODUCTION

Rhinitis and asthma share similar epidemiological, pathophysiological, and clinical features, and have a common inflammatory mechanism linking the upper and the lower airways [1,2]. In Spain, rhinitis affects 22% of the population [3], while asthma is found in 7% [4]. Approximately 70-80% of all asthmatics have concomitant rhinitis, and recent studies point out that rhinitis is a predisposing factor for the development of asthma [5-19]. Chronic inflammation of the respiratory mucosa in rhinitis and asthma is characterized by the participation of a similar network of inflammatory cells and mediators [6,15], and with similar triggering factors [16]. A large body of scientific evidence has suggested a new concept in which rhinitis and asthma – the prevalence of which is increasing worldwide [3,6] – form part of the same airway disease, under the concept of "one airway, one disease" [7]. This concept has also been extended to other diseases with involvement of the nose and lungs [8,9]. A variety of studies have suggested an increased risk for asthma exacerbation in untreated rhinitis patients [10,11]. This in turn may have an impact upon health care expenditure [12], since exacerbations account for up to 70% of the economical cost of asthma [13].

The main objective of the RINOASMAIR study was to evaluate the prevalence of rhinitis in asthmatic patients visited in Spain by Primary Care Physicians (PCP), its characteristics and relationship to the severity of asthma. Furthermore, lung function and asthma exacerbations were also assessed in relation to the presence or absence of rhinitis, the common triggering factors, and the impact of the treatment prescribed by Spanish PCP.

PATIENTS AND METHODS

Study population

A prospective epidemiological study was made on 4,174 asthmatics over 16 years of age, with the participation of 5% of all Spanish PCP (n = 1,027), randomly distributed according to geographical areas. Sample selection was based on systematic randomized sampling of all asthmatic patients seen in PCP

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centers from February to September 2005. Each PCP was required to recruit the first 5 asthmatic patients that visited the clinic. Each PCP finally recruited on average 4.1 asthmatic patients and a total number of 4,174 patients were included in the study. A specific questionnaire was developed and used in the clinic to collect the following data: age, gender, diagnosis of asthma, diagnosis of rhinitis, duration (in years) of rhinitis and asthma, severity of rhinitis according to ARIA [1], severity of asthma according GINA [6], and lung function with bronchodilation (salbutamol). The known triggering factors were also documented: outdoor allergens (pollen), indoor allergens (dust mites, mold, and animal dander), and drugs, previous diagnosis of nasal polyposis, smoking habit, current medications used for rhinitis and asthma, and asthma exacerbations (last month and last three months).

Diagnosis of asthma

Asthma was diagnosed from clinical history, defined as dyspnea with or without cough and/or wheezing, together with reversible airflow obstruction. The bronchial reversibility of obstruction was defined as $FEV_1 < 80\%$ of its theoretical value, with an increase of $\geq 15\%$ after the inhalation of 200 μg of salbutamol. The severity of asthma was classified according to GINA [6] in: intermittent, mild persistent, moderate persistent, and severe persistent. Asthma exacerbation was defined as the worsening of asthma symptoms, with an increased use of rescue medication (beta-adrenergic agonists) and/or non-scheduled visits to the PCP center or emergency department, and/or the need for oral corticosteroids.

Diagnosis of rhinitis

The diagnosis of rhinitis was based on the presence of symptoms (sneezing, nasal itching, nasal congestion/obstruction, and/or rhinorrhea). Rhinitis was classified by duration in intermittent or persistent, and by severity in mild or moderate-severe, depending on the absence or presence of impaired patient's quality of life, and according to ARIA [1] in both treated and non-treated patients. The exacerbation of rhinitis was defined as the worsening of symptoms with an increased use of antihistamines and/or nasal corticosteroids.

