The Heterogeneity Hidden in Allergic Rhinitis and Its Impact on Co-Existing Asthma in Adults: A Population-Based Survey

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Key Words
Allergic rhinitis · Sinusitis · Polyposis · Asthma

Abstract
Background: It has been suggested that there is some overlap between allergic rhinitis (AR), sinusitis and polyposis, but this has not been fully documented. The present study aimed to evaluate the prevalence of these co-existing diseases and their impact on bronchial asthma in the general population of Italy.

Methods: Within the frame of the multicentre Gene Environment Interactions in Respiratory Diseases (GEIRD) study, a postal screening questionnaire including questions about self-reported symptoms of asthma, AR, AR with sinusitis without nasal polyps (AR + SsNP) and AR with sinusitis with nasal polyps (AR + SwNP) was administered. Random samples of subjects aged between 20 and 44 years (n = 5,162) answered the postal questionnaire in 4 Italian centres (Pavia, Sassari, Turin, Verona). In AR subjects, the association among AR only, AR + SsNP, AR + SwNP and bronchial asthma was estimated by the relative risk ratio (RRR) using multinomial regression models.

Results: The prevalence of AR in the sample was 25.4% (95% CI 24.2–26.6). A self-reported diagnosis of AR + SsNP and AR + SwNP was reported by 5.7% (95% CI 5.0–6.3) and by 1.2% (95% CI 0.9–1.5) of the subjects, respectively. Current asthma was reported by 17.5% of the AR subjects. In the adjusted multivariate analysis, the risk of having current asthma (RRR = 2.31, 95% CI 1.29–4.15), of having at least 1 asthma attack per year (RRR = 2.30, 95% CI 1.19–4.46) and of having had an emergency department admission for respiratory diseases (RRR = 5.61, 95% CI 1.81–23.92) was higher for subjects with AR + SwNP than subjects with AR only.

Conclusions: The diagnosis of AR in the epidemiological setting includes heterogeneous upper airway diseases that affect the clinical features of AR and its interactions with asthma.
Introduction

Allergic rhinitis (AR) is the most common immunological disease and its prevalence is continuously increasing, in particular in Western countries [1–3]. This not only affects the burden of the disease on patients [1–5], but also has an impact on bronchial asthma and subsequently leads to increased health care costs [1, 6].

In epidemiology, validated questionnaires are used for the diagnosis of AR. An Italian study showed that the reliability of the question regarding AR seems adequate for epidemiological purposes, but about 20% of the subjects who responded positively to this question had a negative skin prick test or specific IgE levels [7]. Studies focusing on the non-allergic upper airway diseases (such as chronic rhinitis and rhinosinusitis, with and without nasal polyps, NP) showed the importance of the association between these diseases and severe/not controlled asthma, suggesting that these upper airway diseases have a greater impact on asthma than allergy [8–12].

The overlap between allergic and non-allergic upper airways diseases has been discussed in clinical studies, but its epidemiological results remain controversial and poorly defined [13–15]. This study aimed to evaluate the prevalence of AR, AR with sinusitis without NP (AR + SsNP) and AR with sinusitis with NP (AR + SwNP), and investigate whether the interaction between AR and bronchial asthma is affected by concomitant upper airway diseases.

Materials and Methods

The Gene Environment Interactions in Respiratory Diseases (GEIRD; see Appendix) study was a multicentre survey on respiratory health in the general adult population, carried out between 2007 and 2010. In the frame of this study, random samples of about 3,000 subjects from the general population aged 20–44 years (male:female ratio = 1:1) were selected from the registry of the local health authority in each of the four Italian centres of Pavia, Sassari, Turin and Verona [16].

A screening questionnaire on respiratory symptoms was administered to eligible subjects by mail, sent up to three times in cases of non-response, and once by phone for subjects who did not respond by mail. The GEIRD screening questionnaire (available at www.geird.org) is a modified version of questionnaires used in previous studies [17]. It includes self-reported information about respiratory symptoms (asthma, rhinitis and chronic bronchitis, cough and phlegm), environmental exposures (smoking habits) and education level as a proxy of socio-economic status.

