



Office-based ocular procedures for the allergist

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Purpose of review

The aim of this study is to suggest principles for ocular procedures to be performed by allergists in their offices in helping their diagnosis of ocular diseases and suggest better interactions between allergists and ophthalmologists.

Recent findings

Diagnosis of ocular allergy is based on clinical history and signs and symptoms, with the support of in-vivo and in-vitro tests for the identification of the specific allergen. Unfortunately, ocular manifestations are frequently misdiagnosed and not properly managed.

Summary

A multidisciplinary allergist–ophthalmologist approach may improve early differential diagnosis and the prognosis of patients with allergic disease and conjunctivitis through shared management and earlier etiological treatment.

Keywords

allergic conjunctivitis, diagnosis of ocular allergy, sign and symptoms

INTRODUCTION

Ocular allergy is not a single disease but a collection of disorders that may affect the eyelid and conjunctiva and potentially the cornea. In fact, IgE and non-IgE-mediated hypersensitivity disorders include seasonal and perennial allergic conjunctivitis, vernal and atopic keratoconjunctivitis (VKC and AKC), and contact blepharoconjunctivitis (CBC) [1] (Table 1). Understanding the ocular allergic manifestations is very important for the allergist as some patients seen in the allergy clinic may present with unclear ocular signs and symptoms, or only ocular manifestations, which may be the only clue to the diagnosis. Other patients may present with well-documented respiratory or skin-allergic diseases and ocular manifestations may add and confirm the severity of their condition. However, very frequently patients may present with ocular symptoms that mimic an allergic manifestation but are caused by other nonallergic ocular diseases. In these cases, the ocular evaluation is essential to avoid misdiagnosis and nonappropriate topical and systemic treatments. Therefore, it is recommended a close collaboration between allergist and ophthalmologist for the early identification and management of ocular manifestations in daily clinical practice.

Most of the recommendations focus on diagnosis from the ophthalmologist's perspective and not from the allergist point of view. Recently,

ophthalmologist–allergist *diagnostic tools* have been suggested, but still, it has to be defined when and how early referral and diagnosis would be possible for these specialists [2^{••}].

In this review, we would like to suggest principles for ocular procedures to be performed by allergists in their offices in helping their diagnosis of ocular diseases and suggest better interactions between allergists and ophthalmologists.

OCULAR PRESENTATIONS

Most of the patients present to the allergist with skin or respiratory diseases and associated ocular symptoms. Conjunctival symptoms are present in 30–71% of patients with allergic rhinitis [3]. Allergic conjunctivitis alone has been estimated in 6–30% of the general population and in up to 30% of children, alone or in association with allergic rhinitis [4]. Up to 40–75% of VKC patients suffer from other

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KEY POINTS

- Allergic conjunctivitis is not a single disease.
- Allergic conjunctivitis is characterized by one or more of the following symptoms: itching, tearing (commonly with anterior rhinorrhea), and lid edema.
- The severity of ocular allergy ranges from mild and intermittent to seriously debilitating forms.
- Seasonal and perennial allergic conjunctivitis are the most common entities and do not involve the cornea.
- The cornea may be involved in VKC, AKC, or in CBC.
- An accurate clinical history and evaluation of signs and symptoms allow the diagnosis of ocular allergy and the definition of possible sensitizing antigens.
- A close collaboration between allergists and ophthalmologists is recommended.

allergic diseases [4]. AKC is present in up to 40% of atopic dermatitis patients and the comorbidity with atopic dermatitis and asthma is around 90% [5].

A wide variety of ocular surface diseases, including tear film dysfunction (dry eye), blepharitis, infections, toxic, and mechanical conjunctivitis may mimic the clinical pictures of OA [1]. A well-performed anamnesis and external ocular examination may help to understand the cause of the conjunctivitis. The medical history should cover all symptoms (itching, burning, photophobia, discharge, visual changes, pain) associated to the red eye, whether there is unilateral or bilateral eye involvement, the duration of symptoms, the

presence of allergies or systemic diseases, previous treatments, family history, environmental and occupational exposures, seasonal exacerbations, the use of contact lenses, and any type of ocular medication and surgery. Unfortunately, there is no specific clinical and laboratory evaluation suitable for the diagnosis of OA even though clinical history, the presence of itch, skin prick test (SPT), and the identification of serum-specific IgE are the fundamental for the diagnosis [6]. Recognizing *signs and symptoms* and their severity is important for the allergist for taking the decision to refer or not to the ophthalmologist.

