

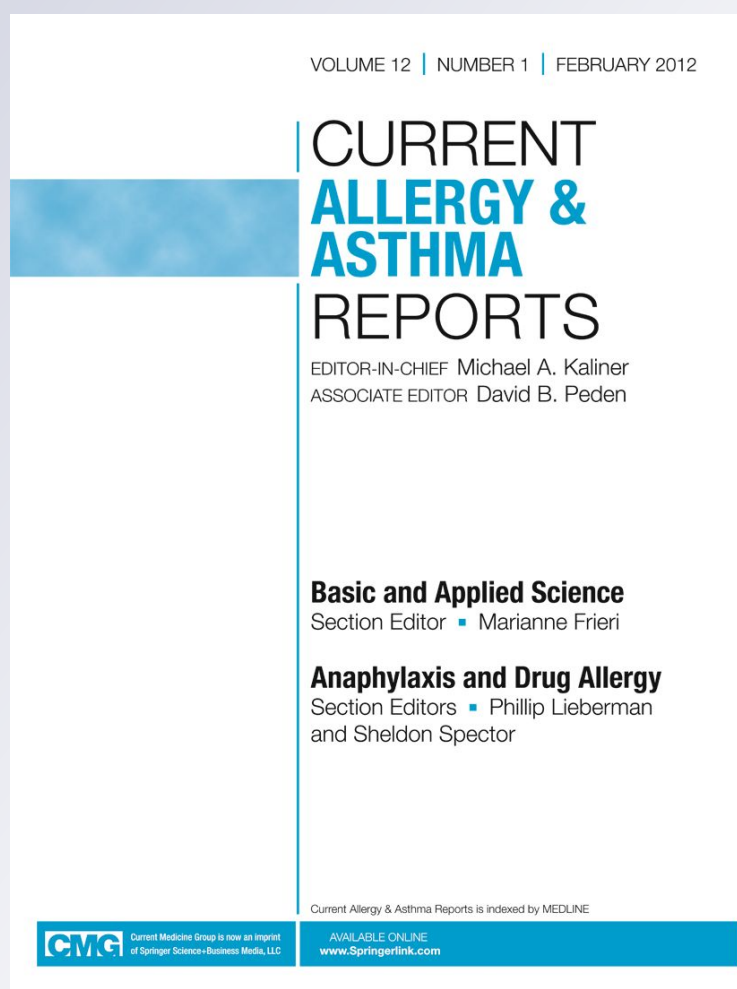
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Diagnostics and New Developments in the Treatment of Ocular Allergies

Osmo Kari · K. Matti Saari

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Abstract About 30% of people suffer from allergic symptoms, and 40% to 80% of them have eye symptoms. Atopic conjunctivitis is divided into seasonal allergic conjunctivitis and perennial allergic conjunctivitis. The treatment of seasonal allergic conjunctivitis is simple: antihistamines, anti-inflammatory agents, or cromoglycate. Perennial allergic conjunctivitis needs longer therapy with mast cell stabilizers and sometimes local steroids. Atopic keratoconjunctivitis requires long-term treatment of the lid eczema and keratoconjunctivitis. Vernal keratoconjunctivitis mainly affects children and young people. It commonly calms down after puberty. It demands intensive therapy, often for many years, to avoid serious complicating corneal ulcers. Giant papillary conjunctivitis is a foreign body reaction in contact lens users or patients with sutures following ocular surgery. Nonallergic eosinophilic conjunctivitis affects mostly middle-aged and older women with eosinophilic conjunctivitis and dry eye. Contact allergic blepharoconjunctivitis is often caused by cosmetics and eye medication. Work-related ocular allergies should be considered as a cause of resistant ocular symptoms in workplaces.

Keywords Allergic conjunctivitis · Seasonal · Perennial · Allergic blepharitis · Atopic keratoconjunctivitis · Contact allergic blepharoconjunctivitis · Dry eye · Eosinophils · Non-allergic eosinophilic conjunctivitis · Treatment · Diagnosis · Vernal keratoconjunctivitis · Ocular allergy · Work-related ocular allergy

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Introduction

Approximately one third of the population worldwide is affected by some form of allergic disease, and ocular allergic symptoms are estimated to be present in 40% to 80% of the affected individuals [1, 2]. The prevalence is greater in Western countries than in Asia or Africa [3]. The costs of allergic conjunctivitis in the form of medication and absence from work are remarkable (eg, in the United States from allergic rhinoconjunctivitis, ~5.9 billion dollars) [4].