Definitions and Conditions

The presence of AR was based on the answer to the question: ‘Do you have any nasal allergies including hay fever?’ Subjects who answered ‘yes’ were classified as subjects with AR and those who answered ‘no’ were classified as a subject without AR. AR subjects were further classified as follows:
- AR only: subjects with AR but without sinusitis or NP;
- AR + SsNP: subjects with AR and who also answered ‘yes’ to the question: ‘Do you suffer from sinusitis?’;
- AR + SwNP: subjects with AR and sinusitis and who also answered ‘yes’ to the question: ‘Do you suffer from nasal polyps?’. The presence of asthma was defined as:
- physician-diagnosed asthma if the subject answered ‘yes’ to both of the following questions: ‘Have you ever had asthma?’ and ‘Was this confirmed by a doctor?’;
- current asthma if the subject had physician-diagnosed asthma and took any medicine for asthma and had had an attack of asthma or experienced at least one among the following asthma-like symptoms: wheezing, chest tightness or shortness of breath in the last 12 months.

We used the following as indicators of asthma severity/control:
- the number of asthma attacks reported by the subject in the last 12 months, classified as: ‘at least 1 asthma attack’ and ‘>3 asthma attacks’;
- the presence of the asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, when a subject with current asthma answered ‘yes’ to the following question: ‘Have you ever been told by a doctor that you have or had chronic bronchitis, COPD or emphysema?’;
- the intake of drugs for rhinitis and asthma based on the answers to the following questions: ‘Have you used any medicine for asthma in the last 12 months (including inhalers, aerosols or tablets)?’ and ‘Have you used any medicine for rhinitis in the last 12 months (including inhalers, aerosols or tablets)?’ A four-level variable was computed to evaluate which type of drugs a subject used: ‘no medicine’ if a subject answered ‘no’ to both questions; ‘only asthma medicine’ if a subjects took medicine for asthma and had not taken medicine for rhinitis in the last 12 months; ‘only rhinitis medicine’ if a subjects took medicine for rhinitis and had not taken medicine for asthma in the last 12 months, and ‘both’ if a subject had taken medicine for both rhinitis and for asthma in the last 12 months.

The presence of chronic cough and phlegm was assessed by a positive answer to the question: ‘Have you had coughing and phlegm on most days for a minimum of 3 months a year and for at least 2 successive years?’ Also, a subject was recorded as having been to an Emergency Department (ED) for respiratory diseases if he/she answered ‘yes’ to both of the following questions: ‘In the past 3 months have you been to an Emergency Department for any reason, excluding accidents and injuries?’ and ‘Was it due to respiratory problems?’

Confounders

The potential confounders considered in the analysis were: gender, age (<30, 30–39, ≥40 years), smoking habits (never smoker, ex-smoker, current smoker), level of education (primary and lower secondary school, upper secondary school, degree) and the season of response (spring, summer, autumn, winter). In addition, the type of contact (mail, phone), percentile rank of cumulative response and centre were included as design confounders in the analysis.
Statistical Analysis
Categorical variables were summarised with percentages and were compared across strata by Pearson’s χ² test.

The associations among different AR overlapping diseases (AR only, AR + SnNP, AR + SwNP) and other outcomes (diagnosed and current asthma, number of asthma attacks, asthma-COPD overlap syndrome, cough and phlegm, and ED visits for respiratory diseases), were assessed using multinomial regression models adjusted for potential confounders (gender, age, smoking habits, level of education, season of response, type of contact, percentile rank of cumulative response and centre). The relative risk ratio (RRR) was estimated by choosing the AR-only group as the reference category. A p value <0.05 was considered statistically significant. Statistical analyses were performed with STATA 12.1 (Stata Corp LP, College Station, Tex., USA).

Results

Prevalence of AR and Demographic Data
Overall, 5,162 subjects completed the questionnaire in the 4 centres. The response rate was 53%, ranging from 37.1% (Pavia) to 67.7% (Verona). The overall prevalence of AR in the study was 25.4% (95% CI 24.2–26.6). The rates of self-reported diagnosis of AR + SnNP and AR + SwNP were 5.7 and 1.2%, respectively (table 1).

