Occupational rhinitis affects occupational asthma severity

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Abstract: Background: The strong interactions between asthma and rhinitis, and the influence of rhinitis in the severity and/or control of asthma, have clearly been demonstrated. Nevertheless, no specific study has been conducted in the occupational setting. Objective: The aim of the study was to assess the severity of occupational asthma and rhinitis and evaluate whether rhinitis is a predictor for increased asthma severity. Methods: We retrospectively reviewed the clinical charts of 72 patients who received a diagnosis of allergic occupational asthma, with or without associated occupational rhinitis. Results: Our findings suggested that persistent asthma tended to be more common in subjects with associated occupational asthma and rhinitis, and occupational asthma severity was associated with occupational rhinitis severity. Moderate-severe persistent occupational rhinitis is a risk factor for persistent occupational asthma. Conclusions: We demonstrated, for the first time in the occupational setting, a significant association between occupational rhinitis and asthma severity.

Key words: Asthma severity, Occupational asthma, Occupational exposure, Occupational rhinitis, Rhinitis severity, United airway disease

Introduction

It is well established that allergic rhinitis and asthma frequently coexist in the same subject¹, and the united airway disease model has been proposed to describe a unique disease with manifestations in different sites of the respiratory system². In addition, large studies have suggested a link between the severity and/or control of asthma and rhinitis in children and adults, particularly an increased severity of asthma in patients with associated rhinitis⁴. In the occupational setting, it has been demonstrated that a majority of the patients diagnosed with occupational asthma (OA) also suffer from occupational rhinitis (OR), particularly when high molecular weight (HMW) agents are involved⁵ and that strong interactions exist between allergic OA and OR⁶. Nevertheless, to the best of our knowledge, no specific investigation on the relationships between allergic OA and OR severity has been performed. The aim of our study was to retrospectively assess the relationships between allergic OR and OA severity and to evaluate whether OR is a predictor for increased OA severity.

Subjects and Methods

We retrospectively reviewed the clinical charts of 72 patients consecutively referred to our clinics for suspected work-related respiratory allergy, who received a diagnosis of allergic OA with or without associated allergic OR in the years 2000-2008. All patients were still exposed to the suspected causative agents when investigated. Fifty-five patients were diagnosed in Italy (Fondazione Salvatore Maugeri, Pavia), and 17 were diagnosed in Spain (Hospital La Paz Institute for Health Research, Madrid). This study conformed to the declaration of Helsinki and was approved by the Internal Review Board of the two Institutes.

All patients underwent skin prick tests (SPTs) and serum specific IgE assessment for common allergens and, when available, for occupational allergens⁵,⁶. Lung function and methacholine inhalation tests were performed as previously described⁷. Patients underwent the recom-
mended diagnostic pathway for OA and OR, including the specific inhalation challenge (SIC) with HMW or low molecular weight (LMW) agents. Each patient signed a consent form for SIC approved by the Ethical Committee of both institutes. SICs were performed using a nebulizer or in inhalation chambers depending on the suspected agent. Rhinitis and asthma severity were established at time of the initial evaluation according to ARIA and GINA Guidelines. OA and OR were diagnosed on the basis of a suggestive clinical history and a positive bronchial and nasal response to SIC, respectively.

Data were analyzed using the Statistical Analysis System (SAS) package for PC (Version 9.3, SAS Institute, Cary, NC, USA). Values for continuous variables are expressed as mean and standard deviation. Differences in continuous variables were tested by the two-tailed t test or non-parametric test (Wilcoxon’s signed-rank test) when appropriate. Differences in proportions were tested by the χ² or the Fisher exact test, when appropriate. The likelihood ratio procedure described by Colombi and Forcina was applied to test the direction of association between asthma and rhinitis. This procedure tests for independence against either positive or unrestricted association; significance levels can be tuned to reduce the risk of concluding that association is positive when the true association is in both directions. Differences were considered significant at p<0.05. Logistic regression models were used to analyze the effect of agents (HMW/LMW), atopy, smoking status, sex, country, age ≥33 years, bronchial reactivity (PD₂₀FEV₁ <740 mcg), severity of occupational rhinitis, and duration of symptoms before the diagnosis of OA (time elapsed between the beginning of asthma symptoms and diagnosis of OA ≥24 months) (predictors) on asthma severity (intermittent and mild persistent vs. moderate-severe persistent or intermittent vs. mild-moderate-severe persistent) (dependent variables). Continuous variables were transformed into categorical variables using distribution above or below the median. The results are given in terms of odds ratio with 95% confidence intervals (CI).