Allergic eye inflammation is a localized allergic condition that is frequently associated with rhinitis and occasionally with asthma but often observed as the only or prevalent allergic manifestation. The symptoms and signs can manifest alone in the eyelids as atopic blepharitis or contact blepharitis. Lid symptoms may occur together with conjunctival symptoms. However, allergic conjunctivitis is the most common manifestation alone or together with lid symptoms. The eye is red and itchy, and there is lacrimation and slight discharge.

Children may have allergic eye symptoms at younger than age 2 years. Young children typically cannot explain their symptoms. Rubbing of the eyes, light sensitivity, redness, lacrimation, and lid or conjunctival edema may indicate ocular allergy.

Visual acuity is usually normal. However, in some severe forms of allergic conjunctivitis, the cornea may be affected by atopic keratoconjunctivitis and vernal keratoconjunctivitis (VKC) [5].

Allergic eye symptoms are mostly connected to atopy. In the age group younger than 14 years, 44.7% with atopy had allergic rhinitis, and 61% of them had conjunctivitis, but only 5% presented with conjunctivitis alone [6•]. Chronic allergic eye disease may occur as VKC. However, the chronic allergic eye diseases should be differentiated from nonallergic eosinophilic conjunctivitis (NAEC) [7, 8•].

Therapy for an allergic eye disease should be started early, be sufficiently intensive, and should be continued

for a long enough period of time to prevent its transformation into a chronic disease. The main goal of treatment is to calm the inflammation early and to prevent complications that can threaten vision and cause dry eye. In some cases of atopic dermatitis and also of atopic blepharoconjunctivitis (ABC), the active therapy can prevent the development of allergic rhinosinusitis or even asthma [9••].

Etiology

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are caused by IgE-mediated environmental airborne allergens such as grass and tree pollens, mites, molds, and animal dander. A minority of allergic eye diseases are of the cell-mediated type, which may manifest solely as blepharitis or blepharoconjunctivitis. The usual causes of the cell-mediated type are cosmetics, nickel, or topical eye medication.

The exact incidences of work-related allergic eye diseases are lacking. A wide spectrum of organic and inorganic materials can cause allergies. In most cases, they are connected to asthma, rhinitis, or dermatitis. Some workers may have only occupational eye symptoms.

Pathomechanisms

The immediate types, SAC and PAC, are IgE-mediated diseases in which T lymphocytes are involved, especially in chronic forms [10]. The peaks of ocular signs and symptoms are related to histamine release from specifically activated mast cells after allergen exposure [11]. Mast cells contain histamine and tryptase. Immediately begins *de novo* synthesis of other mediators, such as leukotrienes and prostaglandins. Mast cells are not only activated in acute forms but also in chronic forms. Histamine and other mediators are responsible for itching [12, 13•]. Activation of vascular endothelial cells and fibroblasts by a single mast cell degranulation can mount a cascade of proinflammatory events that amplify the clinical inflammation [1, 2]. The influence of different mediators is strongest after 5 to 15 min. The chemotactic factors released by mast cells are responsible for accumulation of eosinophils and neutrophils at the site of allergic inflammation. Eosinophils contain granules in which preformed cytokines are rapidly secreted, depending on the stimuli (Fig. 1) [14••].

Conjunctiva is a common site of allergic reactions. It is well-vascularized tissue that contains large numbers of dendritic/Langerhans cells and macrophages [10]. Lymphocytes—both T and B cells—are important cells in allergic reactions. These are divided into CD4⁺ T-helper (Th) cells and CD8⁺ killer T cells. CD4⁺ Th cells are important in the regulation of allergic