The subjects with AR were younger (table 2), fewer were current smokers and they had a higher level of education than those without AR. The distribution of sex and...
education level among the three different groups of upper airway diseases (AR only, AR + SsNP and AR + SwNP) was statistically significant. The percentage of females was lower in subjects with AR + SwNP (36.1%) compared to the other two groups (51.8 and 63.5% for AR and AR + SsNP, respectively). The education level was significantly lower for subjects with AR + SwNP than for those of the other two groups (p = 0.019).

Overlapping Upper Airway Diseases and Asthma

Overall, 23.8% of the subjects with AR had physician-diagnosed asthma and 17.5% of the subjects reported current asthma at the time of the survey (table 3). The prevalence of current asthma and the distribution of the control/severity markers of co-existing asthma varied significantly across the three different groups of AR subjects. In particular, the prevalence of current asthma increased from 15.8% in the AR-only group to 31.2% in the group AR + SwNP (p < 0.001). The same statistically significant trend was found when considering the proportion of subjects who had at least one asthma attack in the last 12 months (p = 0.01), of subjects with the asthma-COPD overlap syndrome (p = 0.03), of subjects with chronic cough and phlegm (p < 0.001), and of those who had been hospitalised for respiratory diseases (p < 0.01). The only exception to this general trend was the prevalence for subjects who had had more than three asthma attacks per year, which was similar in the three groups of upper airway diseases (p = 0.76).

In the multivariate analysis (table 4), after adjusting for potential confounders, the subjects with AR + SwNP had a statistically significant increased risk of having current asthma (RRR = 2.31, 95% CI 1.29–4.15), of having had at least one asthma attack in the last year (RRR = 2.30, 95% CI 1.19–4.46).
CI 1.19–4.46) and of having had an ED admission for respiratory disease in the last 3 months (RRR = 5.61, 95% CI 1.81–23.92) than subjects with AR only.

Finally, the subjects with AR + SsNP and AR + SwNP had a statistically significant increased risk of having cough and phlegm (RRR = 2.59, 95% CI 1.89–3.54, and RRR = 2.91, 95% CI 1.63–5.21, respectively) than subjects with AR only, while the asthma-chronic bronchitis overlap syndrome did not show statistically significant variations among the AR groups.

Overlapping Upper Airway Diseases and Drug Intake for Rhinitis and Asthma

Overall, 54 and 17.5% of subjects with AR had used medication for rhinitis and asthma, respectively, in the last year. After adjusting for potential confounders, in the multivariate analysis we found an increased risk that the subjects with AR + SsNP and AR + SwNP took medications both for rhinitis (RRR = 1.91, 95% CI 1.43–2.54, and RRR = 2.46, 95% CI 1.38–4.40, respectively) and for asthma (RRR = 1.52, 95% CI 1.08–2.15, and RRR = 2.27, 95% CI 1.23–4.19, respectively) than subjects with AR only.

The overall distribution of drug intake for rhinitis and/or asthma across the three different groups of AR subjects is shown in the figure 1. The proportion of subjects who had not used medication in the last 12 months decreased from 46% in subjects with AR only to 28% in those with AR + SwNP, whereas the use of medication for both rhinitis and asthma increased from 11% in AR-only subjects to 28% in subjects with AR + SwNP (p < 0.001).

When we considered the distribution of drugs used only by subjects with current asthma stratified by no asthma attacks and by at least one asthma attack, we found that the proportion who used drugs for rhinitis or for rhinitis was almost 65% in those who had not had an asthma attack and almost 95% in those who had had at least one asthma attack. The distribution of drugs used among the three groups of upper airway diseases was similar both for subjects with no asthma attack and at least one asthma attack (fig. 2).

Discussion

The most important finding of the study was that AR co-existed with sinusitis, with and without NP, in 6.9% of the general population. In particular, the coexistence of rhinosinusitis with and without polyps was reported by 4.7 and 22.5%, respectively, of young adults with AR. In addition, subjects with AR + SwNP had a higher likelihood of having more severe asthma than those with AR only. We will also discuss the reliability of a self-reported diagnosis of sinusitis and the identification of subjects with NP as a subgroup of those with AR.

