

Over diagnosis of persistent allergic rhinitis in perennial allergic rhinitis patients: A nationwide study in Mexico

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ABSTRACT

Background: Allergic rhinitis (AR) symptom phenotypes have been described, and two different classifications exist. The former classification, seasonal versus perennial AR (SAR-PAR), and the Allergic Rhinitis and Its Impact on Asthma (ARIA) classifications, intermittent (INT) versus persistent (PER; ≥ 4 days/wk and ≥ 4 consecutive weeks) and mild versus moderate/severe. ARIA cataloging of INT-PER is based on the patient's description of the frequency of symptoms. This study was designed to (1) describe the epidemiology of these two AR classifications and relate them to one another and to a visual analog severity scale (VAS) and (2) describe how the cataloging of these classifications differs between patients and allergists.

Methods: Skin-prick test–positive AR patients seen nationwide by Mexican allergists completed a validated questionnaire cataloging AR. They recorded demographic data and AR severity on a VAS. The patients' physicians were also asked to classify the AR phenotypes.

Results: Of the patients, 56.5% had INT and 82.2% had PAR and moderate–severe (84.7%) AR. However, 57% of the INT-PAR patients were misdiagnosed as PER-PAR by their physicians. PER patients had more severe disease with a longer clinical history, more PAR, nose and eye symptoms, and a higher VAS score, and only 7% had mild symptoms. VAS values ≥ 7.45 relate to PER (sensitivity, 68%; specificity, 65%). VAS ≤ 6.2 indicated mild and ≥ 6.4 indicated moderate–severe AR. Similar to the adults, in the 2- to 11 year and 12- to 17-year age groups perennial, INT, and moderate–severe AR was the most frequent finding, but the children had more INT ($p < 0.01$) and mild ($p < 0.03$) symptoms, less SAR ($p = 0.03$), and more physician-diagnosed asthma ($p < 0.05$). Public health care (PHC) patients had more INT ($p = 0.016$).

Conclusion: In the PAR group, the physicians' classification of INT-PER often goes astray. PER overdiagnoses might affect treatment decisions because PER is a more severe phenotype. VAS is useful to evaluate severity. In Mexican AR patients, rhinitis symptom phenotypes differ according to age and between private and PHC system patients.

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The importance of allergic rhinitis (AR) as a pathological condition is related to its high prevalence of between 10 and 30% worldwide,^{1,2} its effect on the quality of life of the patients,³ and its relationship to allergic asthma. A cohort study with a follow-up during 40 years showed that 30% of persistent (PER) and 18% of new-onset atopic asthma could be attributed to having childhood rhinitis and eczema.⁴ Different phenotypes of AR can be distinguished. Historically, AR has been subdivided into seasonal and perennial, but in 2001, the Allergic Rhinitis and Its Impact on Asthma (ARIA) classification was introduced, which divides AR symptoms according to duration as intermittent (INT) versus PER and according to severity as mild versus moderate–severe.⁵

Mexico is located between latitudes 14.32° and 32.46° north of the Equator and has a climate that varies from subtropical in the north to tropical in the southeast. The International Study of Asthma and Allergies in Childhood studies found a prevalence of rhinitis in Mexican children between 11.6 and 15.4%,^{1,6} and its risk factors and economic effects have been documented in Mexico^{7,8} and abroad.⁹ In this article, we describe the nationwide point prevalence of the symptom phenotypes of AR (cataloged as seasonal AR–perennial AR [SAR-PAR] and according to ARIA) in patients seen by allergists. We report the relationship of these phenotypes to the visual analog severity (VAS) score and show that the symptom prevalence is linked to age and the level of the health system in which the patient receives medical care (public versus private). We analyzed the differences in the cataloging of AR phenotypes between patients and physicians.

The detailed analyses of the distribution of AR phenotypes and skin test sensitivity patterns in the different climate zones within Mexico are presented in separate documents.

