Epidemiology of allergic conjunctivitis: clinical appearance and treatment patterns in a population-based study

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Purpose of review
To analyse the most recently published studies on the prevalence of allergic conjunctivitis alone or in association with allergic rhinitis, and the clinical and demographic aspects of the disease.

Recent findings
Allergic conjunctivitis or conjunctival symptoms are present in 30–71% of patients with allergic rhinitis. Allergic conjunctivitis alone has been estimated in 6–30% of the general population and in up to 30% in children alone or in association with allergic rhinitis. Seasonal allergic conjunctivitis is the most frequent form; however, studies from tertiary, ophthalmology referral centers report that the chronic forms, such as vernal and atopic keratoconjunctivitis, are the most frequently seen by ophthalmologists. A recent large survey performed at a national level involving 304 ophthalmologists showed that the majority of patients with allergic conjunctivitis suffer annually of few episodes of mild ,intermittent conjunctivitis. However, 30% of patients are affected by frequent episodes with intense and persistent symptoms. Treatment is frequently not appropriate.

Summary
Even though allergic conjunctivitis is often associated to allergic rhinitis, epidemiology studies frequently do not include specific ophthalmological evaluations. An understanding of allergic conjunctivitis disease, its prevalence, demographics and treatment paradigms will provide important information towards understanding its pharmacoeconomics and burden on the national health systems.

Keywords
allergic conjunctivitis, epidemiology, signs and symptoms, survey, treatment

INTRODUCTION

Allergic conjunctivitis, also called ocular allergies, is a common allergic disorder estimated to affect up to 10% of the population worldwide considering that 20% of the population has some kind of allergic disease and half of them may have experienced an ocular allergic manifestation [1]. It has been estimated that, by 2015, half of the population of Europe would have been affected by ocular allergies [2]. The prevalence of allergic conjunctivitis has been difficult to establish and probably underestimated in most epidemiologic studies, because conjunctival symptoms are often not spontaneously reported in medical interviews or in questionnaire-based epidemiologic studies targeting rhinitis and/or asthma. Although several studies suggest a high comorbidity of conjunctivitis and rhinitis, conjunctival symptoms are often considered a minor problem. This is not always the experience from ophthalmologists and from surveys that target specifically ocular symptoms [3]. Few studies considered specifically the prevalence of ocular allergies in the general population but are based on different sources and different search methods. For example, in the United States [4], the prevalence of ocular allergies was calculated considering the third National Health And Nutrition Examination Survey

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KEY POINTS

- Ocular allergies are estimated to affect 6–30% of the general population
- Even though ocular allergy is often associated with rhinitis (30–70%), tools used in epidemiology studies on rhinoconjunctivitis do not include specific ophthalmological evaluations.
- Although most ocular allergic patients presented with recurrent episodes, only a minority receive an allergy diagnostic evaluation.
- The majority of ocular allergy patients have few episodes of mild conjunctivitis annually.
- Approximately 30% of patients with allergic conjunctivitis may have frequent episodes with intense and persistent symptoms.
- Patients with allergic conjunctivitis tend to self-treat and are often treated by nonophthalmologists.

(NHANES III) performed in from 1988 to 1994. The prevalence of ocular allergies symptoms, comorbidities, and their impact on adolescents were studied in a cross-sectional study [5] conducted in 2009 in Brazil, delivering an International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to more than 3000 students. A different approach was used in a survey among ophthalmologists and general medical practitioners from nine countries in Eastern Europe and the Middle East to estimate the percentage of patients presenting with a red eye [6]. A similar approach was used in Portugal with a cross-sectional study [3], in 16 ophthalmology departments of central or regional hospitals, in patients diagnosed with allergic conjunctivitis. We recently conducted in Italy during the spring-summer of 2012, a cross-sectional study [7▪▪] interviewing 3685 patients with the diagnosis of allergic conjunctivitis.

