Mechanisms and Management of Allergic Inflammation in the Eye

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1. Mechanisms of ocular allergy

Three major mechanisms have been reported to be involved in causing diseases included under the umbrella term of allergic conjunctivitis (or ocular allergy of the external eye surface):a) the typical Type I hypersensitivity reaction, where the IgE-mediated release of mast cell and basophil mediators is responsible for symptoms (redness, chemosis, excess tearing and mucus, itching and burning), as a result of vasodilation, exudation, stimulation of glands and nerve endings; b) eosinophilic

inflammation, both dependent and independent by a late-phase IgE mediated reaction; c) conjunctival hyperreactivity, often related to the eosinophilic inflammation but also possibly due to an abnormal tissue response to non-specific stimuli (cold air, pollutants, excess lighting,etc.). These hallmarks of allergic eye disease, although often related to each other, depend on different genetic and environmental factors and may help to identify different phenotypes of ocular allergy with different clinical presentation, severity and treatment.

2. Classification of ocular allergic diseases: SAC, PAC, AKC, VKC, GPC

Seasonal allergic conjunctivitis (SAC) is the most common form of allergy and is associated with sensitization and exposure to environmental allergens, particularly pollen. The perennial form (PAC) usually involves sensitization to mites or to multiple antigens. Both forms are characterized by an onset in childhood or early adulthood; patients present with ocular itching, conjunctival hyperemia, and at times lid and conjunctival edema of varying severity, mild serous or serous-mucous secretions, and/or slight papillary or follicular hypertrophy of the conjunctiva. This symptomatology is chronic in PAC. The only diagnostic factor is the presence of itching: if the patient does not complain of conjunctival or peri-ocular itching, it is almost surely not allergic conjunctivitis.
Vernal keratoconjunctivitis (VKC) is a severe ocular allergic disease that occurs predominately in children. VKC is characterized by intense ocular symptomatology: itching, photophobia, foreign body sensation, conjunctival hyperemia, and mucous secretion, typically accompanied by giant papillae on the upper tarsal conjunctiva, or, in the limbal form, by limbal infiltrates or nodules, or both signs in the mixed form. Corneal involvement is common, characterized by punctate keratitis or sterile corneal ulcers, the result of epitheliotoxic proteins and enzymes released by activated eosinophils. VKC is an IgE- and Th2-mediated disease in which only 50% of patients present a clear allergic sensitization.
Atopic keratoconjunctivitis (AKC) is typical of adult patients, although it can be observed in children with atopic dermatitis. In addition to the cutaneous involvement, AKC can be associated with rhinitis, seasonal rhinoconjunctivitis and asthma. AKC can be a very severe disease due to its prolonged chronicity and exacerbations during the winter months. Frequently the cornea is involved as diffuse superficial epitheliopathy and/or ulcers that result in scarring, irregular astigmatism, or corneal pannus, all of which can compromise visual function. Giant papillary conjunctivitis (GPC) is a non-IgE-mediated inflammation induced most frequently by the use of contact lenses. All types of contact lenses can trigger GPC, as can the use of ocular prostheses, the presence of corneo-conjunctival sutures or protruding scleral buckling. The upper tarsal conjunctiva is subjected to repetitive or constant micro-trauma generated by a conjunctival 'foreign body'; this phenomenon is then complicated by an immune reaction against a protein or residue deposited on the lens.

Table 1. Ocular allergic diseases

Condition	Prevalence	Severity	Causes	Sign/Symptoms
SAC/PAC	Most frequent ocular allergic	Mild/ moderate	Genetic predisposition Associated with rhinitis	Itching Redness

	disease. 10-15% of population		Seasonal allergens (pollens, molds, chemicals) Perennial allergens (dust, animal dander, foods, chemicals	Tearing Watery discharge Chemosis Lid swelling
VKC	Rare Ages 3-20 Under 14 M>F In adults M=F	Severe	Genetic predisposition? Associated with atopic disorders (50%) Th2 up-regulation Non-specific eosinophil activation	Extreme itching Ropy mucous discharge Cobblestone papillae Trantas' dots Keratitis/ulcer Conjunctival eosinophilia
AKC	Rare 2nd to 5th decade of life M>F	Severe/ Sight threatening	Genetic predisposition Associated with atopic dermatis Environmental allergens: food, dust, pollens, animal dander, chemicals	Itching Burning Tearing Photophobia Chronic redness Blepharitis Periocular eczema Mucous discharge Keratitis/ulcer Conjunctival and corneal scarring cataract
GPC	Iatrogenic 2nd to 5th decade	Mild	Trauma induced by contact lens edge, ocular prosthesis, exposed sutures, aggravated by concomitant allergy	Lens intolerance Blurred vision Foreign body sensation Abnormal thickening of conjunctiva Giant papillae
Contact blepharitis/ dermatitis	Not known	Moderate	Contact delayed type hypersensitivity Exogenous haptens (cosmetics, metals, chemicals) Topical preparation (drugs, preservatives)	Eyelid eczema Eyelid itching Conjunctival redness Punctate keratitis