MATERIALS AND METHODS

Study Population

Patients (2–70 years old) with rhinitis symptoms and a positive routine skin-prick test (SPT) who were treated by allergists in 26 centers located across the six climate zones in Mexico were invited to participate in the study. Each center planned to recruit 30 consecutive patients from January 2010 to April 2011. The subjects in the study gave written informed consent (for the pediatric patients, the parents/legal guardian gave consent). The exclusion criteria were related to the factors that influence skin testing, including the administration of allergen immunotherapy over the previous 5 years. The patients were eliminated from final calculations if the blinded SPT from the study was invalid or if they did not fulfill the criteria for rhinitis according to the study validated questionnaire (see later in text). The study was evaluated and approved by an independent ethics committee, Comité de Ética del Instituto Jalisciense de investigación Clínica SA de CV on January 12, 2010.

Study Design and Outcomes

This nationwide multicenter study was conducted as a prospective, cross-sectional study. The subjects in all of the centers underwent an SPT with a blinded set of the 16 most common¹⁰ allergens (standardized allergens from ALK-Abelló, Madrid, Spain, and Biocen, La Habana, Cuba; nonstandardized allergens from Allerquim, Mexico City, Mexico). The SPT was performed in all of the patients with the same batch of allergens and testing device, and we used a standardized SPT technique that was rehearsed in the centers until a proficiency test¹¹ was passed by the study technician before the study began. Once an allergen sensitization to at least one tested allergen was confirmed,

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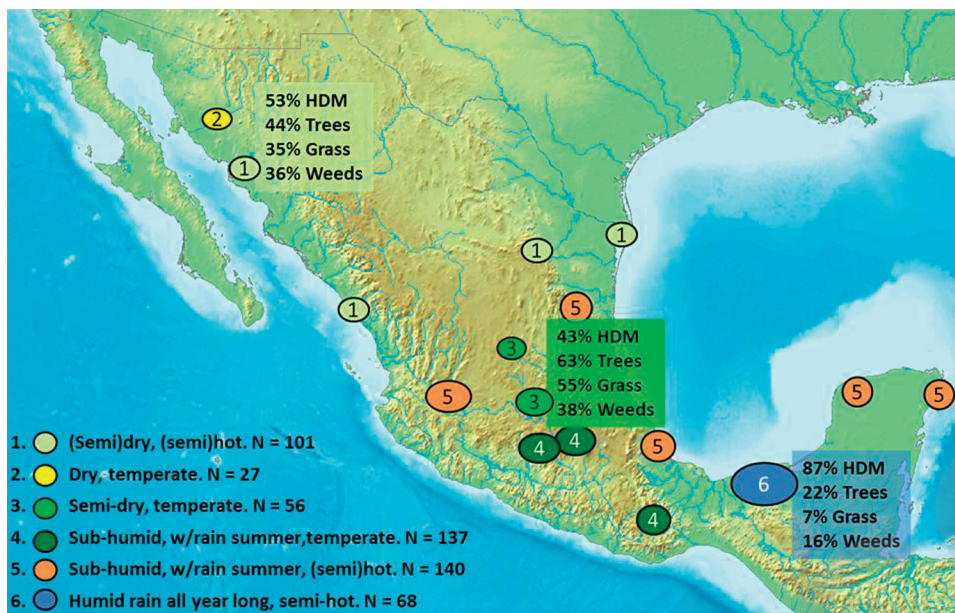


Figure 1. Distribution of the patients over the different climate zones in Mexico and the patients' skin-prick test (SPT) sensitivity as obtained with blinded SPT.

each subject was invited to complete the validated Bauchau and Durham questionnaire on rhinoconjunctivitis symptoms,¹² which allows classification of AR as SAR-PAR according to the former classification and as INT versus PER and mild versus moderate-severe AR, according to the ARIA classification.³ For the young patients, the caregiver completed the questionnaire. A subject was defined as having rhinitis if at least two of the four required rhinitis symptoms (congestion, rhinorrhea, pruritus, and sneezing) were positive and from conjunctivitis if one of the three conjunctivitis symptoms (erythema, pruritus, and lacrimation) were present. The duration of AR was classified in accordance with the original ARIA guidelines as INT or PER, depending on the frequency of symptoms as indicated by the patient (PER, symptoms lasting ≥ 4 days/wk and ≥ 4 consecutive weeks). AR was cataloged as mild if the symptoms did not interfere with daily activities or sleep. The subjects were asked about the duration of their AR symptoms (in years), and they were invited to assess the severity of their symptoms on a VAS ranging from 0 (nasal symptoms not at all bothersome) to 10 cm (nasal symptoms very bothersome).