Triggering allergens

The trigger factors of asthma and rhinitis were classified as outdoor (pollen), indoor (dust mites, cat or dog dander, and mold), or drugs. The identification of outdoor and indoor trigger factors was based on the results of epicutaneous skin-prick tests [14] on the ventral surface of the forearm, using 12 allergenic extracts (*Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria, Aspergillus, Chladosporium*, cat and dog dander, and pollen for grass, weeds, parietaria, olive, cypress, and plane tree). Positive (10 mg/ml histamine dihydrochloride) and negative (0.9% saline) controls were also tested. A positive test was defined by a wheal at least 3 mm in diameter, or of a size equal to or larger than the positive control, after 15 minutes [14].

The triggering drug substances were documented from anamnesis and clinical history (aspirin, non-steroidal antiinflammatory drugs, and antibiotics).

Statistical analysis

Assuming a comorbidity rate of about 70% (according to the international literature), with a level of significance of 0.05, a precision of 5% and a 95% confidence level, the sample size required estimating the prevalence of asthma and rhinitis comorbidity was found to be 3,500 patients. A total of 3,971 patients were finally included in the RINOASMAIR study. The data were entered in a Microsoft Access database for statistical analysis using the SPSS version 12.0 statistical package (Chicago, IL, USA) and STATA (College Station, TX, USA). The comparison of qualitative variables was based on contingency analysis (chi-square). Logistic regression analysis established the relationships between the different variables and asthma and rhinitis comorbidity, estimating the odds ratio (OR), 95% confidence interval (CI) and degree of significance. Multiple regression analysis was performed to determine the influence of rhinitis treatment upon lung function (FEV_1) in patients with asthma and rhinitis comorbidity. Statistical significance was accepted for $p < 0.05$. The Spearman correlation coefficient was used to establish correlations between ordinal variables.

RESULTS

Demographics

Of the 4,174 patients recruited for the study, 203 were excluded: 83 due to a lack of affiliation data in the case report form, and 120 due to non-compliance with the inclusion criteria, and/or incomplete or unclear information. The characteristics for the 3,971 patients considered valid for the study (all diagnosed with asthma at least one year before) are reported in Table 1.

Diagnosis of asthma

The distribution of asthma severity according to the GINA classification was as follows: intermittent (39.8%), mild persis-

Table 1. Characteristics of the asthmatic patients.

	Asthma with rhinitis	Asthma without rhinitis	p <
Patients, N (%)	2,830 (71.2)	1,141 (28.8)	
Age, yr (mean ± SD)	42.8 ± 17.5	50.2 ± 18.6	0.0001
Females, N (%)	1,481 (54.7)	605 (57.7)	NS
FEV_1 * (mean ± SD)	80.2 ± 16.5	76.1 ± 18.2	0.002

NS, non-significant
SD, standard deviation
*With respect to 788 individuals with values for the variables FEV_1 and comorbidity.

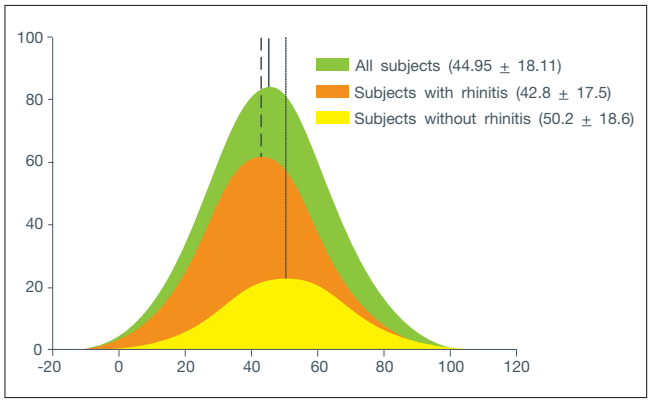

Figure 1. Normal distribution of asthmatic patients with concomitant rhinitis, depending on age (mean age, years). Asthmatic patients with rhinitis were younger (42.8) than asthmatic patients without rhinitis (50.2).

