ORIGINAL CONTRIBUTION

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Validation of ARIA duration and severity classifications in Spanish allergic rhinitis patients - The ADRIAL cohort Study*

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SUMMARY

Introduction: *Allergic rhinitis (AR) is an increasingly prevalent worldwide disease, which has an important impact on quality of life and generates high social and health care costs. The ARIA classification, that considers both the duration and severity of AR, seems more appropriate than previous classifications of AR, but few studies exist on the validation of the severity criteria proposed by the ARIA classification.*

Objectives: *To assess the ARIA duration and severity classification of AR in a large sample population of patients, by investigating whether different degrees of severity correlate with differences in symptom score, quality of life or the patient's self evaluation of impairment. This study also assesses the relationship between AR severity and comorbidities.*

Material and Methods: *An observational, cross-sectional, multicentre study conducted in Spain. AR was classified based on the ARIA criteria, and compared to the classical classification based on allergen exposure. Rhinitis was evaluated by the Total 4-Symptom Score (T4SS) scale, quality of life was measured using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), and disease severity through a Visual Analogue Scale (VAS, 0-100 mm). Comorbidities were evaluated based both on the duration and severity of the symptoms of rhinitis.*

Results: *AR patients, ($n = 3,529$; mean age 37.5 ± 13.4 years; 52.3% women) were included in the study. AR patients were classified as intermittent (51.5%) and persistent (48.5%) based on the ARIA classification, and as seasonal (61.2%), perennial (35.1%), and occupational (3.7%) based on the allergen exposure classification. Significantly higher T4SS, RQLQ and VAS scores were obtained in moderate/severe compared to mild AR. The incidence of asthma was significantly higher in patients with persistent and moderate/severe AR compared to intermittent and mild AR. Asthma was the only comorbidity to reach statistical significance.*

Conclusion: *ARIA classification of severity reflects two different statuses of AR in terms of symptoms and quality of life. Asthma was the only concomitant pathology in which incidence was related to ARIA categories in terms of duration or severity.*

Key words: allergic rhinitis, ARIA, quality of life, severity, epidemiology

INTRODUCTION

Allergic rhinitis (AR) is an increasingly prevalent worldwide disease [(1)] which has an important effect on quality of life and generates high social and health care costs [(2)]. Based on allergen exposure, AR has classically been divided into seasonal (pollens), perennial (mites, molds, and other domestic allergens), and occupational [(3)]. It has been demonstrated that this classification is not completely reliable for a number of reasons: most patients have a mixed type of allergic rhinitis, with multiple allergen polysensitization [(4)], seasonal allergens may induce persistent symptoms while perennial allergens may induce intermittent symptoms [(5)], and asymptomatic allergic

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patients with minimal persistent inflammation may suffer aggravation of the disease due to non-specific irritants and without allergen exposure [6].

In 1999, a Word Health Organization (WHO) workshop on AR released a consensus guideline on allergic rhinitis (Allergic Rhinitis and its Impact on Asthma, ARIA) that developed a new classification based on the duration of symptoms (intermittent or persistent) and introduced a new severity classification based on the impairment of four health related quality of life parameters: sleep, daily activities and leisure, school or work performance, and bothersome symptoms [7]. This document also stressed the importance of the relationship between rhinitis and asthma in an evidence based scheme. The document has been recently revised [2].

Over the last few years, the validity of this new classification has been demonstrated in several epidemiological studies, showing that classical and ARIA classifications are not interchangeable [5,8] and that classification based on duration of symptoms is useful to stratify patients [9].

Different studies, along the same lines, have tried to demonstrate the validity of the proposed new severity classification. However, epidemiological data have shown that there are too many patients in the moderate/severe group, which is very heterogeneous in terms of severity [10-12]. It has been demonstrated that AR patients who are managed using a scheme based on International Guidelines show a significant improvement in symptoms and health related quality of life compared with those evaluated and treated with a non standardized scheme [13].