The treating allergist was also asked to classify the rhinitis symptom phenotypes and to document whether the patient was seen in a public hospital or in private practice. Using the aforementioned data, we analyzed the nationwide prevalence of the AR symptoms and the symptom phenotypes of the AR patients seen by allergists throughout the country. Moreover, we looked for a relationship between the AR phenotypes and the VAS score, age, and level of health care the patient receives. We compared the rhinitis symptom phenotype classification as given by the patients and as evaluated by the physician, considering that the ARIA classification is based on the level of symptoms reported by the patient.

Statistical Analysis

The programmed study population consisted of 90 patients per climate zone to obtain a representative nationwide sample. The sample size calculation was based on an estimated population size of 500,000 AR patients (500 practicing allergists seeing ~ 1000 AR patients/yr), an estimated frequency of PER AR of 60%, with a confidence level of 95% and a confidence interval of 10% (standard error, 0.05). For rhinitis severity (mild versus moderate-severe) and SAR-PAR with an estimated frequency of mild rhinitis and SAR of between 15 and 20%, 57 patients per climate zone are sufficient to achieve the

identical confidence interval. Pearson's χ^2 -tests were used to compare the frequency of the AR symptom phenotypes between the groups, and, if necessary, Yates' correction was applied. The cutoff values for the VAS score are suggested based on the patients' and physicians' evaluations of mild versus moderate-severe AR and based on INT-PER AR. To analyze the correlation between the VAS score and the rhinitis phenotypes, we chose Spearman's ρ because it uses rank order and does not require an assumption of normality in the distribution of the data to be compared.

RESULTS

A total of 529 patients with a valid positive SPT and rhinitis and/or conjunctivitis symptoms were included (aged 2–68 years; 48.2% male). The study population was generally well distributed over the six climate zones in Mexico, as shown in Fig. 1.

The specific rhinitis symptoms as reported by the subjects were nasal congestion in 89.5% of the subjects, nasal pruritus in 87.5%, rhinorrhea in 84%, and sneezing in 92.7%. Of the patients with rhinitis symptoms, 460/521 (88.3%) also had symptoms of conjunctivitis. Forty-two percent of the subjects reported the presence of physician-diagnosed asthma and 37.5% of those agree with the diagnosis of asthma made by his/her physician.

The distribution of the rhinitis symptom phenotypes, according to the ARIA guidelines^{5,13} and pursuant to the former SAR-PAR rhinitis classification, can be found in the left column of Table 1. The majority of the exacerbations are reported during the winter months (92%), followed by autumn (74.6%), spring (73.4%), and summer (67.2%).

The time elapsed between the onset of the allergy symptoms and inclusion in the study was 1 year in 11.8% of the enrolled subjects, 2–4 years in 31.2%, 5–10 years in 32.9%, and >10 years in 24%. Compared with the patients with a shorter duration of AR symptoms, moderate-severe AR (88.3% versus 79.6% $p = 0.007$) and PER (50.2% versus 35.7%; $p = 0.001$) are more frequent in the patients who had had symptoms for >4 years. There is no relationship between SAR-PAR and the duration of AR. The distribution of the AR phenotypes was equal in male and female patients.

INT versus PER AR

Compared with INT, the subjects with PER had more frequent nasal obstruction (85% versus 95%; $p = 0.0002$), rhinorrhea (80%

Table 1 Symptom phenotypes of AR (%) according to patients and allergists (n = 524)

		According to Patient	According to Allergist	p Value
Old classification	Seasonal	17.8	20	ns
	Perennial	82.2	80	ns
	(% seasonal exacerbation in PAR)	(59)	(62)	ns
ARIA classification	Intermittent	56.5	31.4	<0.0001
	Persistent	43.5	68.6	<0.0001
	Mild	15.3	16	NS
	Moderate-severe	84.7	83.9	NS

ARIA = Allergic Rhinitis and Its Impact on Asthma; AR = Allergic rhinitis; PAR = perennial allergic rhinitis; NS = not significant.

