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## Severity and duration of allergic conjunctivitis: are they associated with severity and duration of allergic rhinitis and asthma?

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### KEY WORDS

*Allergic conjunctivitis; allergic comorbidity; allergic respiratory disease; epidemiology; one airway.*

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### Doi

10.23822/EurAnnACI.1764-1489.231

### IMPACT STATEMENT

*The greater the severity and duration of conjunctivitis, the greater the severity and duration of rhinitis and asthma.*

### Summary

**Objective.** The association of allergic conjunctivitis (AC) with rhinitis and/or asthma is poorly understood. The objective of this study was to apply the Consensus Document for Allergic Conjunctivitis (DECA) criteria for the classification of AC to a population of patients with AC to assess the association between the severity and duration of AC and rhinitis and/or asthma. **Methods.** Patients with ocular symptoms of AC who participated in the “Alergológica 2015” study were included. The demographics, classification according to the DECA criteria, etiology, and comorbidities were evaluated by age groups ( $\leq 14$  and  $> 14$  years). **Results.** A total of 2,914 patients (age range, 1-90 years) were included in the “Alergológica 2015” study. Of these, 965 patients (33.1%) were diagnosed with AC (77.5%  $> 14$  years). AC was classified as severe, moderate, or mild in 1.8%, 46.4%, and 51.8%, respectively; and as intermittent or persistent in 51.6% and 48.4% of the patients. AC alone occurred in 4% of patients. AC was mainly associated with rhinitis (88.4%), asthma (38.2%), food allergy (8.3%) and atopic dermatitis (3.5%). In allergic respiratory disease rhinitis preceded AC and asthma developed later. The severity and duration of AC was significantly associated with severity and duration of rhinitis ( $p < 0.001$  for both age groups) and asthma ( $p < 0.001$  only in adults). **Conclusions.** The application of the new DECA classification for AC reveals a direct relationship between AC, rhinitis and asthma respect to severity and duration. These relationships suggest that AC should be considered an integral part of the “one airway, one disease” hypothesis.

### Introduction

Allergic conjunctivitis (AC) is an inflammatory reaction of the conjunctiva mediated by immunoglobulin (Ig)E hypersensitivity. Depending on the geographical area and study design, the estimated prevalence of AC in the general population ranges between 15 and 40% (1-3).

AC is often associated with other atopic conditions such as eczema, food allergy, and especially rhinitis and asthma (4). Since the allergic response often involves the conjunctival surface of the eye as well as the respiratory tract, it has been hypothesized that AC should be considered as part of the “united airway disease”, a concept based on the anatomical and functional links between the upper and the lower respiratory tracts (5-7). Likewise, the concept of allergic respiratory disease (ARD), based on the allergic origin of the disease and its clinical spectrum, includes conjunctivitis, rhinitis, and/or asthma, although not all clinical manifestations must occur simultaneously in patients with ARD (8). The classification of allergic rhinitis and asthma according to duration and severity has made it possible to demonstrate a strong association between both entities (9). For example, it has been observed that the greater the severity and duration of rhinitis, the greater the possibility of being associated with asthma (10). However, the role of AC as a risk factor of rhinitis and/or asthma is poorly understood, possibly due to the lack of a validated classification based on the duration and severity of the disease. We have recently validated the new criteria for classification of AC's severity and control proposed in the Consensus Document on Allergic Conjunctivitis (DECA) (11, 12). The present study aimed to apply the DECA classification to assess the association between the severity and duration of AC and its main comorbidities, rhinitis, and asthma, for the first time.

### Materials and methods

#### Study design and population

The “Alergológica 2015” study was a multicenter, observational, cross-sectional, prospective study of patients consulting an allergist for the first time in public and private health centers in Spain, between March 2014 and March 2015, whose material and methods have been published elsewhere (13-15). The “Alergológica 2015” study was approved by the Clinical Research Ethics Committee of Hospital General de la Defensa, Madrid, Spain. Patients or legal guardians signed written informed consent. In the “Alergológica 2015” study data were collected on an electronic case report form (CRF). The CRF remained open until the diagnostic work-up had been completed for all patients or until the end of the recruitment period. Clinical symptoms, time from the onset of disease to the study inclusion, demographic data (age, gender, and habitat), smoking behavior, and family history of allergic diseases were recorded. Complementary diagnostic tests were performed following the investigator's criteria and consisted of skin tests, specific IgE determinations, functional respiratory tests, provocation tests, and others, following standard clinical practice.