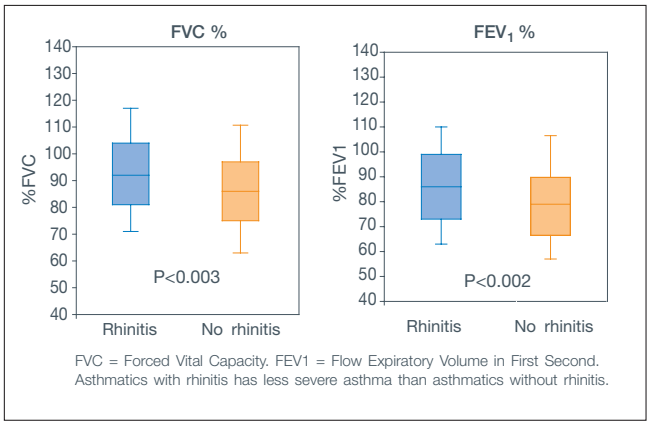

Figure 2. Lung function in asthmatic patients with rhinitis comorbidity. Asthmatic patients with rhinitis had better lung function (FEV_1 and FVC) than asthmatics without rhinitis.

tent (32.7%), moderate persistent (23.9%), and severe persistent (3.2%). Asthma was not controlled, with exacerbations in the previous month, in 62% of the cases.

Diagnosis of rhinitis

Of the 3,971 asthmatic patients studied, 71.2% also had rhinitis. The patients with asthma and concomitant rhinitis were generally younger than those with asthma only (Figure 1), and their asthma was milder (Figure 2, Table 1). In turn, the prevalence of rhinitis was inversely correlated to the severity of asthma. There were no differences in terms of patient gender or smoking habit. Rhinitis was not controlled, with exacerbations in the previous month, in 54.5% of the cases. A statistically significant association was observed between the comorbidity of asthma and rhinitis, and the number of exacerbations in the previous month ($p < 0.001$).

The severity of rhinitis according to ARIA classification was as follows: mild intermittent (37.5%), moderate/severe intermittent (40.6%), mild persistent (11.4%) and moderate/severe persistent (10.4%). According to asthma severity, the prevalence of allergic rhinitis comorbidity was: mild intermittent (84%), mild persistent (74%), moderate persistent (68%), and severe persistent (58%). A positive correlation was established (Spearman

Table 2. Multivariate analysis of the influence of rhinitis therapy upon pulmonary function (FEV1) in patients with asthma and rhinitis comorbidity (adjusted for all variables of the table).

	Coefficient	p	95%CI
Age (for each year))	0.186	<0.001	0.26; 0.11
Gender (female)	0.38	NS	2.20; 2.97
Severity:			
Mild intermittent	1		
Mild persistent	5.17	0.01	8.32; 2.04
Moderate persistent	11.52	<0.0001	14.87; 8.16
Severe persistent	23.43	0.0001	30.41; 16.45
Current smoker	1.45	NS	4.71; 1.81
Treated rhinitis	0.44	NS	5.02; 4.14

