ORIGINAL CONTRIBUTION

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Asthma is more frequently associated with non-allergic than allergic rhinitis in Portuguese patients*

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SUMMARY

Background: *Rhinitis prevalence is increasing worldwide and is frequently associated with asthma, for which it is a risk factor. The aims of the study were to characterise the adult population with rhinitis attending the Cova da Beira Hospital Allergy Clinic, and to assess the relationship between rhinitis and asthma.*

Methods: *In total, 686 patients were characterised by clinical history and anterior rhinoscopy, and classified according to international guidelines. Atopy was determined by skin prick testing to aeroallergens and quantification of specific IgE.*

Results: *Seventy two percent of patients had allergic rhinitis (AR), and 28% had non-allergic rhinitis (NAR). NAR was more frequently associated with older age, perennial symptoms and female gender. NAR patients more frequently had bronchial asthma. In addition, more NAR than AR patients also had drug allergy, pharyngitis, sinusitis and urticaria. AR patients with nasal polyps more frequently had asthma. Grass pollen and mites were the major sensitisers for AR patients. Sensitisation profiles were not significantly different between urban- and rural-based AR patients.*

Conclusions: *Asthma was more frequently associated with non-allergic than with allergic rhinitis. The two types of rhinitis did not differ in clinical severity. Although sensitisation profiles were not different between the urban and rural patients, allergic rhinitis prevalence was higher in urban patients.*

Key words: allergens, rhinitis, human, prevalence

INTRODUCTION

Rhinitis is a symptomatic disorder of the nose characterized by nasal blockage/congestion, rhinorrhea, itching and sneezing. Underdiagnosis is frequent as the disease is often trivialized, despite important impairment in the quality of life, increased medical costs and decreased school and work productivity.

The majority of rhinitis cases generally start in childhood or adolescence in individuals responding to common aeroallergens and are mediated by immunoglobulin E (IgE) (allergic rhinitis or AR) [(1)]. AR is diagnosed by history and examination backed up by specific allergy tests [(2)].

Other patients develop non allergic forms of rhinitis, such as idiopathic rhinitis, hormonal rhinitis, food induced rhinitis, or drug induced rhinitis (non-allergic rhinitis or NAR) (3). NAR includes a number of heterogeneous nasal conditions, in their majority poorly defined in terms of their underlying mechanisms, and with multifactorial aetiology [(4)]. Unlike AR, there are no specific diagnostic tests for NAR. The diagnosis is primarily made by excluding allergy related features and infectious causes, as well as by assessing history of reactions to specific irritant/toxic triggers. In addition, the presence of nasal and blood eosinophilia as well as hormonal status (mainly estrogens) should be analysed. Furthermore, NAR can also contribute to rhinitis symptoms in atopic patients, creating a "mixed" phenotype [(3)].

Based on the time of exposure to allergens, allergic rhinitis has been classified as seasonal allergic rhinitis (SAR), also known as hay fever, and perennial allergic rhinitis. SAR was associated with outdoor allergens, such as pollens, and perennial rhinitis was associated with indoor allergens, such as dust mites, moulds, and animal dander. As this classification was regarded as insufficient, the revised classification adopted by Allergic Rhinitis and its Impact on Asthma (ARIA) divides rhinitis according to frequency and duration of symptoms into "intermittent" and "persistent", and according to severity (based on symptoms and quality of life) into "mild" or "moderate/severe" [(4)].

The prevalence of rhinitis is increasing woldwide [(5)], and the estimated prevalence in Portuguese adults aged between 20

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and 44 years is 17%, as reported by the European Community Respiratory Health Survey (ECRHS) [6]. However, studies describing other features of Portuguese rhinitis patients are scarce in the literature.

In order to increase the current knowledge about rhinitis patients in Portugal we aimed at characterising the adult rhinitic population attending the Allergy Clinic of the Cova da Beira Hospital between the years of 2003 and 2007, as well as assessing the relationship between rhinitis and asthma.