In the present study, adults and children with suggestive AC symptoms fulfilling DECA criteria were retrospectively analyzed (**table I**) (11). The demographics, skin prick test, classification according to the DECA criteria, and comorbidities, were evaluated by age groups ( $\leq 14$  and  $> 14$  years). AC, rhinitis and asthma were classified, respectively, according to DECA criteria (**figure 1**) (11), modified Allergic Rhinitis and its Impact on Asthma (ARIA) criteria (16), and Spanish guide for management of asthma (GEMA) criteria (17).

**Table I - Clinical criteria for suspicion of allergic conjunctivitis (DECA) (11).**

<b>Bilateral conjunctival hyperemia and pruritus (together with at least 3 of the following criteria)</b>
1. Ocular symptoms associated with exposure to suspicious allergens
2. Association with other allergic diseases (rhinitis, asthma, atopic dermatitis)
3. Response to topical pharmacologic therapy (antihistamines, mast cell stabilizers, dual-action agents)
4. Absence of giant papillary conjunctivitis
5. Absence of corneal involvement

### Statistical analysis

Data were expressed as mean  $\pm$  standard deviation (SD). When numeric distribution was markedly asymmetric, median and percentiles (P 25 and P 75) were used. Qualitative variables were calculated based on frequencies and percentages. Data were analyzed both globally and by age groups:  $\leq 14$  years old (pediatric group) and  $> 14$  years old (adults' group). The relationship between qualitative variables was analyzed using the Chi-square test, Chi-square with correction for continuity, or Fisher's exact test. The Chi-squared test was used to analyze relationships between two categorical variables. For the study of concordance, Cohen's Kappa coefficients were obtained for qualitative variables. Agreement was considered fair if the value of Kappa was 0.21-0.40, moderate if 0.41-0.60, substantial if 0.61-0.80, and almost perfect if 0.81-1.00 (18). A statistical significance level of 0.05 was considered for all tests. The software IBM SPSS Statistics v25 for Windows (Armonk, NY, USA) was used for the statistical analysis.

### Results

#### Demographics

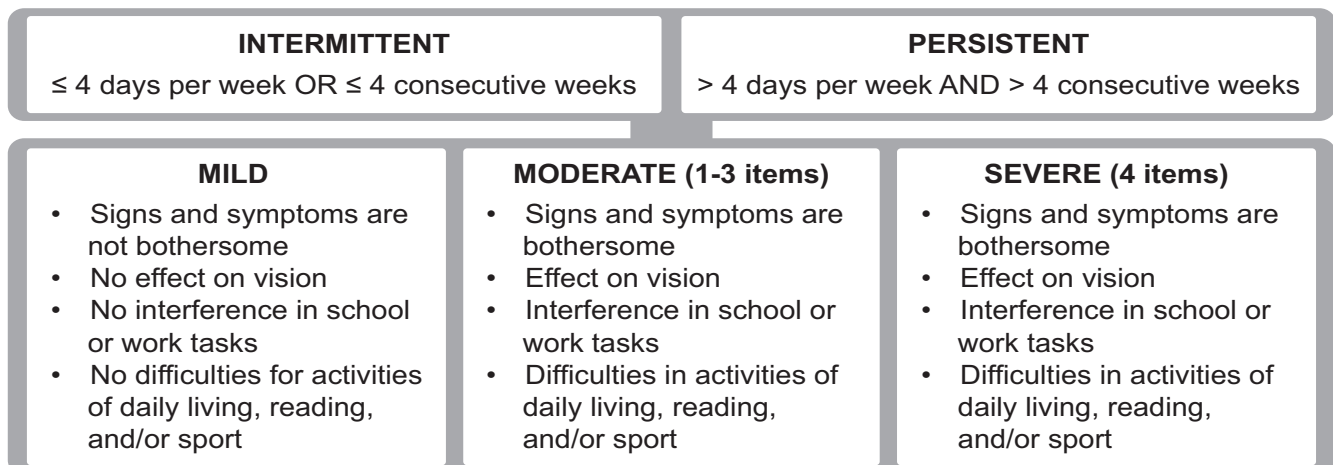
Of the 2,914 patients included in the "Alergológica 2015" study, 965 patients (33.1%) were diagnosed with AC. Of the patients

with AC (age range, 1-90 years), 17.3% were aged  $\leq 14$  years (**table II**). In the pediatric group, there was male predominance (62.0%,  $p < 0.001$ ), but in the adult population, most patients were female (57.4%).