3. Differential diagnosis

At times, pseudoallergic forms, with clinical manifestations similar to allergy but with a non-allergic equivocal pathogenesis, are difficult to distinguish from allergic forms, with their precisely defined pathogenic mechanisms. Several clinical forms may mimic the clinical pictures of ocular allergy (Table2), including tear film dysfunction, subacute and chronic infections, toxic and mechanical conjunctivitis.

Table 2. Differential diagnosis of chronic allergic disease from:

Dry Eye
Blepharitis
Uncorrected visual defects
Chlamydia
'Medicamentosa' (drug-induced conjunctivitis)
Viral Conjunctivitis
Contact lenses intolerance
Non-specific hypereactivity
Hyperuricemia
Toxic conjunctivitis
Mechanichal conjunctivitis

11. Management of ocular allergy

The most common diseases, SAC and PAC, are classic IgE-mediated disorders, in which the therapeutic focus is mostly confined to the suppression of mast cells, their degranulation and the effects of histamine and other mast cell derived mediators. Conversely, severe chronic disorders such as VKC and AKC are both IgE- and T cell-mediated, leading to a chronic inflammation where eosinophil, lymphocyte and structural cell activation characterizes the conjunctival allergic reaction. In these cases, stabilization of mast cells and histamine or other mediator receptor antagonists are frequently insufficient for control of conjunctival inflammation.

Currently available topical drugs for allergic conjunctivitis belong to different pharmacological classes (Table 3): vasoconstrictors, antihistamines, mast cell stabilizers, 'dual-acting' agents (with antihistaminic and mast cell stabilizing properties), non-steroidal anti-inflammatory agents. Corticosteroids are usually not needed in SAC and PAC, and may have potential important side effects if used for periods longer than occasional short cycles to control severe recurrences, if any. In SAC and PAC associated with allergic rhinitis –which represent the majority of cases- topical nasal steroids (and particularly new molecules with low systemic bioavailability, such as mometasone furoate and fluticasone furoate) have been shown to control the nasal-ocular reflex component of eye symptoms without increasing the risk of cataracts or of an increased ocular pressure.

Avoidance of the offending allergens, when practically feasible, should always be the primary therapeutic measure. Non-pharmacologic treatments include tear substitutes and lid hygiene to wash out allergens and mediators from the ocular surface combined with cold compresses for decongestion. Olopatadine, ketotifen, epinastine

and azelastine, which have antihistamine, mast cell stabilizing and additional anti-inflammatory properties (called “double or multiple action”) are presently available and show evident benefits. Mast cell stabilizers (cromoglycate derivatives) or antihistamines may be used in mild forms of the disease.

Decongestant/vasoconstrictors have little place in the pharmacological treatment of SAC and PAC except for the immediate removal of injection for cosmetic reasons, but do have an adverse effect profile locally (glaucoma) and systemically (hypertension).

Corticosteroid formulations (including the so called “soft steroids”) should be reserved for and carefully used in the severe cases which are refractive to other types of medications.

The use of non steroidal anti inflammatory drugs (NSAIDS) can be considered, in some cases, for a short period of time, but have had limited effect on ocular pruritus.

Systemic antihistamines should be used only in patients with concomitant major non-ocular allergic manifestations.