One of the main problems that can be observed comparing the different studies is the definition of ocular allergies and the diagnostic criteria. Ophthalmologists, allergists, pediatricians or general medical practitioners in different parts of the world, but also in the same country, may follow different diagnostic criteria. In general, studies from nonophthalmology centers consider only seasonal/intermittent allergic conjunctivitis (SAC) or perennial/persistent allergic conjunctivitis (PAC) whereas ophthalmologists observe the whole spectra of ocular allergies, which includes vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC), and contact blepharoconjunctivitis (CBC). To unify the nomenclature and classification of ocular allergies combining the ophthalmology and allergy criteria, an European Academy of Allergy and Clinical Immunology (EAACI) task force suggested to include 'ocular allergy' in the 'ocular surface hypersensitivity disorders' dividing the different forms into IgE- and non-IgE-mediated diseases [1,8,9]. In addition, it was suggested that, accordingly to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria, allergic conjunctivitis symptoms should be considered as intermittent or persistent; mild, moderate or severe depending on their evolution and severity. These concepts have not yet been consistently used in clinical practice nationwide [9].

In the present review, we analyse the most recently published studies on the prevalence of ocular allergies, and the clinical and demographic aspects of the disease. The purpose is to highlight the impact of ocular allergies within the general population and within the allergic patients, to stimulate both allergists and ophthalmologists to properly diagnose and managed these diseases, and to raise awareness of the ocular and vision problems related to allergy.

PREVALENCE OF OCULAR ALLERGY

The epidemiology of ocular allergy is based on allergic rhinitis and rhinoconjunctivitis (ARC) studies performed by nonophthalmologists. In the ARIA document, seasonal and persistent ARC affect 3–42% and 1–18% of the population, respectively, depending on different climatic conditions and age groups [1].

In the United States, the epidemiology of ocular allergies was extrapolated by using, as source data, NHANES III [4]. Items from a questionnaire regarding ocular and nasal allergy symptoms in relation to skin prick testing were stratified by age, race, region, and sex. With a sample size of 20 010, three distinct populations with regard to ocular and nasal allergy symptoms were identified: 6% reported ocular symptoms alone, 16% reported nasal symptoms alone, 29% reported both ocular and nasal symptoms (Table 1) [4,5,10–12,13▪▪,14–18,19▪▪]; 47% of this population was asymptomatic. Up to 40% had experienced ocular symptoms at least once in their lifetime, with a peak of symptoms in the months of June and July [4]. Up to 15–20% of those with ocular symptoms reported symptoms throughout each decade of life. Comparing age groups by symptom, older patients (>50 years old) had more frequent isolated ocular symptoms, whereas younger patients had more frequent isolated nasal and combined nasal and ocular symptoms [4]. Interestingly, ocular symptoms were more common than nasal symptoms in relation to animals, household dust, and

Table 1. Epidemiology studies on allergic conjunctivitis

Study name/type	No. of subjects	Age	Location	Methods	Prevalence of allergic conjunctivitis	Reference
NHANES III (1988–1994)	20010	any	USA	Ocular and nasal symptoms/skin prick test	6.4% AC 29.7% ARC	Singh *et al.* [4]
A survey of the burden of allergic rhinitis in Europe (2006)	1482	any	Europe	Itchy/red eyes	71% of ARC	Canonica *et al.* [10]
INSTANT (2006)	4019	>18	France	Watery or itching eyes	52% of AR	Klossec *et al.* [11]
ADSP (2006)	447	>12	USA	Itchy/red eyes	64% of ARC	Schatz [12]
AIRS (2012)	2765	>5	USA	Telephone survey Itchy/red eyes	34%	Bielory *et al.* [13▪▪]
Navy soldiers (2000–2003)	19425	22.7±4.4	Italy	Itchy eyes	64% of SAR 46% of PAR	Ciprandi *et al.* [14]
AC in children with asthma, rhinitis and eczema (2002–2004)	458	5–15	Denmark	Itchy/red eyes	30%	Gradman *et al.* [15]
Alergologica-2005 study	917	<14	Spain	Ocular and nasal symptoms	ARC 44.7%	Ibanez *et al.* [16]
ISAAC Phase III (1993–1997) Aït-Khaled *et al.* [17]	670242	13–14	Global	Nasal symptoms + itchy/red eyes	ARC 14.6%	
School Eye Health Initiative (2008)	818	5–19	Pakistan	Ophthalmology examination	19.2%	Baig *et al.* [18]
ISAAC Phase I (2009)	3120	13–14	Brazil	ISAAC modified	20.7%	Geraldini *et al.* [5]
ISAAC (2005–2006)	2150	10–17	Italy	Itchy/red eyes	19.2%	Cibella *et al.* [19▪▪]

AC, allergic conjunctivitis; AR, allergic rhinitis; ARC, rhinoconjunctivitis; PAR, persistent allergic rhinitis; SAR, seasonal allergic rhinitis.

pollen allergens. It can be speculated that, in older patients, the 'isolated ocular symptoms' may be related to other ocular surface disorders such as dry eye.