versus 89%; $p = 0.01$), and individual eye symptoms and allergic conjunctivitis (85% versus 93%; $p = 0.01$). Physician-diagnosed asthma was similar in both groups. In the PER group, there were more patients with symptoms that had started 5–10 years ago (40%), as opposed to the INT patients, who primarily reported having symptoms after 2–4 years (37.5%). The PER patients had more severe disease, with 7.1% reporting mild symptoms versus 21.9% of the patients in the INT group ($p < 0.0001$) who reported mild symptoms. There was a median VAS score of 8.1 for the PER patients, as opposed to a median VAS score of 6.8 for those with INT AR. (see the further analysis later in text). As opposed to the INT subjects, the PER patients more frequently reported symptoms in the spring (67.7% versus 80.7%; $p = 0.0012$), summer (62% versus 73.1%; $p = 0.01$), and autumn (69.7% versus 80.8%; $p = 0.005$), and as a consequence, PAR is more frequent in the PER group (78.1% versus 88.2%; $p = 0.003$).

Compared with the SAR group, the PAR patients had slightly more frequent nasal obstruction (82% versus 91%; $p = 0.004$) and fewer “mild symptoms” (10% versus 30%), but there were no differences in the other nasal symptoms, the presence of allergic conjunctivitis, or the years of duration of the symptoms. There were no differences between conjunctivitis or asthma comorbidity between the mild or moderate-severe patients.

SAR-PAR versus ARIA Classification of Rhinitis Symptoms

The relationship of the former classification of rhinitis symptoms (SAR-PAR) to the ARIA classification (INT-PER) is shown in Fig. 2.

Patients' and Physicians' Evaluation of AR Symptom Phenotypes

In the right column of Table 1, the physicians' evaluation of the AR symptom phenotypes is shown. A statistically significant difference was found in the evaluations by the patients and physicians of INT-PER. On further analysis, it became clear that in the subgroup of PAR, the physicians tended to overestimate the percentage of patients with PER symptoms. The evaluations by the physicians of INT-PER in the SAR patients are adequate and concur with the patients' classifications.

Correlation between VAS Score and AR Symptom Severity and Duration Phenotypes

An analysis of the correlation between the patients' VAS score (0–10) and the patients' severity assessment of mild versus moderate-severe rhinitis show that the boxplots pertaining to the 25–75 percent

Types of allergic rhinitis in the old and ARIA classification: patients' vs. physicians' evaluation