MATERIALS AND METHODS

Patients

A mixed sample of rhinitis patients (78% AR and 22% NAR) referred by General Practitioners and ENT surgeons to the Allergy Outpatient Clinic of the Cova da Beira Hospital between 2003 and 2007 for presumed allergic rhinitis were sequentially studied.

Diagnosis and examination

The diagnosis of rhinitis was based upon clinical history, physical examination with anterior rhinoscopy, and response to medication. Skin prick testing to aeroallergens and determination of total and specific IgE were also performed in rhinitis patients to determine the presence of atopy. Sensitisation profiles were analysed both by skin prick tests and specific IgE. Skin prick testing included a first panel containing the 35 most prevalent aeroallergens in the region. According to results from this initial battery, as well as from clinical history, a second panel with more specific aeroallergens was also tested. For presentation of results, among the other allergens, the grass family (Gramineae) was divided into "grass" (non-cultivated Gramineae) and "cereal" (cultivated Gramineae).

Assessment of severity and frequency of disease was based on the revised classification of allergic rhinitis adopted by ARIA, even for non-allergic rhinitis [4]. All patients were specifically assessed for concurrent asthma by filling in a questionnaire, clinical examination and lung function testing (for those patients with a positive questionnaire). In addition, patients were also examined to assess other existing co-morbidities.

The designation of "non-allergic" was applied when the history, skin prick testing, and serum specific IgE measurements included in the allergy examination were all negative.

County administrative centres with predominantly industrial or tertiary services were considered "urban". Remaining centres were regarded as "rural". The study protocol was approved by the Hospital Ethics Committee.

Statistical analysis

All data were analysed using non-parametric tests. Results are expressed as medians and range. Wilcoxon signed rank test was used for comparisons within groups and Mann Whitney U test (continuous variables), Chi-square test or Fisher's Exact Test (categorical variables) were used for comparison between groups. The association of various clinical parameters was analysed using the Spearman rank correlation test. A p value of less than 0.05 was considered significant. All analyses were performed using Minitab 14 for Windows.

RESULTS

The total population analysed included 1092 patients, which represents 86% of all the patients in our clinic. From those, we excluded all patients under 18 years of age, and patients without a permanent residence in the region. In addition, 32 patients were excluded because of discordance between clinical history, skin prick tests and specific IgE tests. Patients with hormonal, infectious or anatomic rhinitis were also excluded.

Six hundred and eighty six patients, all adult Caucasian, (473 females), living in the Cova da Beira area were included for further study.