Globally, 66.0% of patients with AC referred family history of atopy, rhinitis (52.0%), asthma (29.5%), and conjunctivitis (23.4%). Most of the patients lived in urban areas (62%) and were non-smokers (74%). Exposure to pets was referred by 15.5% of patients.

#### Skin prick tests

The pollens were the most frequent allergen detected by skin tests in the population, both children and adults (**table II**). Grass pollen was the most frequent sensitization (49%), followed by *Olea europaea* (37%). Among the mites, the most prevalent were *Dermatophagoides pteronyssinus* (27.9%), *D. farinae* (20.8%), and *Lepidoglyphus destructor* (6.5%). The most prevalent mold was *Alternaria alternata* (4.5 %). Cats (12%) and dogs (8.5%) were the most frequent sensitizations to animals. Sensitization to hamsters was related to pet ownership ( $p < 0.01$ ).

**Figure 1 - Criteria for the Classification of AC according to the DECA criteria (11).**

**Table II** - Demographic and clinical characteristics of the patients with confirmed AC included in the "Alergológica 2015" study.

Variable	≤ 14 years (N = 167)	> 14 years (N = 748)	Total (N = 965)
Gender (female), N (%)	N = 163	N = 734	N = 897
Female	62 (38.0)	422 (57.4)	484 (54.0)
Male	101 (62.0)*	312 (42.6)	413 (46.0)
Allergen, N (%)	N = 167	N = 748	N = 915
Pollens	102 (61.1)	490 (65.5)	592 (64.7)
Mites	53 (31.7)	217 (29.0)	270 (29.5)
Animal dander	17 (10.2)	125 (16.7)**	142 (15.5)
Molds	13 (7.8)**	29 (3.9)	42 (4.6)
AC classification, N (%)	N = 156	N = 683	N = 839
Intermittent mild	57 (36.5)	242 (35.4)	299 (35.6)
Intermittent moderate	21 (13.5)	111 (16.3)	132 (15.7)
Intermittent severe	0 (0.0)	2 (0.3)	2 (0.2)
Persistent mild	25 (16.0)	111 (16.3)	136 (16.2)
Persistent moderate	50 (32.1)	207 (30.3)	257 (30.6)
Persistent severe	3 (1.9)	10 (1.5)	13 (1.5)
<b>Comorbidities, N (%)</b>			
Allergic rhinitis	155 (92.8)	698 (81.8)	853 (88.4)
Intermittent mild	27 (17.4)	109 (15.6)	136 (15.9)
Intermittent moderate	21 (13.5)	120 (17.2)	141 (16.5)
Intermittent severe	1 (0.6)	1 (0.1)	2 (0.2)
Persistent mild	24 (15.5)	73 (10.5)	97 (11.4)
Persistent moderate	75 (48.4)	331 (47.4)	406 (47.6)
Persistent severe	7 (4.5)	64 (9.2)	71 (8.3)
Allergic asthma	79 (47.3)	290 (38.8)	369 (38.2)
Occasional episodic/intermittent	36 (45.5)	127 (44)	-
Frequent episodic	21 (26.6)	-	-
Persistent mild	-	78 (27)	-
Persistent moderate	22(27.8)	83 (29)	-
Persistent severe	-	2 (0.7)	-
Food allergy	9 (5.3)	65 (8.6)	80 (8.3)
Atopic dermatitis	16 (9.5)*	15 (2.0)	34 (3.5)