**Results**

Fifty-five subjects (76%) were from Italy, and 17 (24%) were from Spain. Twenty-five (35%) subjects had been diagnosed with OA-only, 7 because of HMW and 18 because of LMW agents. Forty-seven (65%) subjects had been diagnosed with associated occupational asthma and rhinitis (OAR), due to HMW agents in 24 and LMW agents in 23 subjects. The causal agent was more frequently a HMW agent in subjects with OAR (p=0.06), particularly in Italian subjects (p=0.005). Spanish subjects were older and a greater proportion was male compared with Italian workers (p<0.005). No significant differences were found between OA-only and OAR subjects in age, sex, smoking habits, personnel, or family history of atopy. Duration of exposure and symptoms before diagnosis of OA and OR, basal FEV₁, and bronchial hyperreactivity (PD₂₀FEV₁ to methacholine) did not differ between the OA-only and OAR groups (Table 1). The time elapsed between the beginning of asthma symptoms and diagnosis tended to be shorter in subjects with OAR than in those with OA only. No differences were found in mean FEV₁ before and after SICs. Asthma severity (intermittent/mild persistent/moderate-severe persistent) was associated with OAR (p=0.03 by χ² test). The Colombi and Forcina procedure indicates that independence may be rejected in the direction of positive association when using a choice of significance levels, which is moderately conservative against positive association. However, because the evidence in the direction of positive association is not terribly strong, an extremely conservative version of the same procedure would lead to rejection of positive association. Persistent asthma tended to be more common in subjects with OAR (p=0.07). Patients with moderate-severe persistent OR more frequently had moderate-severe persistent asthma compared with those without rhinitis or with intermittent or mild persistent OR (64% vs. 38%, p<0.005) (Table 2). Nocturnal respiratory symptoms were more frequent in subjects with moderate-severe persistent OR than in those with intermittent OR and in those with OA only (72% vs. 27% and 32% respectively, p<0.01). Post-SIC FEV₁% falls were greater in Italian than in Spanish subjects (p<0.05). Moderate-severe persistent OR was a predictor for persistent OA (odds ratio 19.0, 95%, CI 3.5-102.3). PD₂₀FEV₁ <740 μg, LMW agents, moderate-severe OR, age ≥33, a lapse between onset and diagnosis of OA of >24 months, and current smoking were associated with moderate-severe persistent OA (Table 3). After adjusting for sex, smoking habits, age, atopy, and country, moderate-severe persistent OR was associated with the presence of nocturnal respiratory symptoms (odds ratio 9.3, 95%, CI 2.5-34.6).

**Discussion**

Rhinitis is common in adult subjects with asthma and impairs asthma control and severity as well as asthma-related quality of life. Our retrospective study also showed an association between the severity of rhinitis and asthma in the occupational setting, although this association was statistically weak (Table 2 and 3). This may be due to the small number of subjects (25 with OA vs. 47 with OAR) or due to a possible different effect of occupational agent vs. non-occupational agents. As previously reported, most subjects showed the coexistence of asthma and rhinitis (OAR group). In the latter, persistent asthma tended to be more common than in subjects with OA, and moderate-severe persistent OR was associated with persistent OA and nocturnal respiratory symptoms. The shorter time interval between the beginning of
asthma symptoms and diagnosis in subjects with OAR suggested that the coexistence of rhinitis induces the patients to refer to a physician earlier than subjects with bronchial impairment only, possibly because of the impact of the two concomitant diseases on the quality of life.