NS, non-significant

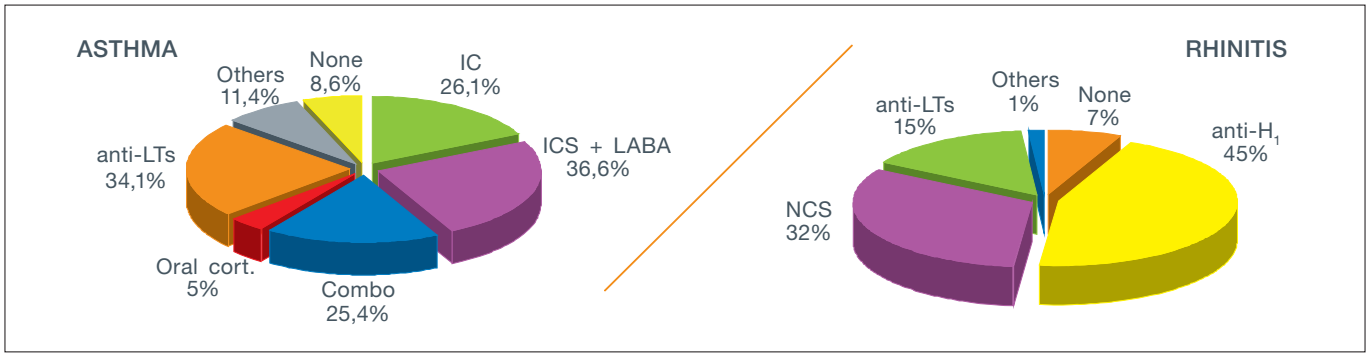

Figure 3. Treatment of asthma and rhinitis in the patients of the RINOASMAIR study. A) Asthma: 62% of asthmatics were treated with the combination of inhaled corticosteroids and long acting beta agonists. Other administered drugs were: antileukotrienes (34.1%), inhaled corticosteroids in monotherapy (26%), oral corticosteroids (5%), and other treatments (11.4%), while 8.6% of patients received no treatment for their rhinitis. B) Rhinitis: patients were treated with intranasal corticosteroids (32%), antihistamines (45%), antileukotrienes (15%), while 7% of asthmatics with rhinitis received no treatment. IC: inhaled corticosteroids; IC+LABA: inhaled corticosteroids combined plus long acting beta 2 agonists; combo: inhaled corticosteroids with long acting beta 2 agonists combined in a single inhaler; anti LTs: antileukotrienes; nasal CC: nasal corticosteroids; anti H1: antihistamines.

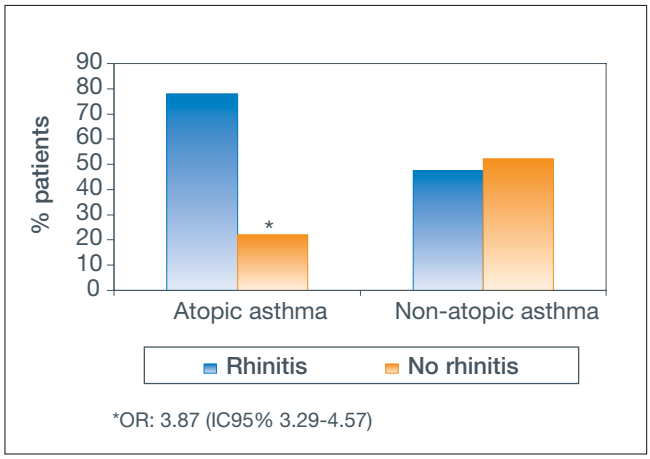

Figure 4. Relationship between rhinitis and atopy in asthmatic patients. A clear relationship was observed between rhinitis comorbidity and the presence of atopy in the asthmatic patients. Among atopic asthma patients, 77.9% reported concomitant rhinitis, a significant difference ($p < 0.0001$) also being observed between the atopic and non atopic asthmatics.

rho = 0.33; $p < 0.0001$) between the severity of asthma and the severity of rhinitis.

The medication used by PCP in the treatment of asthma and rhinitis is shown in Figure 3. The asthmatics with rhinitis in which rhinitis was subjected to therapy (antihistamines, antileukotrienes, or nasal corticosteroids) showed better non significant lung function (FEV_1: 78.6%) than asthmatics with rhinitis who received no rhinitis treatment (FEV_1: 79.1%), according to the multivariate analysis, taking FEV_1 as dependent variable and the treatment of rhinitis as independent variable, and incorporating age, gender, smoking and the severity of asthma as potential confounding factors (Table 2).