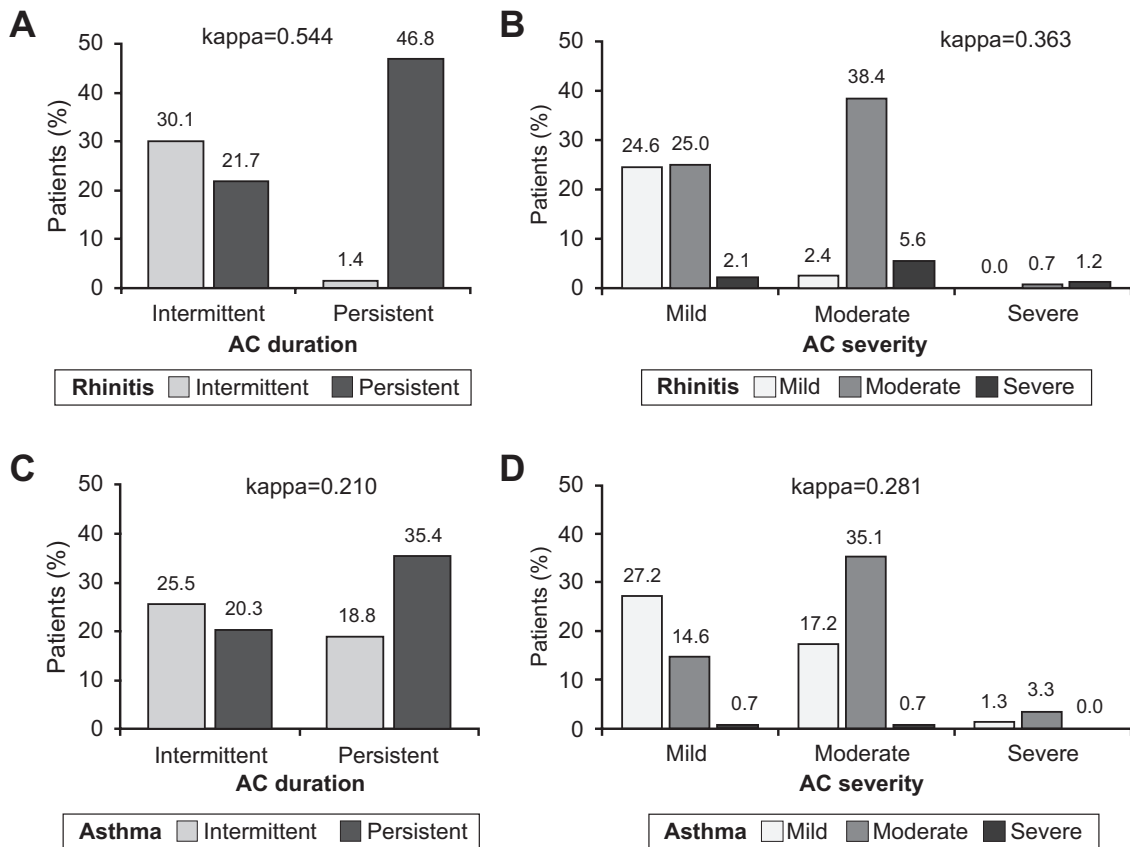
\*p &lt; 0.05; \*\*p &lt; 0.001.

**AC classification**

All patients were classified according to duration and severity using the validated DECA classification (**table II**). The severity of the AC symptoms was mild in 51.8% of the patients, moderate in 46.4%, and severe in 1.8%. Concerning duration, intermittent and persistent AC was observed in 51.6% and 48.4% of patients, respec-

tively. The duration and severity of AC were similar in pediatric and adult populations ( $p = 0.947$ ). Thus, AC was intermittent in 50.0% and 51.9% of the pediatric and adult populations, respectively; persistent in 50.0% and 48.0%; mild in 53.9% and 51.6%; moderate in 61.5% and 66.0%; and severe in 1.9% and 1.5% of the pediatric and adult populations, respectively (**table II**).

**Figure 2** - Association between AC and rhinitis or asthma. (A) Duration of AC and rhinitis ( $\kappa = 0.544$ ;  $p < 0.001$  for both age groups); (B) Severity of AC and rhinitis ( $\kappa = 0.363$ ;  $p < 0.001$  for both age groups); (C) Duration of AC and asthma in adults ( $\kappa = 0.210$ ;  $p < 0.001$ ); (D) Severity of AC and asthma in adults ( $\kappa = 0.281$ ;  $p < 0.001$ ).



### Comorbidities

The most frequent comorbidity was rhinitis in 88.4% of the patients (92.8% and 81.8% in the pediatric and adult groups, respectively, without a significant difference between the two age groups), followed by asthma in 38.2% of the patients (47.3% and 38.8% in the pediatric and adult groups, respectively, also without a significant difference between the two age groups) (table II). The third most frequent comorbidity was atopic dermatitis among patients in the pediatric group (9.5%,  $p < 0.001$ ) and food allergy among adult patients (8.6%). Isolated AC was found only in 36 patients (4%), with no differences between children (3.0%) or adults (4.1%) ( $p = 0.66$ ). When the development of allergic disease and comorbid pathologies was considered, food allergy was the first to appear in time, with a mean  $\pm$  standard deviation time from onset of the symptoms to the time of the study of  $19.0 \pm 13.4$  years, followed of atopic dermatitis ( $7.7 \pm 10.8$  years), rhinitis ( $5.0 \pm 7.9$  years), conjunctivitis ( $4.5 \pm 7.2$  years), and asthma ( $1.9 \pm 2.1$  years).