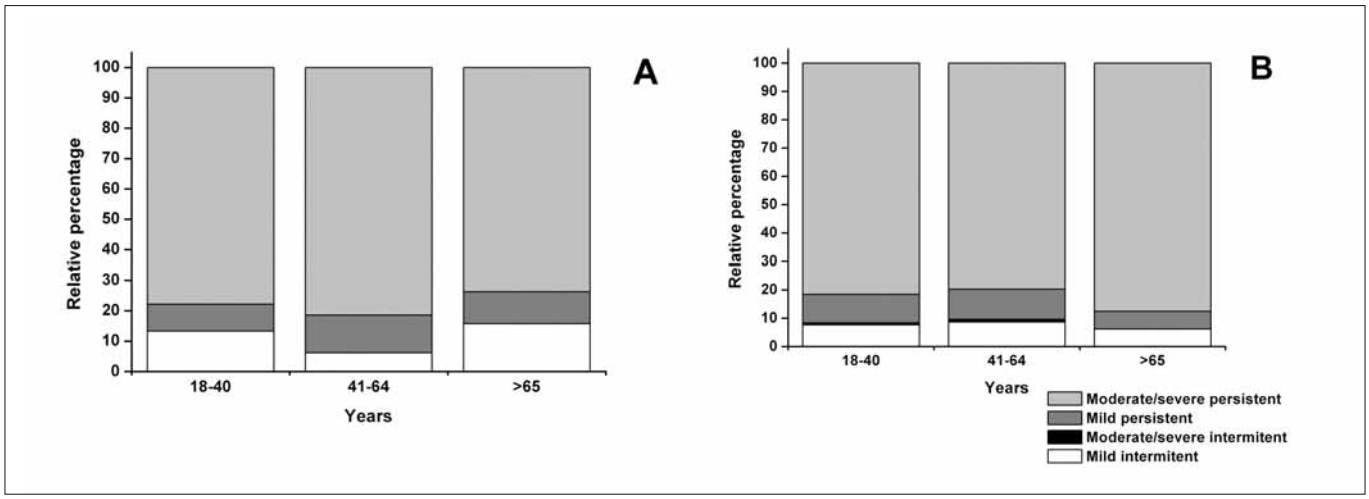

Figure 1. Profiles of disease severity in different age groups of non-allergic rhinitis (Panel A) and allergic rhinitis (Panel B) patients. Patients were grouped into three age groups and severity was assessed according to ARIA guidelines. Severity did not increase with age and was not statistically different between the two groups.

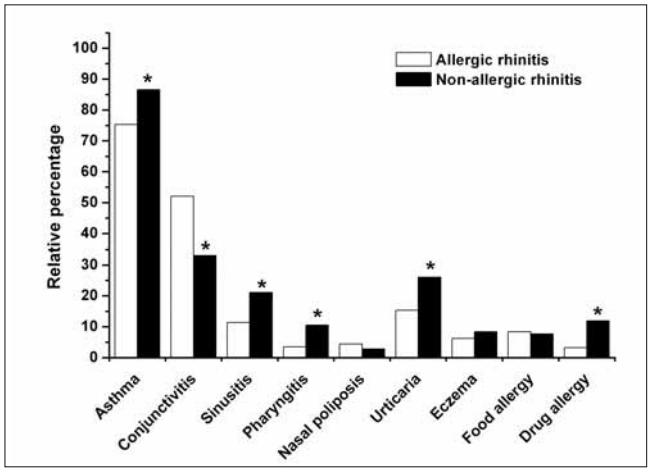

Figure 2. Main co-morbidities associated with rhinitis. Allergic rhinitis patients (light columns) had a higher prevalence of conjunctivitis, whereas non-allergic (dark columns) rhinitis patients had a higher prevalence of asthma, sinusitis, pharyngitis, urticaria, and drug allergy.

Seventy two percent (494) of the patients had a diagnosis of AR and twenty eight percent (192), had NAR. Demographically, there were significant differences between the two groups. There were more women among NAR than among AR patients, with female: male ratios of 3.6 and 1.9, respectively ($p = 0.001$). In addition, AR patients were significantly younger than NAR patients (median age 33 (18-102) vs. 47 (18-84) years, $p = 0.001$). Smoking habits (recorded as pack-years) were not different between AR and NAR patients.

Rhinitis was classified according to the old practice that divided it into seasonal and perennial. As expected, we observed that seasonal symptoms were more common in AR than in NAR patients (36.7% vs.15.5%, $\chi^2 = 22.354$, $p < 0.001$).

Patients were divided into three age groups; severity and duration of symptoms were classified according to the ARIA guidelines (4). Severity did not increase with ageing, either in AR or in NAR patients ($\chi^2 = 0.704$ for allergic and 2.844 for non-allergic, $p > 0.05$). Moreover, there were no differences in terms of severity between AR and NAR ($p > 0.05$) (Figure 1).

Rhinitis is frequently associated with bronchial involvement (even in NAR) and with other diseases. We studied clinical associations present in our population and observed that the great majority of them also had asthma. Although overall there were more allergic than non-allergic asthmatic patients, a significantly higher percentage of NAR than AR patients had concurrent asthma (87% vs 75%, respectively; $p < 0.001$; Chi-square Test). Severity of rhinitis did not correlate with that of asthma. In addition, a significantly higher percentage of NAR than AR patients had sinusitis, pharyngitis, urticaria and drug allergy. In contrast, a lower percentage of NAR than AR patients had conjunctivitis (Figure 2).