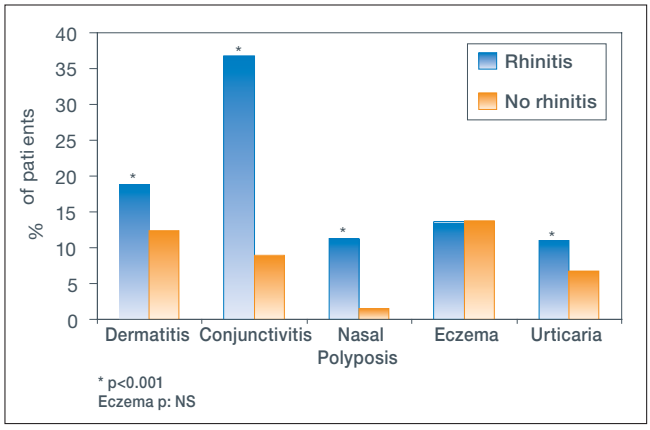

Figure 5. Associated diseases in asthmatic patients with rhinitis. Patients with asthma and concomittant rhinitis (bars in blue) showed a significant (*, $p < 0.001$) greater prevalence of associated diseases than asthmatics without rhinitis (bars in orange) in the prevalence of conjunctivitis (37% versus 8%), nasal polyposis (10% versus 2%), atopic dermatitis (18% versus 13%), and urticaria (9.8% versus 6%) but not in eczema (12.8% versus 13%)(p: NS, not significant).

Atopy and triggering factors

The most frequent reported trigger factors were outdoor (68.8%) and indoor (38.6%) pneumoallergens, exercise (22.9%) and, to a much lesser extent, drugs (5.3%) and foods (4.7%). A positive prick test for some pneumoallergen was recorded in 75.7% of asthmatics (n = 3163). Atopy, expressed as a positive skin prick test, was significantly associated to concomitant rhinitis (OR: 3.88; 95%CI: 3.29 – 4.57) (Figure 4).

Other comorbidities

In addition to asthma, asthmatic patients also reported conjunctivitis (37%), chronic rhinosinusitis or nasal polyps (10%), atopic dermatitis (18%), eczema (12.8%), and urticaria (9.8%). Moreover, patients with asthma and concomitant rhinitis reported a greater prevalence of associated diseases ($p < 0.001$) than asthmatics without rhinitis (Figure 5).

DISCUSSION

RINOASMAIR is an epidemiological study that describes Primary Care practice in Spain in relation to the diagnosis and management of rhinitis in asthmatics. The results are of importance, since there is little published information on the management of rhinitis by PCP. The prevalence of asthmatics with concomitant rhinitis was found to be very high in Spain: 71% of asthmatic patients seen in PCP centers reported to suffer from rhinitis, and these patients were younger and had milder asthma than asthmatics without rhinitis. The presence of rhinitis was even more frequent among atopic individuals that represented almost two-thirds of all the asthmatics included in the study. In addition, the severity of asthma and the severity of rhinitis were correlated, and comorbidity of asthma and rhinitis was associated to an increased number of asthma exacerbations in the previous month. These results reinforce even more the main message of the ARIA guidelines [1], which recommends the routine investigation of rhinitis in patients with asthma and viceversa.

Asthma and rhinitis are highly prevalent disorders that commonly coexist or precede one to each other [15], and rhinitis being regarded as a risk factor for the development of asthma [16]. Both disorders share the same pathophysiological mechanisms mainly characterized by the presence of chronic inflammation of the respiratory mucosa, with participation of a similar network of inflammatory cells and mediators [17]. Nasal provocation, as well as segmental bronchial provocation in non-asthmatic seasonal rhinitis patients induces eosinophilic inflammation in both bronchial and nasal mucosa, with the consequence of respiratory symptoms [18]. It therefore, makes sense that treatment of one respiratory tract segment may influence the other, and that rhinitis treatment may influence the course of asthma.