The association between AC with rhinitis or asthma in the adult and pediatric population is shown in figure 2. A moderate concordance was found between the duration of the conjunctivitis and allergic rhinitis ( $\kappa = 0.544$ ,  $p < 0.001$ ) and a fair concordance ( $\kappa = 0.363$ ,  $p < 0.001$ ) between the severity of both pathologies in the population (figure 2 A, B). We found that AC in adults has a fair concordance with asthma in severity ( $\kappa = 0.281$ ,  $p < 0.001$ ) and duration ( $\kappa = 0.210$ ,  $p < 0.001$ ) (figure 2 C, D). This association was not observed in the pediatric population either in duration ( $p = 0.111$ ) or severity ( $p = 0.075$ ).

### Discussion

This study retrospectively explored the usefulness of the newly validated DECA classification of AC in both children and adults seeking consultations with allergy specialists in Spain. The study showed that, according to the DECA criteria, the most common presentations of AC were intermittent mild and

persistent moderate, both in pediatric and adult populations. It also revealed that allergic rhinitis and asthma were prevalent comorbidities of AC in all patients.

Concerning the prevalence of AC, this study showed that AC is highly prevalent (33%) among allergic patients in Spain. Similar rates of AC have been reported worldwide (3). In a prospective study of 458 allergic patients aged 5-15, 30% were diagnosed with AC (19), and there was also male predominance (63%), in agreement with our study. Despite the high prevalence of AC, it has been frequently ignored by both physicians and patients, which has resulted in underdiagnosed and undertreated patients, especially when it is associated with other allergic diseases such as rhinitis and/or asthma (20).

Overall, AC was mainly associated with rhinitis and asthma (88.3% and 38.3% of patients, respectively). The association was more prominent in children than in adults (93% with rhinitis and 47% with asthma). Similar results have been observed in related studies (19, 21). Also, studies have shown that AC presents isolated in only 5-6% of patients (22, 23), which is in agreement with our results (4% isolated AC). Likewise, other authors have reported that rhinitis without conjunctivitis is very infrequent (6.7%) (24).

It is well known that a family history of atopic diseases such as allergic rhinitis or allergic asthma increases the likelihood of other allergic disorders (25). The presence of ocular symptoms increases the role of rhinitis as a risk factor for asthma compared to rhinitis alone (26), but it is unknown whether the duration and severity of conjunctivitis could influence the severity and duration of its comorbidities. In this study, using the new AC classification, we have verified that, in adults, the greater the severity and duration of conjunctivitis, the greater the severity and duration of rhinitis and asthma. In the pediatric group, we also observed a significant correlation between the severity and duration of AC and rhinitis, which was found not significant in asthma.

We have not found any published study on the onset of AC in relation to its comorbidities, to place it chronologically in the so-called allergic march. Some studies have shown how rhinitis from the clinical point of view precedes asthma (27). In our study we indirectly found that rhinitis discreetly preceded conjunctivitis while the onset of asthma was later.

Following on the evidence that justifies allergic rhinitis and asthma as members of the "one airway, one disease" hypothesis, we suggest that there are epidemiological relationships, and severity and duration correlations between AC, rhinitis and asthma, which would allow the inclusion of AC in the "united airway disease" concept. The application of the new DECA classification for AC is consistent and complementary with that currently in use for rhinitis severity and duration, and could reduce the heterogeneity of the information on AC. The main limitations of this study are that it was not specifically designed for patients with AC and the retrospective nature of

the analyses. It would be interesting to develop a prospective survey to carry out a detailed epidemiological study to better understand AC in the general population.

## Conclusions

The DECA classification for AC has allowed direct relationships between AC, rhinitis, and asthma in terms of clinical severity and duration. This relationship can be considered as one more argument to include AC an integral part of the one airway concept.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Acknowledgements

The authors acknowledge Francisco López de Saro, PhD (Trialance SCCL) for medical writing support.

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