We used anterior rhinoscopy to detect and characterise nasal polyposis. No significant differences in terms of the percentage of patients with nasal polyps were observed between AR and NAR patients (4.4% (22 patients) vs 2.8% (5 patients); $p = 0.399$; Fisher's Exact Test). Nasal polyposis was not associated with more severe rhinitis in either RA ($p = 0.11$; Chi-square test) or NAR ($p = 1.0$; Fischer's Exact Test) patients. Curiously, in AR ($p = 0.05$; Chi-square test) but not in NAR ($p = 0.61$; Fischer's Exact Test) patients, there was a trend for significant association of nasal polyposis with the presence of bronchial asthma. Finally, in AR patients, nasal polyposis was not significantly associated with preferential sensitisation to seasonal or perennial allergens.

As expected, total serum IgE was significantly higher in allergic than in non-allergic patients (median 177 (3-5000 kU/L) vs. 26 (<2-865 kU/L), $p < 0.001$). There was no correlation between total IgE levels and features of allergic sensitisations (wheal size on skin prick tests or specific IgE levels).

In AR patients, the frequency of sensitisations evaluated by skin prick testing was 64.7% for grass pollen, 61.4% for mites, 59.2% for cereal pollen, 56.6% for weed pollen, 49.5% for tree pollen, 32.7% for cat dander, 29.4% for dog dander, and 23.5% for moulds and fungi. The frequency of sensitisation evaluated by specific IgE tests was slightly different, but directly correlated with that from skin prick tests: 60.3% for grass pollen, 55.33% for mites, 51.3% for cereal pollen, 55.0% for weed pollen, 45.6% for tree pollen, 13.3% for cat dander, 11.7% for dog dander, and 2.7% for moulds and fungi. The percentage of monosensitised AR patients, as assessed by skin prick testing, was 7.0%, with 4.0% of them monosensitised to mites, 0.9% to grass pollen, 0.5% to tree pollen, 1.2% to weed pollen, 0.2% to

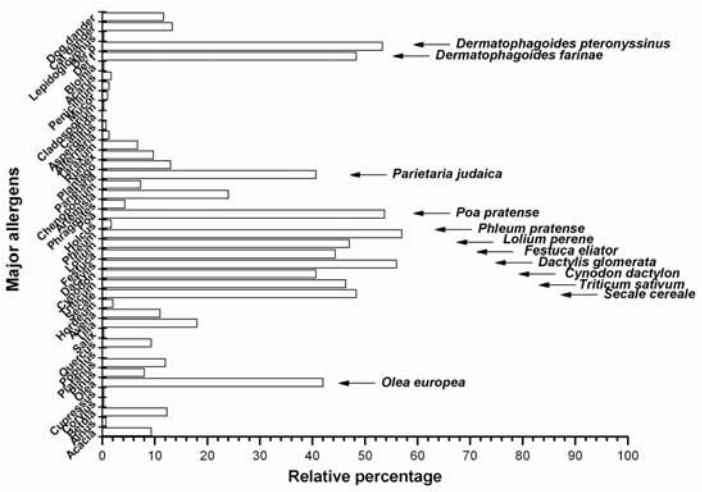

Figure 3. Major aeroallergens in allergic rhinitis. Allergen sensitisation was evaluated by skin prick test with a battery of the most common aeroallergens in the local flora, as well as mites, moulds and animal dander.