The aim of this study was to assess both the classical and ARIA (duration and severity) classifications in a large sample of AR patients, verifying whether different degrees of severity imply differences in symptom scores, quality of life, or the patient's self evaluation of impairment. In addition, this study assessed the relationship between the severity of allergic rhinitis and the incidence of comorbidities.

MATERIALS AND METHODS

Study population

An observational, cross-sectional, multicentre study was performed by 760 investigators from allergy, otorhinolaryngology and general practice centers in Spain, between March and May 2006. Patients aged 18 years or older with an established diagnosis of AR based on positive skin prick tests or specific serum IgE to clinically relevant allergens were consecutively included in the study. All patients signed a written informed consent to participate in the study. The protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona.

Study outcomes

Patients' demographic data and clinical assessment of AR were collected during a single visit using a written case report form where the investigator filled in the type of AR according to the classifications based on allergen exposure (seasonal, perennial, occupational) and ARIA, both as regards duration (intermittent – symptoms appearing less than 4 days a week or less than 4 weeks - or persistent – more than 4 days a week and more than 4 weeks -) and severity (mild – none of the following is present: 1. sleep disturbance, 2. impairment of daily activities, leisure and/or sports, 3. impairment of school or work and 4. symptoms not troublesome - or moderate/severe – if any of them is present -). The Total 4 Symptom Score (T4SS) was also assessed by the total (0 to 12) of nasal symptoms: nasal congestion, rhinorrhea, sneezing, and nasal itching, scored from 0 (not present) to 3 (intense). In addition, patients were asked to evaluate the severity of their disease over the last week using a visual analogue scale (VAS, 0-10 cm) and to complete the Rhinitis Quality of Life Questionnaire (RQLQ) [14].

The T4SS scale is widely used in the evaluation of therapeutic interventions for allergic rhinitis [15]. The visual analogue scale is a quantitative measure largely validated in many diseases that has been used to assess the severity of rhinitis as well as the efficacy of therapeutic interventions. It has recently been shown that it can assess the severity of rhinitis graded according ARIA guidelines [16]. The RQLQ consists of 28 items distributed in 7 domains, where the lower the score the better the

Table 1. Allergic rhinitis patients - epidemiological data.

		Total	IAR	PER	p^*
Gender, n (%)	Male	1684 (47.7%)	872 (47.9%)	812 (47.5%)	NS
	Female	1845 (52.3%)	947 (52.1%)	898 (52.5%)	NS
Age, years (mean ± SD)		37.5 ± 13.4	37.6 ± 13.7	37.4 ± 13.2	NS
ARIA severity	Mild	2328 (66%)	1330 (73.1%)	998 (58.4%)	< 0.0001
n (%)	Moderate/severe	1201 (34%)	489 (26.9%)	712 (41.6%)	< 0.0001
Severity items	Abnormal sleep	517 (14.7%)	209 (11.5%)	308 (18%)	< 0.0001
affected,	Daily activities/sports impairment	809 (22.9%)	352 (19.4%)	457 (26.7%)	< 0.0001
n (%)	Work/school impairment	373 (10.6%)	140 (7.7%)	233 (13.6%)	< 0.0001
	Troublesome symptoms	870 (19.7%)	358 (19.7%)	512 (29.9%)	< 0.0001

IAR: Intermittent allergic rhinitis. PER: Persistent allergic rhinitis. ARIA: Allergic rhinitis and its impact on asthma. NS: Not statistically significant.
* Statistical significance using Chi-square test between intermittent and persistent allergic rhinitis.

health related quality of life. For the global RQLQ score, the minimal important difference has been established at 0.5 [17]. The RQLQ has been translated into and validated in Spanish [18].

Finally, the prevalence of diagnosed AR comorbidities (asthma, conjunctivitis, atopic and contact dermatitis, drug and food allergies) and concomitant treatments were also recorded.