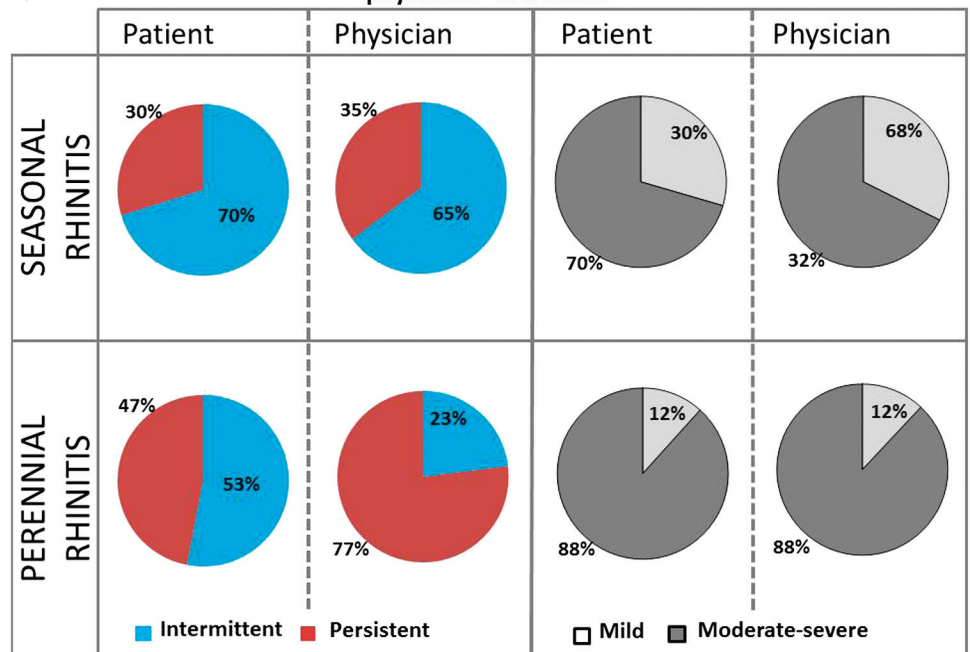


Figure 2. Allergic rhinitis (AR) symptom subtypes. The Allergic Rhinitis and Its Impact on Asthma (ARIA) classification intermittent/persistent (INT-PER) and mild/moderate-severe according to the evaluation by the patients and physicians is plotted against the former AR seasonal and perennial classifications. INT is the most frequent form in both groups, but PER was less rare in the perennial AR (PAR) group ($\chi^2 = 10.0$; $p = 0.0015$). In the perennial group, the duration as judged by the patient and the physician differs significantly ($N = 419$).

tiles do not overlap (Fig. 3, left part): 75% of the mild patients provided a VAS score <6.2 , and 75% of the moderate–severe patients provided a VAS score >6.4 . A VAS score <6.2 corresponds to mild rhinitis, and a VAS score >6.4 corresponds to moderate–severe rhinitis. These cutoff values result in a positive predictive value of 94.8% and a negative predictive value of 39.7%. Thus, 6.3 could be established as the cutoff value between mild and moderate–severe AR. We analyzed the correlation between the patients' VAS score and the physicians' severity assessment of rhinitis (mild versus moderate–severe), and only weak cutoffs can be defined because the 25–75 percentile boxplots overlap. We found a Spearman's rank correlation coefficient of $\rho = 0.41$ between the VAS scores and the patient severity assessments, corresponding to a correlation significant at the level of 0.01 (two-tailed test). This correlation was better than the correlation between VAS and the assessment by the physicians ($\rho = 0.304$; Fig. 3 B).

In addition to the relationship between the severity classification and VAS, we showed a relationship between VAS and INT versus PER. The VAS score with the highest Youden index (indicating the value with the optimum balance between sensitivity–specificity) is 7.45. A VAS score of 7.45 detects PER with a sensitivity of 0.68, a specificity of 0.654, and positive and negative predictive values of 0.448 and 0.58, respectively. A VAS score <4.85 indicates INT with a sensitivity of $>90\%$ (negative predictive value, 91.9%), and a VAS score >8.95 indicates PER with a specificity of $>90\%$ (positive predictive value, 21.8%).

AR Phenotype Distribution per Age Group

The study included patients from 2 years of age onward and we were able to analyze the data set regarding three age groups: children (2–11 years), adolescents (12–17 years), and adults. Figure 4 reveals a significant difference in the frequency distribution of the AR symptom phenotypes according to the age groups, with more mild and INT symptoms in children and more seasonal AR in adults. This finding is in agreement with the fact that more adult patients report exacerbation of their symptoms in spring (73% versus 57%; $p < 0.004$). The analysis of the individual symptoms of rhinitis and conjunctivitis showed no differences between the age groups in the frequency of nasal pruritus, sneezing, rhinorrhea, or obstruction. Although allergic conjunctivitis was as frequent in children, the symptom of lacrimation

was less frequent ($p < 0.0001$). Physician-diagnosed asthma was more frequent in the children <12 years of age ($p < 0.0001$) and adolescents ($p < 0.05$) than in the adult group.

AR in Patients Seen in Private Practice or in Public Health Care

Forty-two percent of our AR patients visited the public health care (PHC) system, which provides consulting for a very low fee or no fee. Compared with the patients that receive medical care in the private sector, they had more INT (63.8% versus 52.7%; $p = 0.016$); there was no difference in the severity of the symptoms (median VAS scores, 7.0 [standard deviation = 2.0] and 7.4 [standard deviation = 1.9], respectively [not significant]). There was a tendency to a higher rate of physician-diagnosed asthma in the PHC system (47.1% versus 39%, not significant).