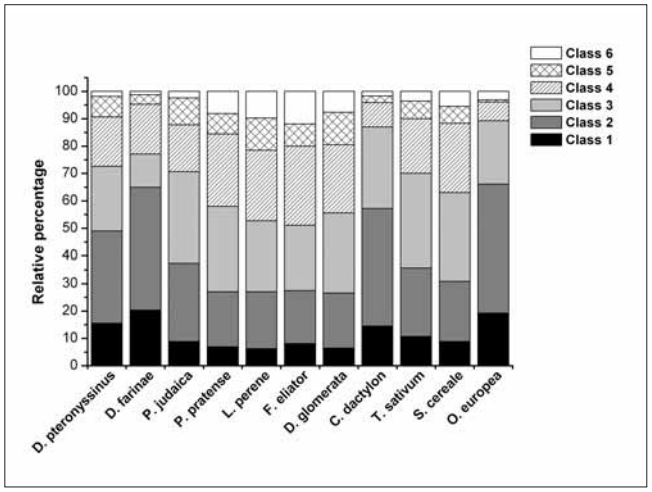

Figure 4. Degree of sensitisation to aeroallergens in allergic rhinitis patients. The degree of sensitisation, as analysed by specific IgE levels, was different between the major aeroallergens

cat dander and 0.2% to dog dander. There were no AR patients monosensitised to cereal pollen or moulds.

The major allergen sensitisers, as evaluated by skin prick testing and specific IgE, were mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grasses (*Phleum pratense, Dactylis glomerata, Lolium perenne, Festuca eliator, Poa pratensis* and *Cynodon dactylon*), cereals (*Secale cereale and Triticum sativum*), olive tree (*Olea europea*), and the weed *Parietaria judaica* (Figure 3).

In spite of similar prevalence of these major allergens, there were significant differences in terms of the class/level of sensitisation as measured by wheal size and specific IgE values ($\chi^2 = 161.692$, $p < 0.0001$, Figure 4), with higher sensitisation levels, (classes 5 and 6) more prevalent with grass pollens.

We then went on to compare several features between urban and rural AR patients. Our population included 226 urban and 268 rural AR patients. The samples were paired for age and gender.

The sensitisation profile was not significantly different between urban- and rural-based rhinitis patients, and the level of sensitisation was similar for all the allergens ($p > 0.05$).

Furthermore, there were no differences regarding severity of rhinitis between rural and urban allergic rhinitis patients and the same was valid for NAR patients.

However, AR prevalence as compared to NAR was higher in urban- than in rural-based patients (77.3 vs. 68.2; $p = 0.009$; Chi-square test).

DISCUSSION

Rhinitis is a major public-health problem that is increasing in prevalence in most developed countries [7]. Many people with rhinitis self-manage the condition with over-the-counter products, do not seek a physician's help, confuse it with recurrent infectious disease, or indeed do not recognize rhinitis as a condition needing treatment. This leads to subdiagnosis and impaired quality of life.

In the present study, we present data from a Portuguese patient population with rhinitis. As far as we know this is the first full characterisation of Portuguese rhinitic patients, involving not only epidemiological but also clinical aspects. We studied several aspects involving rhinitis in an allergy outpatient clinic. Our diagnosis of rhinitis was based upon subjective clinical symptoms as reported by the patients, but also on more objective aspects such as anterior rhinoscopy, allowing characterisation of turbinate swelling and rhinorrhea. Furthermore, the latter technique was also crucial for confirming the presence of nasal polyposis in our patients.

In the present study, twenty eight percent of our rhinitis patients were non-allergic. These NAR patients were older, predominantly female, and, very interestingly, had a higher prevalence of asthma than AR patients, In line with these findings, the ECRHS reported a frequency of 25% of NAR, a higher prevalence of rhinitis among women and a stronger association with asthma among NAR patients [8]. Overall, our patients had a high prevalence of bronchial asthma. This is in contrast with the known prevalence of asthma in patients with allergic rhinitis in the general population, which may average between 25% and 40% [4,7].

However, since we are a specialised clinic and not a general practitioner office, most patients referred to our outpatient clinic tend to have more severe and long-standing rhinitis, which increases the likelihood of having developed concurrent bronchial asthma.