Visual disturbance

When visual disturbance is present, if mild and caused by symptoms such as itching and tearing, the ophthalmological evaluation may not be immediate even though always recommended. If visual disturbance is associated with foreign body sensation, photophobia, mucus discharge, eyelid pseudo-ptosis, and, especially, pain, referral to ophthalmology should be recommended as soon as possible. It is not necessary for the allergist to perform visual acuity tests; however, it is strongly recommended to investigate if a patient with and without ocular symptoms complains of vision disturbance also in view of potential side-effects of treatments.

Red eye

One of the most common ophthalmic manifestations is a red eye. The 'red eye' is not a diagnosis; it is caused by reactive dilation of conjunctival blood

Table 1. Clinical features of major ocular allergy diseases (adapted from [2**])

	SAC	PAC	VKC	AKC	CBC
Presentation	Intermittent	Persistent	Persistent ± intermittent exacerbations	Chronic	Chronic ± intermittent exacerbations
Allergic mechanism	IgE mediated	IgE mediated	IgE and non-IgE-mediated	IgE and non-IgE mediated	Non-IgE mediated
Background	Atopic	Atopic	Childhood ± atopic	Adult atopic	Nonatopic
Eyelids	Not involved	±Palpebral edema	Eyelid edema	Eczema + meibomitis blepharitis	Erythema, eczema
Conjunctiva	Follicles and/or papillae	Follicles and/or papillae	Giant papillae	Papillae ± fibrosis	±Hyperemia Follicles
Limbus	Not involved	Not involved	±Thickened + Tranta's dots	±Thickened ± Tranta's dots	Not involved
Cornea	Not involved	Not involved	SPK ± ulcer ± vernal plaque	SPK Ulcer, plaque, opacities, neovascularization	Not involved

AKC, Atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; NA, not affected; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; SPK, superficial punctate keratitis; VKC, vernal keratoconjunctivitis.

vessels and is one of the most consistent signs of ocular response to pathologic stimuli [7]. Ocular hyperemia or conjunctival redness can be a sign of several and very different conjunctivitis disorders (infectious, allergic, iatrogenic, mechanical), blepharitis, traumatic abrasions, and dry-eye disease, just to mention the most frequent ones [1,2²²].

Ocular *redness* in ocular allergy most frequently presents with a bilateral, diffuse location. Conversely, localized hyperemia is suggestive of subconjunctival hemorrhage or episcleritis. Redness mostly localized to the exposed conjunctival area, but absent in the area protected by the eyelids are suggestive for a dry-eye disease. Unilateral red eye is not a typical sign of allergy even though asymmetrical forms are possible. In viral conjunctivitis, but in general in conjunctival infections, the symptoms are often unilateral at onset and become bilateral after 1 or 2 days.

Hyperemia maybe scored using photographic scales such as Mac Monnies to minimize subjective observer variability.

Itching and tearing

Itchy and tearing or 'watery eyes' are common symptoms of ocular allergy. In particular, itching is the hallmark subjective symptom of OA. It indicates the release of histamine from conjunctival mast cells and the activation of H1 receptors on nerve endings [1]. However, itching is present in patients affected by blepharitis, especially if related to eyelash infestation, and sometimes by dry-eye patients.

Tearing is a nonspecific symptom consequence of lacrimal glands response-reflex to several stimuli including conjunctival and nasal sensory nerve endings. Tearing in response to cold is a typical response of thermal receptors, which may be exaggerated in patients with tear film dysfunction.

Continuous unilateral or bilateral tearing (epiphora) associated with persistent conjunctivitis is suggestive of punctal occlusion in toxic conjunctivitis. Continuous unilateral tearing with or without conjunctival redness is suggestive for a lower obstruction of the lacrimal drainage system. In these cases, a digital pressure in the area of the lacrimal sac induces a mucopurulent discharge coming from the lacrimal (usually inferior) puncta.