DISCUSSION

This study presents a nationwide analysis of the AR symptom phenotypes from SPT⁺ AR patients diagnosed by allergists in Mexico. This study is the first to confirm the data found in European studies; the former seasonal–perennial classification is entirely different from the INT–PER ARIA cataloging.¹² In our population, the AR symptoms are generally perennial, INT, and moderate–severe. The structure of the PHC system in Mexico is such that only patients in the public and social security health systems need a referral to see an allergist. The patients who receive medical attention in the private sector can visit a specialist without referral. As such, this study included subjects that are a *mélange* of first- and third-level patients. INT is more frequent among patients seen in the PHC system in which services are free of charge. In the three age groups, PAR, INT, and moderate–severe rhinitis prevailed, but children had a higher frequency of mild symptoms and the adults had more PER and seasonal rhinitis (Fig. 4).

Having a full data set on the rhinitis symptom phenotypes and a VAS score for all of the subjects permitted us to analyze the relationship between the phenotypes and the VAS scores. The PER patients had more severe disease as reflected by the following: a longer clinical history; more frequent PARs; more frequent nasal obstruction, rhinorrhea, and eye symptoms; a higher VAS score; and 7% of the

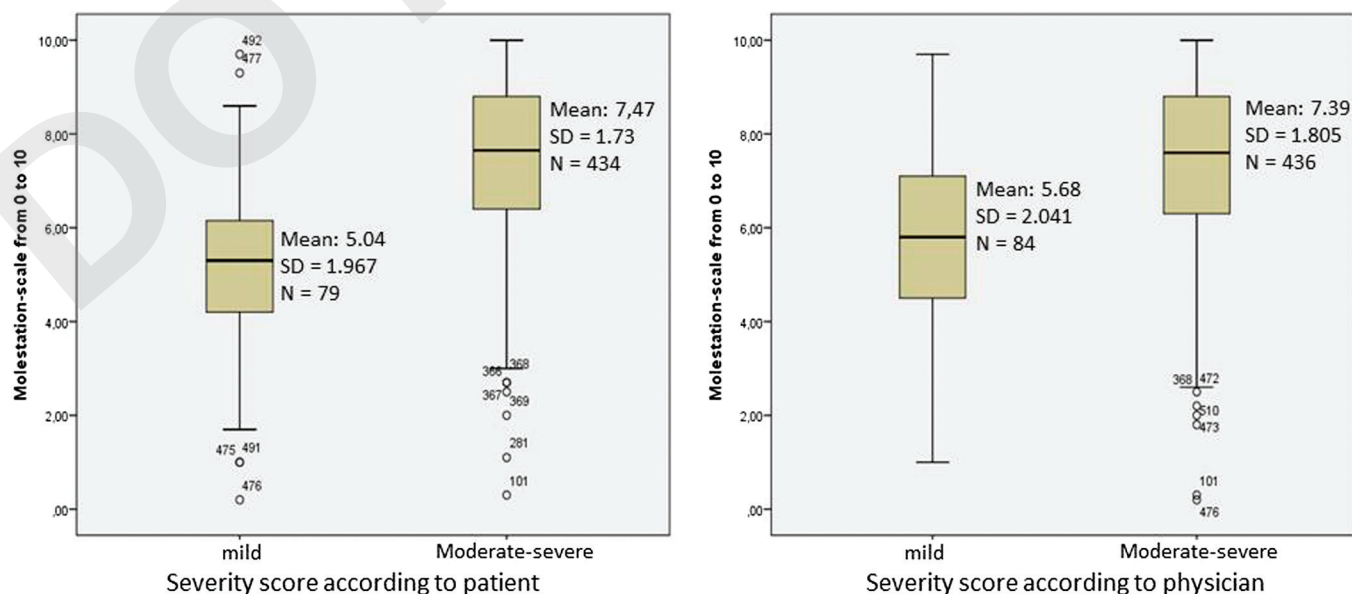


Figure 3. Boxplots of the relationship between the molestation visual analog severity scale (VAS) score and symptom severity. (A) The relationship between the molestation VAS score (0–10) and the severity evaluation of the allergic rhinitis (AR) symptoms (mild versus moderate–severe) by the patients. (B) The relationship between the molestation VAS score (0–10) and severity evaluation of the AR symptoms (mild versus moderate–severe) by physicians.