In recent years, the key concept of "one airway, one disease" has emerged [4]. The majority of allergic asthma patients concomitantly have rhinitis, and some of the AR patients have asthma [4,7]. In the ECRHS, an association between asthma and rhinitis was observed (even in non-atopic individuals), and asthma attacks were reported more often where there were high prevalences of nasal allergies [6,9]. This association between rhinitis and asthma was not fully explained by shared risk factors, (including total IgE levels, parental history of asthma, or sensitization to allergens), or genetic predisposition to atopic diseases [8]. Moreover, rhinitis is a significant risk factor for the occurrence of asthma, independently of allergy [10]. In a study by Leynaert et al., asthma was strongly associated with rhinitis not only among atopic subjects (odds ratio (OR) = 3.1; 95% confidence interval 2.4 - 4.0), but also among non-atopic subjects (OR = 6.2; 95% confidence interval 4.3 - 8.8) [9]. In addition, having co-morbid allergic rhinitis is a marker for the presence of more difficult to control asthma and worsened asthma outcomes [11,12]. Concomitantly, there is considerable reduction in asthma morbidity in individuals with asthma and rhinitis, when the latter is properly treated [7].

Curiously, in our study, more NAR than AR patients had drug allergies, most of these were related to aspirin intolerance. Some NAR patients had concomitant asthma, aspirin intolerance and urticaria. Aspirin and other anti-inflammatory drugs can precipitate adverse reactions in bronchial asthma and urticaria. There is also a distinct clinical syndrome, "aspirin-induced asthma" or the aspirin triad, characterised by nasal polyposis, aspirin sensitivity and asthma [13].
Similarly, in our study, chronic pharyngitis and sinusitis were more frequent in NAR. This is most likely due to the fact that rhinitis tends to be more difficult to control in these patients and is often associated with more persistent post-nasal dripping that may contribute towards inflammation in the pharynx.

In a survey in a representative sample of the Belgian population, that evaluated both AR and NAR, the authors found a high prevalence of self-declared rhinitis, with AR being about three times more prevalent than NAR. In addition, AR patients suffered from a greater number of co-morbidities (asthma, skin allergy and food allergy), and displayed a more severe profile than NAR patients [14]. However, no clinical evaluation was carried out to confirm the diagnosis, and no data on IgE mediated allergy were known.
A similar study in Danish adolescents and adults showed that subjects with AR more often suffered from asthma, food allergy and conjunctivitis, whereas patients with NAR suffered more frequently from recurring headaches and sinusitis [15]. This study included clinical evaluation, spirometry and skin prick testing; however, as it is very clearly pointed out by the authors, only the 10 most common allergens were tested and no total or specific IgE was measured, leading to overlooked subjects with AR being included as NAR patients.

Nasal polyposis is a factor that can significantly decrease the quality of life of rhinitic patients and even worsen underlying bronchial asthma. It was curious to notice that, although a relatively high percentage of our patients had moderate/severe persistent rhinitis, the prevalence of nasal polyposis was low, both in AR and NAR patients. We believe that the prevalence we found is representative of the true values within this population since all patients were also specifically asked about nasal obstruction (visual analogue score) and were analysed using anterior rhinoscopy. However, since not all patients were co-jointly observed with the ENT Department, not all patients underwent nasal endoscopy or CT scan of the nose and nasal sinuses. We therefore have to accept that some patients with clinically silent nasal polyposis may have escaped our diagnosis.

Overall, no significant differences in terms of the percentage of patients with nasal polyps were observed between AR and NAR patients, in our study. This is not surprising since various reports in the literature, focusing on the relationship between allergy, rhinitis and nasal polyposis have shown discrepant results. In fact, although some authors have shown a higher prevalence of allergy in patients with nasal polyposis, varying between 54 and 64% [16,17], others have not shown any association at all [18-20]. Differences in the methodological approach as well as different genetic populations may account for these discrepancies.
In our study, nasal polyposis was not associated with more severe rhinitis in either RA or NAR patients. This was surprising since we expected the more relevant underlying inflammation in patients with more severe underlying rhinitis to be associated with a facilitated development of nasal polyps.