Statistical analysis

A descriptive analysis of the studied population, both in terms of demographic characteristics and the distribution of patients according to allergen exposure and ARIA classifications, was performed. Analytical statistics included a cross-comparison analysis of the two classifications and an analysis of the differences between the scores of severity evaluations (total symptom score (T4SS), visual analogue scale (VAS), and RQLQ quality of life questionnaire) in the two different degrees of ARIA severity. The Chi-square test was used to calculate p-value of the differences between means and standard deviation. Some of the variables did not have a normal distribution, so that non-parametric statistics (Mann-Whitney test) were used, expressing results in median and 25-75 percentiles. Correlations between the different severity evaluations and between them and the two ARIA degrees of severity were calculated. A logistic regression was used to calculate the correlation between the categorical variable ARIA severity and the numerical T4SS, RQLQ or VAS. Finally, the incidence of AR comorbidities was analyzed according to the severity of allergic rhinitis using ARIA criteria.

RESULTS

AR classification

Patients with AR (n = 3,529), aged 37.5 ± 13.4 years (52.3% women) were included in the study. Table 1 shows the demographic characteristics of the study population. All patients were taking or have taken some kind of anti-allergic medication during the month prior to the inclusion in the study, most of them oral antihistamines. Based on the ARIA classification half (51.5%) of the patients were classified as having intermittent AR and half (48.5%) as having persistent AR, while, using the classical allergen exposure classification, patients were grouped as seasonal (61.2%), perennial (35.1%), and occupational (3.7%). A crossed comparison of both classifications revealed that 34.4% of seasonal AR patients had persistent AR, while 26.2% of perennial AR patients had intermittent AR (Table 2).

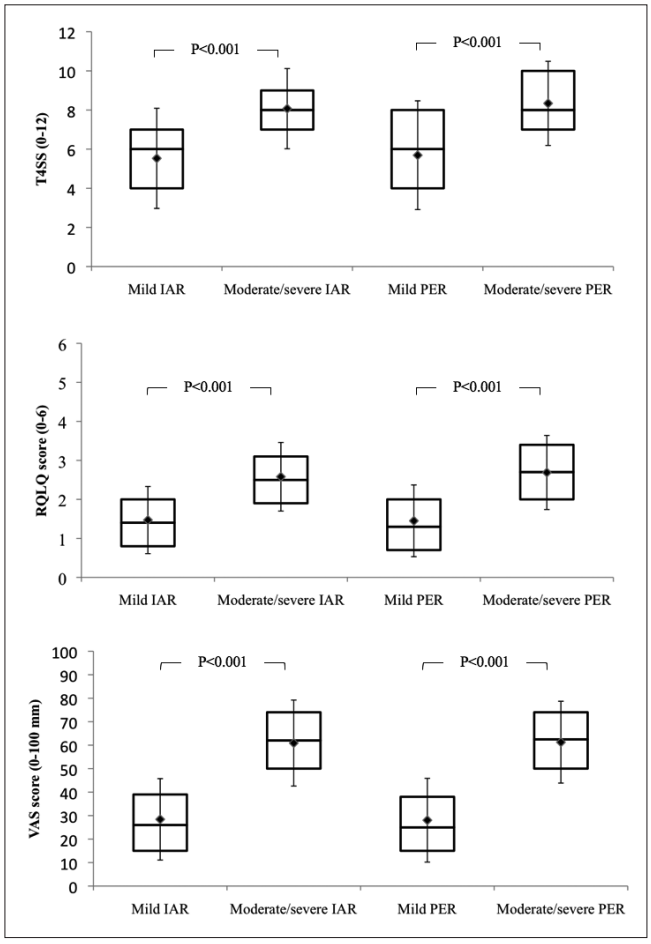

Figure 1. Impact of allergic rhinitis severity on symptom score (T4SS), patients' self evaluation of quality of life (RQLQ) and patients' overall assessment of the disease (VAS). Data are reported in median and 25-75 percentiles (boxes) and mean and standard deviation (diamonds and error bars). IAR: intermittent allergic rhinitis. PER: Persistent allergic rhinitis. A non-parametric test was used (Mann-Whitney) for statistical comparisons.