Treatment of VKC requires a multiple approach attitude that includes conservative measures and the use of drugs. Patients and parents should be made aware of the long duration of disease, the chronic evolution and its possible complications. The potential benefits of frequent hand and face washing along with avoiding eye rubbing have to be emphasized. Exposure to non-specific triggering factors such as sun, wind and salt water should be avoided. The use of sunglasses, hats with visors and swimming goggles are recommended.
The use of drugs should be well planned in patients with a history of VKC. Mast cell stabilizers including disodium cromoglycate, nedocromil, spaglumic acid, lodoxamide and topical antihistamines can be initially used and continued at a decreased frequency if effective. Newer topical formulations with combined mast cell stabilizing properties and histamine receptor antagonist, as olopatadine and ketotifen, may be more efficient. Non-steroidal anti-inflammatory drugs such as ketorolac, diclofenac and pranoprofen may be considered for steroid-sparing. These drugs however, should be used for a limited period of time only. Oral aspirin at doses of 0.5-1 gram/day may be beneficial.
Moderate to severe VKC may require repeated topical steroid treatment to down-regulate conjunctival inflammation. “Soft corticosteroids” such as clobetasone, desonide, fluorometholone, loteprednol and rimexolone may be considered as first corticosteroid preparations and used carefully. Doses are chosen based on the inflammatory state. Instillation frequency of 4 times/day for 10-15 days is recommended. The “harder” corticosteroids formulations of Prednisolone, Dexamethasone or Betamethasone have to be used as a second line and as a last resort for the management of the most severe cases.
Cyclosporine A (CsA) 1% or 2% emulsion in castor or olive oil is the first choice for treating severe VKC and can serve as a good alternative to steroids.
Systemic treatment with oral antihistamines or anti-leukotrienes can reduce the severity of ocular flare-up of disease manifestations in patients with additional non ocular allergies.
Severe cases not responding to topical therapy may require treatment with systemic corticosteroids (prednisone 1mg/kg a day) for a short period of time.
Corneal complications have to be carefully monitored and anti-inflammatory therapy adjusted accordingly. Secondary microbial infection can be prevented by prescription of antibiotics for a period of one week.

Surgical removal of corneal plaques is recommended to alleviate severe symptoms and to allow for corneal re-epithelization. Giant papillae excision with or without combined cryotherapy may be indicated in cases of mechanical pseudoptosis or the presence of coarse giant papillae and continuous active disease.
More invasive procedures such as oral mucosal grafting should be avoided. Amniotic membrane transplantation, on the other hand, may be considered to promote healing. If a systemic hypersensitivity to identified allergens exists, specific immunotherapy may be considered.

The overall management of AKC involves a multidisciplinary approach. Identification of allergens by skin or blood testing is important for preventive measures. Cold compresses and regular lubrication may provide symptomatic relief. Tear substitutes help remove and reduce the effects of allergens and the release of mediators reducing the potential for corneal involvement. Lid hygiene is essential. It prevents infectious blepharitis, improves meibomian gland function and tear-film quality. Prolonged use of topical anti-allergic drugs and mast cell stabilizers may be required. Topical antihistamines may be useful for the relief of itching, redness and mucous discharge.
Topical corticosteroids are effective, but should be used only when other topical treatments are not providing sufficient benefits. Brief periods of intensive topical corticosteroid therapy are often necessary to control the local inflammation in severe cases. Topical cyclosporine may improve the signs and symptoms in steroid-dependent patients, thus reducing the need for corticosteroids to control the ocular surface inflammation.
Systemic antihistamines are often used to reduce itching and control widespread inflammation in patients with active skin involvement. Systemic corticosteroids may be necessary in severe cases. Systemic cyclosporine may be an alternative to systemic corticosteroids for the relief of severe AKC.

Prevention is the most important management step in GPC. In patients with contact lenses GPC, discontinuation of lens wear may be necessary. Restarting lens wear with a different type or design may be tried. Mild GPC symptoms may be alleviated by mast cell stabilizers or antihistamine agents. Tear substitutes can be used to minimize conjunctival trauma.

Table 4. Topical Ocular Allergy Medications

Class	Drug	Indication	Comments
Vasoconstrictor/ Antihistamine Combinations	Naphazoline/ Pheniramine	- Rapid onset of action	- Short duration of action - Tachyphylaxis - Mydriasis - Ocular irritation - Hypersensitivity - Hypertension - Potential for inappropriate patient use
Antihistamines	Levocabastine Emedastine	- Rapid onset of action - Relief of itching - Relief of signs and symptoms of SAC	- Short duration of action
Mast cell stabilizers	Cromolyn Nedocromil Lodoxamide NAAGA Pemirolast	- Relief of signs and symptoms	- Long-term usage - Slow onset of action - Prophylactic dosing

Antihistamine/ mast cell stabilizers (dual-acting)	Azelastine Epinastine Ketotifen Olopatadine	- Treatment of signs and symptoms of SAC - Rapid onset of action - Long duration of action - Excellent comfort	- Bitter taste (azelastine) - Non reported serious side effects
Corticosteroids	Loteprednol Fluormetho-lone dexamethason e	- Treatment of allergic inflammation - Use in severe forms of allergies	- Risk for long-term side effects - No mast cell stabilization - Potential for inappropriate patient use - Requires close monitoring

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