Prevalence of the Upper Airway Diseases

Overall, about 25% of the subjects reported AR; about 6% reported AR plus sinusitis with and without NP, and the prevalence of these was similar across the centres. Concerns about the self-reported diagnosis of chronic rhinosinusitis [18, 19] have led to the development of a specific questionnaire to diagnose chronic rhinosinusitis in the epidemiological setting [20].

A recent postal survey performed in Europe, using the EP3OS criteria questionnaire, found that the prevalence of chronic rhinosinusitis in the general population was 10.9%, with relevant variations of prevalence in the different geographical areas. In the only Italian centre participating in that survey (Palermo), the prevalence was 10.8% (6.9% self-reported doctor diagnosis) [21].

In the EP3OS study, the diagnosis of chronic rhinosinusitis includes patients with and without NP, while the diagnosis of chronic rhinosinusitis is limited only to the young adult subjects with AR in our survey. Although the diagnosis of sinusitis was only assessed in subjects with AR and consisted of a single question in the question-
naire, we might suppose that the prevalence found in our survey is consistent with that found in Italy. The prevalence of AR + SwNP found in our survey is in line with the estimated prevalence found both in Europe, which ranged from 2 to 4% of the general population [22], and that found in a specific survey in France (2.1%) [23]. However, other studies [24] found a higher prevalence of polyposis than our survey, which could be due to the fact that it was not in a population-based study. Overall, the reliability of the self-reported diagnosis of chronic rhinosinusitis and of AR + SwNP in our survey seems to be acceptable.

Impact of AR on Asthma

The increase in drug intake for rhinitis suggests an increase in severity from AR to AR + SwNP [25]. Moreover, the association between the severity of the upper airway diseases and the impact on asthma in the non-adjusted analysis seems to confirm the United Airways Diseases hypothesis [1, 26]. After adjusting for potential confounders, the results show the presence of two different subsets of subjects within the AR group. The first includes subjects with AR and sinusitis, and the second those with polyposis.

In the first group, the increase in the proportion of subjects who took medication for rhinitis and asthma suggests an increase in the severity of the upper airway diseases, which does not correspond to an increase in the indicators of asthma severity (at least one asthma attack) and the ED visits for respiratory diseases. Despite the increase in drug intake in the group of subjects with polyposis, it is evident that there is poor asthma control in this case.

We hypothesise that the positive responses to the question on the presence of NP enables the identification of two different asthma phenotypes in the AR subjects: the first, ‘early-onset allergic asthma phenotype’, mainly determined by allergen-specific adaptive Th2 cells, is generally steroid sensitive [27], the second, ‘late-onset eosinophilic asthma phenotype’, is driven by allergen-independent innate lymphoid cells, with the responsiveness characterised by being refractory to steroids [28]. Although these two pathogenic mechanisms are not mutually exclusive, as confirmed by the detection of allergic sensitisation in patients with nasal polyposis [23], the role of the main pathogenic mechanism seems to be clear [29]. When the severity of the upper airway diseases increased, a similar prevalence of the most unstable subset of asthmatic subjects (about 3% of them) was unexpected. This may be due to poor adherence to the asthma therapy, which is very common in patients with AR only and mild asthma [30]. Furthermore, this seems to be consistent with recent studies on the presence of mast cells at the alveolar level in subjects with AR and uncontrolled asthma [31–33].
Strengths and Limitations
The strength of this study is that we found the heterogeneity hidden in the diagnosis of AR obtained from the questionnaire. This is in contrast to the simple model used to compare AR and asthma (i.e. subjects with NP within those with AR), and our finding suggests that their interaction should be considered with more caution.

The main limitation of our survey is that we could not determine the allergic pathogenesis of the upper airway diseases without cutaneous, serological [34] or any other clinical tests, which also influence the reliability of the self-reported diagnosis of upper airways comorbidities, such as the diagnosis of chronic rhinosinusitis with and without polyps. Another important limitation is the lack of any information about the type, duration and the adherence to therapy for rhinitis and asthma. The only information available for this was whether a subject had or had not used medication for rhinitis and/or asthma in the last 12 months.

Appendix
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