Taken together, all these findings show, for the first time in the occupational setting, that the severity of rhinitis affects the severity of occupational asthma. These data should be considered as a further recommendation to pay more attention to rhinitis symptoms in subjects exposed to work-related allergens. Because OR is considered an early marker of an occupational respiratory allergy\(^5\), early detection of nasal symptoms may represent a unique op-

**Table 1.** Characteristics of the 72 subjects with occupational asthma and rhinitis

| Subjects | OA (n=25) | OAR (n=47) | OA+OAR (n=72) | P value* |
|----------|-----------|------------|---------------|----------|
| Age, years (mean ± SD) | 34.6±12.2 | 34.4±12.0 | 34.5±12.0 | NS |
| Sex (male/female) | 12/13 | 28/19 | 40/32 | NS |
| Smoking (yes/no/ex) | 7/14/4 | 14/21/12 | 21/35/16 | NS |
| Smoking, pack-years (mean ± SD) | 5.8±7.8 | 11.2±11.1 | 9.7±10.4 | NS |
| Atopy, n (%) | 15 (60) | 27 (57) | 42 (58) | NS |
| Nocturnal symptoms, n (%) | 8 (33) | 24 (51) | 32 (45) | NS |
| Asthma severity (intermittent/mild persistent/moderate-severe persistent) | 9/16 | 8/39 | 17/21/34 | 0.03 |
| Asthma severity (intermittent vs persistent) | 9/16 | 8/39 | 17/21/34 | 0.07 |
| Rhinitis severity (intermittent/mild persistent/moderate-severe persistent) | 12/13 | 26/21 | 38/34 | NS |
| Country (It/Es) | 20/5 | 35/12 | 55/17 | NS |
| Latency OA, months (mean ± SD) | 101±106 | 103±141 | 102±129 | NS |
| Latency OR, months (mean ± SD) | - | 97±133 | - | - |
| Basal FEV\(_1\), % predicted (mean ± SD) | 102±16 | 100±13 | 100±14 | NS |
| Basal PD\(_{20}\)FEV\(_1\), μg (mean ± SD) | 1309±1387 | 1474±1362 | 1417±1363 | NS |
| Post-SIC FEV\(_1\), % predicted fall (mean ± SD) | 29±8 | 26±6 | 27±7 | NS |

OA, occupational asthma; OAR, occupational asthma associated with occupational rhinitis; HMW, high molecular weight (flours, alpha-amylase, Lepidoglyphus, latex, mushrooms, laboratory animals); LMW, low molecular weight (methacrylate, isocyanates, wood, persulphate salts, aldehydes, potassium bicarbonate, benzalkonium chloride, sodium bisulfate, cyanocrylate); It, Italy; Sp, Spain; PD\(_{20}\)FEV\(_1\), Methacholine provocative dose causing 20% fall in FEV\(_1\); SIC, specific inhalation challenge. *P value: OA vs OAR; NS, not significant.

**Table 2.** Distribution of severity of occupational asthma and rhinitis

| Occupational rhinitis\(^a\) | Absence, intermittent or mild persistent, n (%) | Moderate-severe persistent, n (%) |
|-----------------------------|-----------------------------------------------|----------------------------------|
| n=47 | n=25 |
| Occupational asthma\(^b\) | Interrupted | 15 (32) | 2 (8) |
| Mild persistent | 14 (30) | 7 (28) |
| Moderate-severe persistent\(^c\) | 18 (38) | 16 (64) |

\(^a\) Severity of occupational rhinitis assessed by ARIA guidelines

\(^b\) Severity of occupational asthma assessed by GINA guidelines

\(^c\) Chi-Square=6.25; p value<0.005
Predictors of moderate-severe persistent occupational asthma, after adjusting for sex, smoking status, atopy and country

| Predictors                                      | Odds ratio | 95% CI      |
|-------------------------------------------------|------------|-------------|
| Moderate/severe OR                              | 4.1        | 1.1-15.3    |
| PD_{20}FEV<sub>1</sub> ≤740 μg                  | 7.7        | 1.2-30.0    |
| LMW agent                                      | 6.4        | 1.5-27.6    |
| Age ≥33                                         | 8.5        | 1.8-39.1    |
| Lapse onset-diagnosis OA ≥ 24 months            | 4.0        | 1.1-15.1    |
| Current smoker                                  | 10.2       | 2.0-51.7    |

CI, confidence interval; PD_{20}FEV<sub>1</sub>, methacholine provocative dose causing 20% fall in FEV<sub>1</sub>; LMW, low molecular weight; OR, occupational rhinitis; OA, occupational asthma.

opportunity to prevent OA. Moreover, the identification of nasal symptoms may allow a better management of patients with concomitant OA.

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