AR severity

As regards severity, 66% of patients were classified as mild and 34% moderate/severe, the troublesome symptoms item being the most affected and the work/school impairment item the least affected (Table 1). Patients with moderate/severe AR showed a significantly higher T4SS score in comparison with patients with mild AR. A similar result was obtained when quality of life (RQLQ) of patients with moderate/severe was compared to mild AR, the difference being above the minimal important difference. Severity assessed using VAS was consistent with RQLQ, being significantly higher for patients with moderate/severe compared to patients with mild AR (Figure 1).

Table 2. Cross-tabulation of ARIA and allergen based (SAR/PAR) classifications.

		Allergen based classification, n (%)			
		All	Seasonal	Perennial	Occupational
ARIA Classification	All	3529 (100%)	2161 (100%)	1239 (100%)	129 (100%)
N (%)	Intermittent	1819 (51.5%)	1417 (65.6%)	324 (26.2%)	78 (60.5%)
	Persistent	1710 (48.5%)	744 (34.4%)	915 (73.8%)	51 (39.5%)

Correlations between the different severity assessments were: EVA vs. T4SS 0.44 ($p < 0.0001$), EVA vs. RQLQ 0.52 ($p < 0.0001$) and T4SS vs. RQLQ 0.53 ($p < 0.0001$), in mild allergic rhinitis, and EVA vs. T4SS 0.45 ($p < 0.0001$), EVA vs. RQLQ 0.51 ($p < 0.0001$) and T4SS vs. RQLQ 0.46 ($p < 0.0001$), in moderate-severe allergic rhinitis. Correlations between the two allergic rhinitis severity categories using ARIA definitions and the different severity assessments were: vs. VAS: R^2: 0.40, OR: 1.09 (positive correlation), CI: (1.0860; 1.0982) ($p < 0.0001$), vs. T4SS: R^2: 0.20, OR: 1.54 (positive correlation), CI: (1.4915; 1.6015) ($p < 0.0001$), vs RQLQ: R^2: 0.26, OR: 3.78 (positive correlation), CI: (3.4394; 4.1737) ($p < 0.0001$). Significance means that variables are correlated. A good measure of association is R^2. An Odds Ratio (OR) higher than 1 means a positive correlation.

AR comorbidities

Asthma was the only comorbidity whose incidence increased in correlation to ARIA severity of AR (Figure 2). Asthma was more frequent in patients with persistent (41.6%, $p < 0.0001$) than in those with intermittent (31.5%) AR, while the asthma incidence in patients with moderate/severe (41.1%, $p = 0.001$) was higher than in those with mild (34.1%) AR. Conjunctivitis ranged from 51% to 55.6% among the different severity categories but without statistical significance. Other recorded comorbidities were: atopic dermatitis (range = 16.5% to 19.7%), contact dermatitis (range = 8.6% to 12.4%), drug allergy (range = 9.0% to 11.9%), and food allergy (range = 6.0% to 11.0%).

DISCUSSION

One of the main findings in this study is that the distribution of AR patients classified by the ARIA severity criteria is 66% for mild and 44% for moderate/severe among Spanish AR patients. This finding differs from data published in other European countries (10,19-21) in which the prevalence of moderate/severe predominates (69%) among AR patients.