An European survey found that among patients with allergic rhinitis, itchy/red eyes and watery eyes were reported by 71% and 67% of patients, respectively [10]. In a French, cross-sectional observational survey, 31% of the population-based sample suffered from allergic rhinitis and 52% of patients with allergic rhinitis described ocular symptoms, with 57% of subjects suffering from ocular symptoms for more than 5 years, mostly (92%) during the pollen season [11]. Similarly, a survey on 447 patients with allergic rhinitis revealed that 64% of patients experienced itchy/red eyes, whereas 43% reported watery eyes [12], demonstrating that ocular allergy is part of the burden associated with allergic rhinitis.

More recently, a survey conducted in the United States on 2765 people at least 5 years old with a diagnosis of allergic rhinitis or ocular allergies showed that the most common symptoms rated as 'extremely bothersome' were nasal congestion (39%), followed by red/itchy eyes (34%) [13▪▪].

On the contrary, ocular allergies have been reported to be twice as common as allergic rhinitis [20]. In particular, the prevalence of PAC seems to be underestimated by both ophthalmologists and allergists [21]. In a large cohort of navy soldiers, the comorbidity with perennial allergic rhinitis was reported in 46% of patients [14].

PREVALENCE OF OCULAR ALLERGY IN CHILDREN

The largest body of epidemiological data on prevalence of allergic symptoms has been collected from the ISAAC studies using a standardized questionnaire related to symptoms of rhinitis, eczema and asthma. The prevalence of ocular allergies is estimated by answer to the question 'in the past 12 months has this nose problem been accompanied by itchy-watery eyes?'. This question does not detect individuals who may have allergic conjunctivitis in the absence of rhinitis confirming that more specific questionnaires associated with other instruments are needed. In the Phase III ISAAC, a worldwide increase in the prevalence of ARC was observed; the variations were considerable within the test centers, but they were large among the centers

and there was no consistent regional pattern [22]. In the 5- to 15-year age group, 30% of children with either asthma, rhinitis or eczema were estimated to suffer from concomitant allergic conjunctivitis [15] (Table 1).

In a different study [16], the prevalence of ARC in children younger than 14 years was 44%, making this disease the most frequent allergic disorder in the child population consulting in allergy services in Spain. However, in the same study only 5% of children presented with conjunctivitis alone. In another 13–14-year age group involving 670 242 children across 232 centers in 97 countries, the prevalence of nose and eye symptoms was 14% [17].

The prevalence of allergic conjunctivitis among Karachi schoolchildren age 5–19 years was studied including an ophthalmological assessment with the slit lamp [18], therefore with objective criteria for diagnosis alongside the presence or history of itching. Of the 818 children included, 19% had allergic conjunctivitis, with boys more affected.

In a recent study [5] conducted in Brazil, the prevalence of ocular allergies symptoms, comorbidities, and their impact in adolescents was studied in 13- and 14-year-old children using a modified ISAAC questionnaire which included eight items on ocular symptoms. Allergic conjunctivitis diagnosis was considered when more than three episodes of ocular itching were reported in the previous 12 months. Results obtained from 3120 adolescents showed that ocular itching occurred in 51% of them. The most frequently associated symptom was tearing (74%), followed by photophobia (50%) and foreign body sensation (37%). The prevalence of allergic conjunctivitis in this large cohort was 20%, affecting more females than males. Severe interference in daily activities was reported by 30%. These data confirm that symptoms of ocular allergies are common, frequently associated to other allergic diseases, and impact the daily activities of adolescents.

A similar cross-sectional study [19▪▪] was conducted on a random sample of 2150 schoolchildren, using skin prick tests and a self-administered questionnaire on respiratory health investigating the impact of allergic rhinitis and ARC on daily activities. The prevalence of rhinitis alone was 18% and rhinitis associated with conjunctivitis 20%. Conjunctivitis was associated with a higher level of allergic sensitization and ocular symptoms increased the role of rhinitis as a risk factor for asthma and its impact on daily activities in children.