Types of allergic rhinitis according to age (N = 524pts)

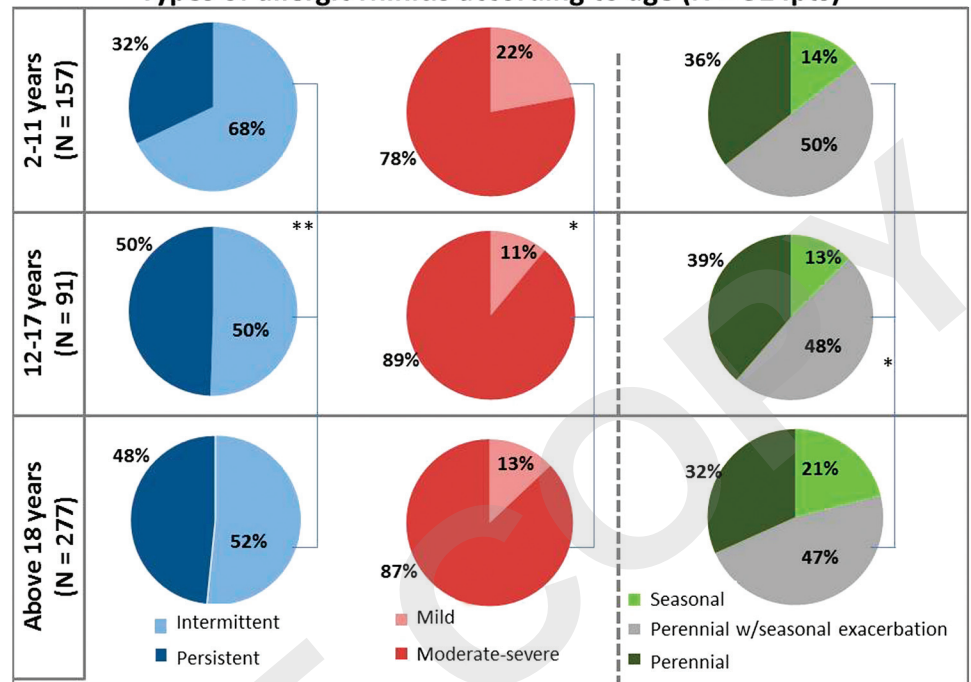


Figure 4. The frequency distribution of the allergic rhinitis (AR) symptom classifications according to age groups: children (2–11 years), adolescents (12–17 years), and adults (≥ 18 years). (A) The Allergic Rhinitis and Its Impact on Asthma (ARIA) classifications of intermittent–persistent (INT–PER) and mild–moderate/severe. Children have more INT AR than adolescents ($p = 0.007$) and adults ($p < 0.001$). Children have more mild classifications of AR than the adolescents ($p = 0.03$) and adults ($p = 0.02$). (B) The former classification, seasonal AR–perennial AR (SAR–PAR). The adults have more SAR than the children and adolescents combined ($p = 0.03$).

patients reporting mild symptoms. We assigned cutoff values for VAS related to the INT–PER classification; the VAS values >7.45 relate to PER–AR with a sensitivity and specificity approaching 70%. We found sufficient correlation to give a cutoff value of VAS: mild rhinitis and moderate–severe rhinitis correspond to a VAS score under and over 6.3, respectively. Because the number of patients in the moderate–severe group was markedly higher than those in the mild group, the positive predictive value of $\sim 95\%$ is excellent, but the negative predictive value is low. Our cutoff values are similar to those found by Bousquet *et al.*¹⁴ Applying their values to our population, the positive and negative predictive values show approximately zero variation.

Table 2 shows the comparison of the Mexican data on INT–PER to other data sets.^{12,15–28} The prevalence of INT–PER rhinitis varies widely according to the population studied. This finding might point to true differences in the AR phenotypes. Our study shows the crucial importance of the data collection method in regard to whether it is patient or physician based. In our investigation, the rhinitis symptom phenotypes were classified by the patient and the treating allergist. This classification method allowed us to compare both perceptions. The patients and physicians generally agree on the SAR–PAR classification, but the INT–PER classification differs markedly. Many patients with INT symptoms are diagnosed by the physicians as having

Table 2 Prevalence of INT and PER rhinitis in several epidemiological studies (2009–2012)