Importantly, there was a trend for AR (but not NAR) patients with nasal polyposis to have bronchial asthma ($p = 0.05$; Chi-square test). This important finding is in line with what has been described by others, in terms of general asthma. For instance, in a population-based study, Johansson et al, described that nasal polyps were more frequent in patients with bronchial asthma [21]. However, some authors have reported that non-allergic asthma is more frequently associated with nasal polyposis [22]. The discrepancy between these results and our own may be due to the low numbers of patients with nasal polyps who were not allergic in our patient population. Another possibility is that the differences may be due to the number of years with the disease, which was not similar in the two studies. Finally, and since our patients tended to have a high proportion of patients with moderate/severe rhinitis, genetic differences may account for the observed differences. In fact, some genetic polymorphisms in IL-1 and IL-4 genes have been described in some populations, which increase or decrease the likelihood of developing nasal polyps [23,24]. Such polymorphisms should also be studied in our population.

Grass pollen is the major cause of pollinosis in the Mediterranean region of Europe [25]. In our AR patients, major allergic sensitisers included the Gramineae family (grass and cereal pollens) and mites, with a low percentage of monosensitization. This is in line with what was reported by two other studies in areas of the Iberian peninsula [26,27]. We used a battery of 35 screening aeroallergen extracts some of which were mixtures of allergens. Although, theoretically, this approach may be associated with a higher rate of false positive results, we do not believe this is the case since we used highly tested commercial extracts each of which was selected by our team as the ones having the highest positive predictive value. Furthermore, clinicians performing the tests were highly trained in the technique.
In the present study, we provide, for the first time, data on the magnitude of sensitisations for the major allergens in Portuguese AR patients. We show that there are significant differences in terms of the level of sensitisation, as measured by specific IgE classes. Accurate identification of the specific cause of allergic rhinitis is important for the implementation of avoidance measures and immunotherapy.

Epidemiological studies carried out in different geographical regions in the world have shown a significant and consistent association between levels of airborne pollutants (diesel exhaust particles, ozone, nitrogen dioxide, and sulphur dioxide) and increased asthma and rhinitis symptoms [29]. Similar data was obtained from experimental studies carried out in humans and animals [30]. In addition, rural living, especially on a farm, has been inversely associated with asthma, hay fever and atopy in children [31,32]. Thus, the "rural protection phenomenon" may be a combination of both mechanisms.

Surprisingly enough, in terms of allergen sensitisation in urban- and rural based AR patients, we found no differences in prevalence. This is in disagreement with a similar study which demonstrated that the prevalence of AR was higher in urban than in the rural patients [33]. Furthermore, This is because in urban areas, pollen grains can interact with fuel residues and combustion products, and this may modulate the allergenic epitopes and increase their allergenicity [29].

One limitation of our study is that the sample of adults with rhinitis was drawn from a specialized allergy practice, and may differ significantly from the general population of patients with rhinitis, since patients treated by specialists appear to have more severe symptoms than those seen by general practitioners. In addition, severity of rhinitis in these patients was classified at the first appointment, even though many of them were not treatment naïve at that time. Previous studies in Portugal obtained discrepant results from those presented here, but different methodological approaches were used, as the majority of them were only questionnaire-based, whereas our study also included clinical parameters (anterior rhinoscopy) [26,27].

In summary, in this study, bronchial asthma was more frequently associated with NAR than with AR. However, the two kinds of rhinitis could not be differentiated in terms of severity of clinical symptoms. Nasal polyposis was more frequently associated with bronchial asthma, in allergic patients.

The major allergens in the area were grass pollen, cereal pollen, mites and olive tree. Interestingly enough, the magnitude of sensitisation was different among the major allergens, with Graminea pollen as both one of the major allergens and the one with the highest levels of sensitisation.

Urban and rural-based AR patients had no different sensitisation profiles, and could not be differentiated in terms of severity of their disease.

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