In case of mucopurulent or purulent discharge, infectious conjunctivitis should be suspected. Be aware that itching, sticky mucous discharge and tearing are significant for a diagnosis of VKC and AKC.

Photophobia and pain

Photophobia is a nonspecific symptom and refers as an experience of discomfort or pain to the eyes

because of light exposure and frequently associated to the corneal involvement in OA. Pain is not a typical symptom of OA but indicates a corneal involvement in VKC and AKC. Specifically, children with VKC with a new onset of pain or photophobia should be strongly suspected as having shield ulcers or vernal plaques in the upper cornea and referred to an ophthalmologist.

IN OFFICE OCULAR EXAMINATION BY ALLERGIST

Allergists do not use the slit lamp to examine the ocular surface; however, it is always a good practice, in case of eye symptoms, to observe, by daylight or direct light, not only the face, but particularly the lids, the eyelid margin, the palpebral, and bulbar conjunctiva (Table 2).

Eyelid

The *eyelid skin* should be carefully observed for the presence of any type of dermatitis. Dermal involvement of the eyelids includes hyperemia, swelling, and excoriation. Lid eczema is a specific marker for AKC or contact dermatitis.

Blepharitis is a common inflammatory infectious or noninfectious condition of the *eyelid margin* and one of the major causes for discomfort and ocular surface disease. The most common inflammatory phenomena of the lid margin associated glands induce a typical clinical entity called hordeolum or chalazion. Hordeolum is an infectious process, whereas chalazion is purely inflammatory manifesting as a lipogranuloma as the results from obstruction of the meibomian gland orifice with thicker lipid secretion.

Blepharitis is classified as anterior, posterior, or mixed. Anterior blepharitis involves the lash-bearing region of the lid margin and it is often associated with staphylococcal infection. Posterior blepharitis affects the meibomian glands (meibomian gland dysfunction) and the posterior lid margin.

Both anterior and posterior blepharitis can be associated with seborrheic dermatitis. Scales and their debris shed from the scalp, eyebrows, and from the face induce irritation of the ocular surface and can exacerbate a preexisting blepharitis.

Posterior blepharitis is often associated with acne rosacea. Facial signs of rosacea are more evident in the flush areas. However, often the skin signs are subtle and patients do not seek dermatology consultation.

Because of typical symptoms of blepharitis are foreign body sensation, itchy eyelids, and epiphora, allergic conjunctivitis should be considered as

Table 2. Differential diagnosis of allergic from nonallergic conjunctivitis

	Allergy	Dry eye	Blepharitis	Toxic	Mechanical	Infections
History	Typical	Significant	–	±	–	–
Symptoms	Itching Tearing	Burning Foreign body sensation Discomfort Pain	Burning Itching Discomfort	Discomfort Burning	Discomfort Pain	Burning Discomfort Stickiness
Signs	Redness Lid swelling Papillae Eczema Limbal inflammation	Decreased BUT Decreased tear meniscus Abnormal Schirmer's test SPK	Abnormal lid margin Collarettes on lashes Meibomitis Hordeolum Chalazion	Redness Follicles	Redness SPK	Intense redness Secretion Tearing Swelling
Discharge	Serous/Mucus	Mucus	Serous/Mucus	Serous	Mucus	Mucopurulent/ Purulent
Cytology	Eosinophils/ Neutrophils/ Lymphocytes	Altered epithelial cells/ Lymphocytes	Neutrophils	Neutrophils/Altered epithelial cells/ Lymphocytes	Neutrophils	Neutrophils

BUT, Break-up time; SPK, superficial punctate keratitis.

differential diagnosis. However, both blepharitis and allergic conjunctivitis may coexist.