Study	INT (%)	PER (%)	Details on Population	n
Larenas-Linnemann 2013, Mexican study (current article)	56.5	43.5	AR patients, SPT ⁺ seen by allergists (SAR, 20%; PAR, 80%)	524
Mohammadi 2008, Iran ¹⁶	38.5	61.5	Rhinitis patients at clinic, 85% SPT ⁺	206
Klossek 2009, France ¹⁷	50	50	Interview patient at home	601
Zhang 2009, China ¹⁸	74.4	25.6	Telephone interview, self-reported rhinitis	~3400
Ciprandi 2008, Italy ¹⁹	27	73	POLISMAIL study, AR patients with SPT positivity	418
Cuvillo 2010, Spain ²⁰	51.5	48.5	AR patients with SPT/IgE ⁺ ; Q filled out by investigator (SAR, 61%; PAR, 35%)	3,529
Samolinski 2009, Poland ²¹	47.7	53.3	AR diagnosed by physician (SAR, 50.5%; PAR, 49.5%)	1382
Han 2009, China ²²	56	44	Q at school, 9- to 10-yr-old children	277
Asha'ari 2010, Malaysia ²³	31	69	Physician completed Q	90
Jauregui 2010, Spain ²⁴	59.5	40.5	Children 6–12 yr, SPT ⁺ , allergist-diagnosed AR (SAR, 60.7%; PAR, 39.3%)	1275
Navarro 2011, Spain ²⁵	52	48	Physician-completed Q	4040
Valero 2012, Spain ²⁷	29.7	70.3	HDM SPT and IgE ⁺ AR patients seen by specialists	519
Alexandropoulos 2012, Greek ²⁶	45.1	54.9	Retrospective chart review of an outpatient clinic	711
Popov 2012, Bulgaria ²⁸	38.8	61.2	Nasal symptom patients, no SPT	1685
Maio 2012, Italy ³⁴	66.2	33.8	GPs	

INT = intermittent; PER = persistent; GPs = general practitioners; HDM = house-dust mite; PAR = perennial allergic rhinitis; Q = questionnaire; SAR = seasonal allergic rhinitis; SPT = skin prick test.

PER symptoms. This finding is especially true for the patients with PAR (Fig. 2).

The significance of the patient-directed questions specific to the ARIA classification is clear in a comparison of the physician-based AR symptom subtype diagnosis with the patient-based ARIA classification. A similar discrepancy between the patient report and the physician diagnosis of INT-PER rhinitis was elegantly shown in a very recent study in Bulgaria.²⁸ There is an additional issue that might explain the PER prevalence differences found in Table 2. The ARIA classification of the AR duration is not completely firm because exactly 4 days and exactly 4 weeks are not included in the INT or the PER. The majority of investigators consider PER in cases in which the symptoms persist for ≥ 4 weeks,¹² as we did, but a number of investigators consider PER as the diagnosis if symptoms persist for >1 month.²⁹

In a recent supplement of *Allergy and Asthma Proceedings*, the burden of AR was analyzed in a number of surveys conducted in the United States, Latin America, and South-Asian Pacific region.³⁰ The authors conclude that despite a number of global variations in nasal allergy triggers and treatments, patients generally experience identical symptoms and have comparable experiences with various medications, which fail to address completely the needs of the patients.³¹ The burden of AR is substantially underestimated.³² In our study, we did not apply a quality-of-life questionnaire or a more-detailed symptom evaluation, which might have enabled us to differentiate between moderate and severe patients, as was shown by Valero *et al.*³³

In conclusion, the former SAR-PAR classification is not helpful for directing patient care because it relates quite poorly to symptom severity and duration. Although 80% of the Mexican AR patients are PAR, their case management should not be uniform. Correct cataloging of the AR symptom phenotypes according to the ARIA classification is crucial because this system is the basis for therapeutic approaches. In our study, 44% of our patients had PER symptoms that required more intensive management. We confirmed that in the cases in which the INT-PER diagnosis is solely based on the assessment by the physician, there might be a tendency toward misjudgment, and for AR phenotyping, we strongly recommend the use of a simple patient-completed questionnaire such as appears on the ARIA website. The use of a VAS to assess severity can be helpful, but caution should be taken when interpreting the lower scores because the negative predictive value is low.

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