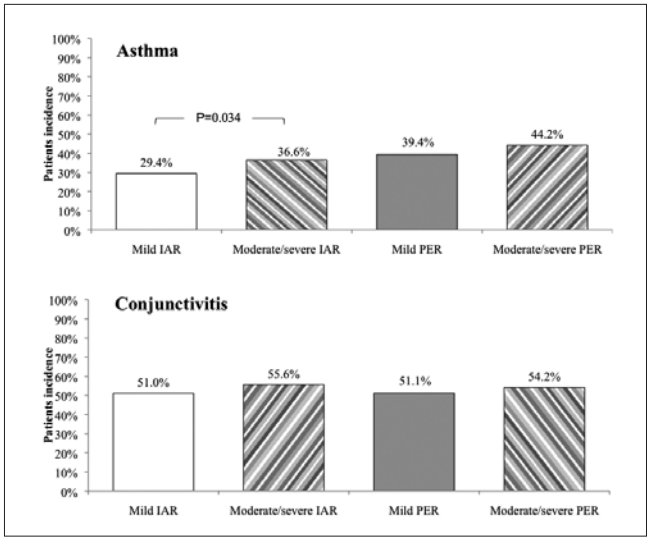

Figure 2. Incidence of asthma and conjunctivitis according to ARIA classification of allergic rhinitis, either by duration or severity. IAR: intermittent allergic rhinitis. PER: persistent rhinitis. Statistical significance is shown when reached (Chi-square test).

However, we found the results consistent with previously published data concerning the differences between the ARIA classification and the allergen exposure classification. The percentages of AR patients reclassified in each group are quite similar (a little lower) to those obtained in these studies [5,9].

The primary objective of our study was to assess the ARIA severity classification in terms of symptoms score and quality of life. We found very significant differences in those two parameters when comparing the two degrees of ARIA severity, assuming that these two statuses truly reflect a different degree of illness. Few studies have focused on this simple approach. Bousquet et al. have shown that ARIA categories of AR gave significantly different scores in Juniper's quality of life questionnaire [10]. Valero et al. found that the four ARIA severity items for the classification of AR were significantly associated with the RQLQ global score while three were associated with the TSS4 score [12]. In this interesting study the authors reported a substantial heterogeneity between symptoms and quality of life impairment in those patients classified as moderate to severe, using ARIA criteria. They proposed to differentiate between moderate to severe using a new criterion: when 1 to 3 items were affected the disease was moderate while involvement of the 4 items represented a severe AR. Van Hoecke et al. have also found statistical differences between the two ARIA severity classes of AR in terms of symptoms and medication consumption [11,22], and they also found an imbalance between mild and moderate/severe prevalence, so they proposed a different criterion to classify as mild, moderate, and severe, based on the three possible combinations of answers to two questions modified from the four originals from ARIA. The recently published ARIA 2008 update [2] has borne this in mind, but argues that this change could make the classification more complex for the practicing doctor without providing him with a significant improvement in clinical practice.

In our study we found a statistically significant correlation between AR severity, as defined in ARIA, and the incidence of asthma, which is more frequent in the persistent and moderate/severe AR subgroups. Asthma was the only concomitant pathology in which this correlation was demonstrated to be significant. It has been shown that AR is a risk factor for asthma [23] and that severity and persistent nasal symptoms have been correlated to an increased risk of asthma [24], but few studies have documented the relationship between ARIA severity of AR and the risk of having asthma. Bousquet et al. have shown, in a cross-sectional study, that the prevalence of asthma was associated with the duration and severity of the AR [20].

The main criticism of our study is that each AR patient was receiving or has received some treatment at the time of the survey, so that the inclusion of patients in each severity group was done retrospectively. However, it has been demonstrated that the severity of allergic rhinitis is independent of its treatment [16] as mentioned in the ARIA update [2], implying that this requirement of ARIA classification may be revised. This observation should be taken into account because, in clinical practice, the evaluation of patients previously treated with antihistamines and/or nasal corticosteroids is very common and they need to be correctly classified in order to improve their treatment.

CONCLUSIONS

Since managing AR patients according to international guidelines seems to result in a better quality of life and symptom control, it is important to provide useful criteria for AR diagnosis and classification when using AR guidelines. The ARIA classification has been shown to better reflect the clinical features of AR patients than previous assessments. Our study reports that the classification of AR patients through ARIA severity criteria reflects two different quality of life and symptoms score statuses, which implies two different degrees of severity which may be of importance in terms of treatment decisions. In addition, asthma was the only concomitant pathology which showed a significantly higher incidence in moderate/severe and persistent AR.

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