Conjunctiva

To evaluate the superior palpebral conjunctiva, the lid eversion is necessary. The papillae or giant papillae (>1 mm diameter) form raised elevations, especially in the upper tarsal conjunctiva mimicking a cobblestone paving. They are composed of a core of capillaries covered by hypertrophic epithelium. Even though papillary response of the tissue is not specific only of allergy, they are frequently present in chronic allergy, particularly in VKC and AKC. A diffuse thickness of the upper tarsal conjunctiva may also be present but not easily seen without the slit lamp. Papillae must be distinguished from follicles, which appear as diffuse small pink-grayish little bumps at the tarsal conjunctiva and the lower fornix. They are also a nonspecific conjunctival response to chronic irritation, either mechanical, chemical, or microbial. In children, however, they are normally observed in large numbers in the lower fornix conjunctiva. The structure of follicles is a dense infiltration of lymphocytes in the subepithelial tissue.

Granulomas appear as nodular or pedunculated elevations in chronic inflammations. Pyogenic, foreign bodies, sarcoidosis, and infections such as tuberculosis, leprosy, and tularemia are characteristically associated with conjunctival granulomata.

Scarring or cicatrization of the conjunctiva is a feature of several chronic inflammatory (noninfectious) conditions such as ocular cicatricial pemphigoid, Stevens Johnson Syndrome, and in linear IgA conjunctivitis or after severe chemical

conjunctivitis, burns, or in trachomatous chronic infectious/inflammatory reaction in endemic areas. Contraction and shrinkage of the conjunctiva may lead to symblepharon, ankyloblepharon, lid malposition, and trichiasis. All these cases should be referred to the ophthalmologist for appropriate testing and diagnosis.

A conjunctival sign relatively specific of VKC/AKC is the presence of Trantas dots (white/gray inflammatory infiltrates at the limbus) that may be visualized by macroscopic examination. They appear as grayish thickness between the conjunctiva and the cornea surmounted or not by little white dots. They may be confused with limbal and corneal involvement in the course of posterior blepharo-keratoconjunctivitis or ocular rosacea, especially in children.

Cornea

Corneal involvement, present only in VKC and AKC, is a marker of severity. Superficial corneal epitheliopathy, neovascularization, and scars are nonspecific, whereas shield ulcers and plaques are much more suggestive of severe VKC and AKC. These signs are not easily seen without the slit lamp and corneal staining; however, in case of any irregular corneal reflex to the light or suspected opacification of the cornea, the patient should be referred to the ophthalmologist as soon as possible. If the patient is a contact lens user, any suspected corneal involvement should be referred to as an emergency.

ALLERGY TESTING

Even though the relationship between allergen sensitivity and allergen exposure is sometimes easy to

Table 3. Local tests for ocular allergy

Test	Indication	Advantages	Disadvantages
Conjunctival provocation with allergens	Positive clinical history of allergy but prick test/IgE negative Define the most important allergen in patients with several positive skin tests To evaluate desensitization	Confirm conjunctival responsiveness	Few allergens available Expensive Time consuming Rare systemic side-effects
Cytology	To evaluate the quality and quantity of inflammation	Presence of eosinophils indicative of allergy	Absence of eosinophils does not exclude allergy
Tear IgE	Suspected sensitization and negative allergy tests	Local IgE production	Low-volume samples Not practical Not standardized

assess, particularly in seasonal forms, allergen identification is the common allergist's practice. SPTs are unanimously considered the gold standard and the first-line approach for identifying IgE-mediated sensitization, also for the diagnosis of OA [2²²,8]. Biological assays such as specific IgE measurements are only used in specific cases. When medical history suggests contact allergy, non-IgE-mediated test are relevant, especially in cases of CBC [1] and patch tests explore the reactivity to preservatives or additives in eye drops, cosmetics, or professional allergens that may be involved [9].

LOCAL TEST THAT CAN BE PERFORMED BY THE ALLERGIST

Local tests can be performed either to assess the specific or nonspecific reactivity of the ocular surface to allergens or potential irritants, or to assess the type and the severity of the inflammation or the damage induced on the tissues (Table 3).