PREVALENCE OF DIFFERENT OCULAR ALLERGIC DISEASES

Ocular allergy includes different clinically distinguished diseases such as SAC, PAC, VKC, AKC, and CBC. In particular, VKC and AKC require an ophthalmological evaluation for diagnosis and a close follow-up [9]. Giant papillary conjunctivitis (GPC), a disease related to contact lenses wear and somehow similar to mild forms of VKC, is not considered any longer an allergic disorder, but included in the ocular nonallergic hypersensitivity disorders [9] and still included by ophthalmologists within the allergic conjunctivitis.

The prevalence of the different ocular allergies diseases has some variation between different geographic areas of the world not only because of genetic differences and environmental factors, but also because of the lack of standardization in the assessment of ocular symptoms [9]. We and others previously reported that there is a large population of patients with only ocular symptoms [20] and with only local tissue allergen sensitivity [23] who may have negative allergy tests. Therefore, it is quite common that patients with ocular symptoms request an ophthalmological evaluation only or before an allergy consultancy. Some of these patients may not have been included in the ARC epidemiology studies or surveys previously reviewed.

To characterize the clinical and demographic aspects of allergic conjunctivitis seen in ophthalmologic settings, we recently performed a cross-sectional study [7▪▪] surveying consecutively 3685 patients (mean age 38 ± 19 years; 55% females) with the diagnosis of ocular allergies. Subjects were enrolled by 304 ophthalmology centers across different geographic regions in Italy. A simple structured questionnaire was administered in addition to ophthalmological evaluation. Results showed that SAC was the most frequent ocular allergies form, followed by PAC, VKC, AKC, CBC and GPC (Table 2) [7▪▪,24–26]. A positive family history of allergy was reported in 43% of patients but only 40% of patients had a history of other allergic manifestations. Only 35% of patients underwent a diagnostic evaluation of allergic sensitivities with positive results in 82% of this subset. Notably, patients with comorbidities resulted positively to allergy tests in 98%. From these results, two considerations can be made: the majority of patients with ocular symptoms did not report any other associated allergic manifestations; patients with comorbidities almost always had an IgE-mediated sensitization while around 20% of patients with only ocular symptoms were negative to allergy tests. This may suggest: the diagnosis of ocular allergies was not correct in several patients; the mechanisms involved in some of the ocular allergies diseases are non-IgE-mediated; standard allergic tests do not reveal a possible local sensitization.

Interestingly, 26% of patients included in our survey reported that the current episode was the first

Table 2. Prevalence of the different ocular allergic diseases

Country	No. of patients	SAC (%)	PAC (%)	VKC (%)	AKC (%)	CBC (%)	GPC (%)
Italy [7▪▪]	3685	55	18	9	7	7	4
Japan [24]	1079	81.2	10.6	3.8	4.4		
Brazil [25]	207		10.1	38.6	38.6		
Thailand [26]	445		81.8	10.6	4.7		2.9

AKC, atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; GPC, giant papillary conjunctivitis; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; VKC, vernal keratoconjunctivitis.

occurrence of ocular allergy which may reflect indirectly an increase of prevalence of OA. Up to 68% of patients reported fewer than five episodes of conjunctivitis in the previous year. Regarding symptoms and their severity, itching was present in 90% of cases, redness in 85%, tearing in 76%. In particular, in SAC and PAC, redness (85%) and itching (92%) were the predominant signs and symptoms while keratitis was absent. In VKC, itching and redness were present in more than 90% of patients, tearing in 86%, photophobia in 80%, papillae in 75%, and keratitis in 30%. In AKC, in addition to the typical signs and symptoms of redness and itching, the eye lid skin was involved in 37% of patients, and the cornea in 38%. Considering the severity of signs and symptoms in relation to the their frequency and duration, severe itching, redness, photophobia and tearing more than four times/week and for more than 4 weeks were reported in 25% of the entire patient population, showing that a quarter of patients with ocular allergies may have a severe and persistent disease. Pollen was reported as the most frequent trigger; however, exposure to nonspecific environmental conditions, pollutants and cigarette smoke was also frequently reported.

In our Italian survey, 76% of patients had previously used one or more medications for the treatment of allergic conjunctivitis using two or more medications in 60% of cases. The most used medications were the over the counter decongestant/antihistamines, followed by corticosteroids, topical antihistamines, systemic antihistamines, mast cell stabilizers and antibiotics (Fig. 1).