To our knowledge, this is the first study in Spain assessing the prevalence of rhinitis in asthmatic patients visited in the

Primary Care setting from a prospective perspective and, at the same time, analyzing the influence of rhinitis therapy upon lung function. In accordance to other European studies [19-21], the prevalence of rhinitis among asthmatic patients is very high in Spain. Other recent Spanish studies that have investigated on the comorbidity of rhinitis and asthma either in Pulmonology [22] and Allergology [23] setting fully coincide with the prevalence of rhinitis comorbidity in asthma reported by PCP in the RINOASMAIR study, although the favorable influence of rhinitis therapy on lung function in the study performed in the Pulmonology setting was not observed in the present study. On the other hand, the lower prevalence of rhinitis among older asthmatic patients is in accordance with the remission of rhinitis with advancing age reported by a number of studies [24]. The association between atopy and rhinitis comorbidity clearly found in our study agrees with the findings from other studies, although a similar association among non-atopic asthmatics reported by other studies was not observed in the present study [20]. The higher age range of our serie could account for these differences between studies.

Although the new ARIA guidelines [1] stresses the need for integral management of the airways and for determining the presence of rhinitis in asthmatics on a routine basis, it appears that little attention is paid to rhinitis comorbidity among asthmatics and to its treatment and influence on asthma in the PCP setting in Spain. A number of studies have reported the worsening of asthma in patients with concomitant rhinitis. Some studies, including some small patient's series, have failed to detect the relationship between asthma exacerbation and rhinitis comorbidity [25], while other studies involving larger population-based samples [26,27] have reported a significant correlation between asthma and rhinitis comorbidity as well as an increase in the number of asthma exacerbations, emergency visits, hospital admissions, and use of health care resources. In that direction, our study found a significant correlation between concomitant rhinitis and asthma exacerbations in the previous month, although no influence was found of rhinitis treatment in the lung function.

A number of recent studies have reported this impact of rhinitis treatment on decreasing the risk for asthma exacerbations compared to untreated patients [10,11]. In contrast, a recent Cochrane systematic review [28] reported no significant improvement in asthma symptoms, lung function or bronchial hyper-responsiveness to methacholine among patients treated with nasal corticosteroids versus not treated patients. The scant sensitivity of the lung function tests in measuring airways inflammation could account for this finding. Further studies on the influence of rhinitis treatment upon asthma control, involving more sensitive techniques to assess airway inflammation such as induced sputum eosinophilia or exhaled nitric oxide, are needed in order to resolve this apparent contradiction in the recommendations of the ARIA guidelines.

Following the ARIA recommendations [1] whereby optimum rhinitis treatment can improve asthma, there is a clear need for combined treatment of the upper (rhinitis) and lower (asthma) airways. A number of studies have shown that the addition of montelukast to inhaled budesonide in asthmatic patients with concomitant allergic rhinitis (analysis of the COMPACT trial) causes a significantly greater efficacy in reducing bronchial obstruction than doubling the budesonide dose [28], or that montelukast used to treat patients with asthma and concomitant rhinitis (PRAACTICAL trial) improves asthma control and reduces the use of health care resources [30,31]. Therefore, it is essential to develop integral management strategies for rhinitis and asthma taking this new body of evidence into account, and causing a reduction in the cost of treatment of these patients, since inadequate rhinitis treatment in asthmatic patients may result in poorer asthma control, with more exacerbations and poorer lung function.

A potential weakness of the present study is the seasonal nature (February to September 2006) of the data collection from patients, since the absence of a full-year registry may have influenced documentation of asthma exacerbations. On the other hand, the existence of atopy has been only based on the presence of a positive skin prick-test to some pneumoallergen.

The high prevalence of rhinitis among asthmatic patients in Spain strengthens the fact that PCP should identify and treat rhinitis that is intimately linked to asthma. The results of our study clearly show a correlation between asthma severity and rhinitis severity, as well as an increased number of asthma exacerbations in patients with rhinitis compared to those without rhinitis. In conclusion, the RINOASMAIR study clearly supports the main message of the ARIA guidelines [1] regarding for an integral management, both diagnosis and treatment, of the upper and lower respiratory tract.

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