The *conjunctival allergen provocation test* (CAPT) evaluates the inflammatory response of the conjunctiva to topical allergen application [1,10,11²²] triggering the same signs (redness, chemosis, and lid swelling) and symptoms (itching and tearing) as those of a natural allergen exposure. Even though the test may be useful in the daily clinical practice, it requires an ophthalmic examination to rule out any ocular inflammation before performing the test [11²²]. A standardized protocol with a definition of inclusion and exclusion criteria has been recently proposed. Itching and redness are still the main criteria to achieve a positive response [12]; however, a total ocular symptom score (range 0–13) is recommended with a considered positive response when it reaches 5 [11²²]. The CAPT should be considered when multiple sensitizations are suspected or when medical history suggests an allergen sensitization but SPT are negative.

To quantify and qualify the type of inflammation, *cytological tests* are easy to be performed but not commonly used. Tear cytology requires few microliters of tears obtained by glass capillary tubes. Conjunctival scrapings are performed using a spatula or a brush. Precolored slides or rapid dyes can be used for a quick evaluation. Impression cytology refers to the application of a cellulose acetate filter on the ocular surface to remove the superficial epithelial layers [13]. Conjunctival biopsy (performed under topical anesthesia by the ophthalmologist) is required when a neoplastic disease or autoimmune disease is suspected. Samples can be used for immunostaining, flow cytometry, RNA, or DNA extraction, all depending on the number of cells collected.

In ocular allergy, neutrophils, eosinophils, and lymphocytes can be found in tears with different cellular profiles in acute and chronic phases [14,15]. The presence of eosinophils is highly significant for an allergic inflammation.

Corneal and conjunctival staining could theoretically be performed also by nonophthalmologists inserting a wetted fluorescein strip in the inferior conjunctival fornix, and using the blue cobalt light plus-minus yellow filter to observe the corneal surface. The test is positive if even small or punctate a yellow-green stain remains on the corneal surface. However, it is recommended to consult the ophthalmologists in any suspect of corneal involvement.

Table 4. When ophthalmologist should refer to allergist

Patients suffering from recurrent or persistent episodes of conjunctivitis with itchy eye and no allergy test performed
Patients suffering from acute or recurrent episodes of conjunctivitis and family or personal history of allergy
Patients suffering from recurrent eyelid edema
Patients suffering from eyelid eczema/eyelid dermatitis

Table 5. When allergist should refer to ophthalmologist

Patients suffering from
Acute red eye
Ocular pain
Photophobia
All patients with blurred vision and/or reduction in visual acuity
All patients with history of ocular inflammation
Patients with lid or lid margin hyperemia
Patients with diagnosis of ocular allergy but negative allergy tests to perform conjunctival provocation test
Patients with suspected or diagnosed ocular allergy but negative response to treatments
Patients with persistent use of corticosteroids
Children diagnosed with VKC
Patients diagnosed with AKC

VKC, Vernal keratoconjunctivitis; AKC, atopic keratoconjunctivitis.

The *Schirmer test* could theoretically be performed by nonophthalmologists inserting the nitrocellulose Schirmer strip into the inferior conjunctival fornix and measuring the length of wetted strip within 5 min. Values below 10 mm reflect a reduced production of tears [16].

Patients with high total tear IgE have a high probability of allergic sensitization; however, measurement of tear allergen-specific IgE should be a more specific diagnostic marker of allergic sensitization [17,18]. Increased tear levels of tryptase, histamine, and eosinophil cationic protein have been considered biomarkers of OA [17,19–21]; however, excluding assays for total IgE and MMP-9 specifically designed for tears, no local tests have been standardized for clinical use.

CONCLUSION

Cooperation between allergists and ophthalmologists is essential for a better understanding and evaluation of allergic disease activity and/or related conjunctivitis. This leads to earlier diagnosis, better management and the achievement of the best outcomes for the patient.

Patients with ocular symptoms and allergic diseases should be referred to an ophthalmologist to categorize ocular disease (Tables 4 and 5).

A multidisciplinary allergist–ophthalmologist approach may improve early differential diagnosis and the prognosis of patients with allergic disease and conjunctivitis through shared management and earlier etiological treatment, designed to establish the optimal treatment strategy and to prevent potential complications.

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There are no conflicts of interest.

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- of special interest
- of outstanding interest

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