This is one of the largest surveys performed at a national level that has focused specifically on ocular allergies, involving the specialist that directly evaluated eye signs and symptoms and considered a differential diagnosis. Although this is not an epidemiological study, it reflects the impact of allergic patients on the ophthalmology centers and the Italian health system, and the use patterns for treatment.

A similar cross-sectional study [3] surveying consecutively 220 patients with the diagnosis of ocular allergies observed in 16 ophthalmology outpatient departments was conducted in Portugal. Similarly to our results, the most frequent allergic eye symptoms

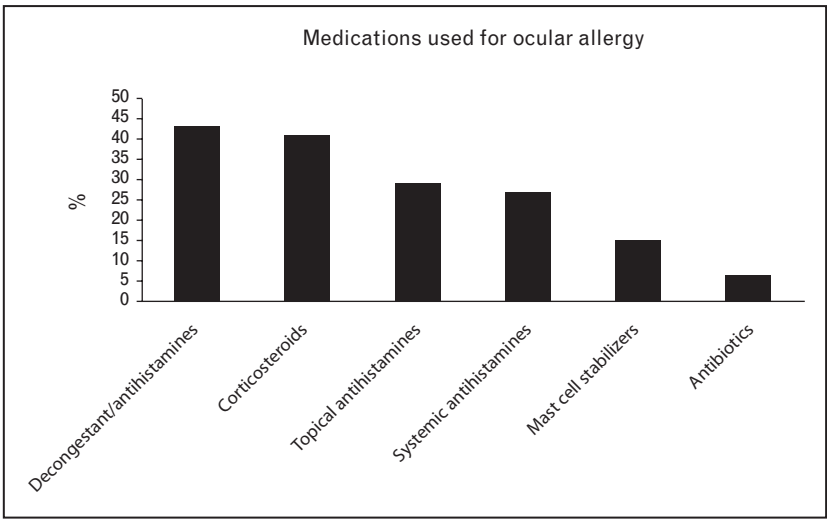

FIGURE 1. Medications used in patients affected by ocular allergic diseases. The most used medication were the over-the-counter decongestant/antihistamines (43%), followed by corticosteroids (41%), topical antihistamines (29%), systemic antihistamines (27%), mast cell stabilizers (15%) and antibiotics in (6%).

were itching (94%), tearing (84%), photophobia (67%), but also pain (51%). A quarter of this population had more than five episodes of ocular allergy in the previous year, most of them presented associated comorbidities (rhinitis 46%, asthma 15%) and 38% had a family history of allergy; 19% of these patients had an appointment with an ophthalmologist as a first action but most of them (56%) started with self-treatment measures. Also in Portugal, a previous allergy diagnostic evaluation was done only in 37% of subjects.

In a single tertiary center cohort study [24], among a total of 1079 ocular allergies cases, SAC, PAC, AKC and VKC accounted for 81.2%, 10.6%, 4.4% and 3.8%, respectively. The epidemiological data from single or multiple referral centers may mislead the frequency of single ocular diseases [25,26] (Table 2).

CONCLUSION

Although the ARIA initiative recognized conjunctivitis as a frequent comorbidity of allergic rhinitis [1], ocular symptoms are often under-diagnosed and are increasingly recognized as a distinct disorder that imposes its own burden on medical costs and patient's QoL, especially in those with persistent moderate/severe eye symptoms [27].

There are very few rigorously designed surveys that address the specific condition of ocular allergies in its various forms. The majority of the surveys have been predominantly concerned with respiratory allergic symptoms with questions added that incorporate some ocular symptoms without specific ocular examination. It must be considered that 'red, itchy and watery eyes' as a symptom complex may be present in other ocular conditions such as blepharitis or tear film dysfunctions, which are very common, but are not 'allergic' disorders.

Ophthalmology, multicenter, territorial, outpatient cohorts to study the prevalence of ocular allergies may include not only patients with all forms of SAC and PAC but also those with the more severe and complex diseases such as VKC, AKC and CBC. For sure, the mild conditions will rarely present to an ophthalmology referral hospital, therefore single, tertiary center cohorts immediately introduce a bias towards the more severe forms.

To have a better picture on the epidemiology of ocular allergies, there is a real need for the development of validated questionnaires specifically addressing ocular allergy combined with objective measure of specific sensitization and ocular allergic signs and symptoms.

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Conflicts of interest

There are no conflicts of interest.

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