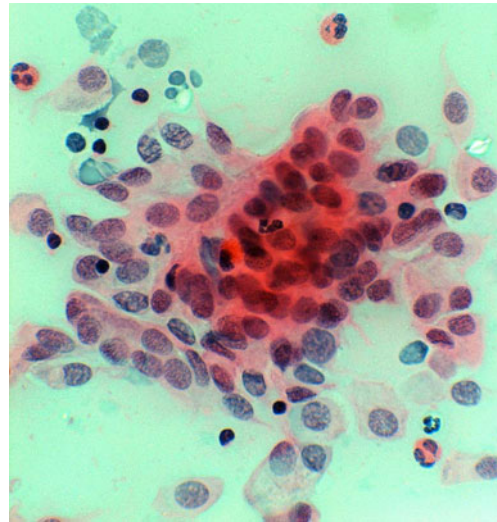


Fig. 1 Conjunctival brush cytology

reactions. These cells can be further divided into Th1 and Th2 cells. Th1 cells are activated in the classic delayed-type hypersensitivity reaction and in some autoimmune diseases. The activation of Th2 cells leads to the anaphylactic type of hypersensitivity reaction. The subclasses of Th cells (Th1, Th2) require different kinds of cytokines to be activated [13•]. T cells start and regulate the immune response. Interleukin (IL)-4 has an essential role in differentiating Th cells into Th2 cells.

The activated Th cells regulate the maturation of B lymphocytes to mature, antibody-producing B cells and plasma cells. The maturation of B lymphocytes into IgE-producing cells requires, in addition to IL-4, direct contact between pre-B and Th cells.

The prerequisite for the immune reaction is that the antigen must be recognized and presented to the cells, which are responsible for the development of the immune response. The antigen-presenting cells in the conjunctiva are the Langerhans cells, which present the antigen to T lymphocytes.

In the cell-mediated type of reaction (delayed type or type IV), T cells recognize the antigen and start the inflammatory reaction. Typical delayed-type reactions are contact dermatitis and Mantoux (tuberculin) reaction. Macrophages activated by Th cells destroy intracellular bacteria but also cause other delayed inflammatory reactions, including the contact hypersensitivity of the skin and tuberculin reaction. These reactions reach their peak in 24 to 72 h.

Treatment modalities vary in different forms of ocular allergic diseases. A recent review analyzed 362 trials, from which only a few fulfilled all the criteria of good clinical design, so there is a lack of criteria for optimal management of ocular allergic diseases [15•].

Examination of Patients

A good patient history and clinical examination are essential. When the diagnosis is not clear, some laboratory examinations are needed. When an infection is suspected, bacterial and viral specimens are taken. By using the conjunctival brush cytology, it is possible to see typical epithelial changes and inflammatory cells and to make the differential diagnosis as dry eye. The spectrum of inflammatory cells can provide guidance about the quality of the inflammation. Particularly if eosinophils are seen, an allergic inflammation is suspected. Eosinophils can also be seen in some infections.

When the patient history is clear and the symptoms are typical of SAC, the allergy tests are usually not needed. In suspected cases in which diagnosis is not clear, a basic skin prick test or specific serum IgE determinations (ImmunoCAP) are recommended. Especially in children, a good allergy examination is mandatory. The total serum IgE itself is not enough to prove ocular allergy.

When the patient also has suspected allergic blepharitis, epicutan tests should be done. If contact allergy to eyedrops is suspected, an epicutan test should be done with the drops used (sometimes also as a prick test). When there is strong doubt about allergy, or an immunotherapy is planned, an ophthalmic challenge test can be conducted. It should be done with standardized water-soluble allergen extracts (SQ-quality, ALK-Abello). The test always should be done blinded to the patient with the diluent as placebo in the other eye [16]. Many mediators are increased in specific ocular challenge [17]. In occupational allergy, some substances can be tested, but in most cases, direct tests are not possible.

Seasonal Allergic Conjunctivitis

SAC is the most common allergic disease of the eye. Its type is an anaphylactic, immediate, IgE-mediated (type I) allergy. It is also called hay fever conjunctivitis. SAC is usually caused by exposure to pollen, and the symptoms are limited to the season. Some patients may have exacerbations of symptoms year round (eg, from animals, mites, and seldom from foods or molds), and different allergens appear in different geographical areas.

SAC is usually an acute or subacute manifestation characterized by peaks of self-limiting symptoms. Itching of the eyes is the most characteristic symptom. Other symptoms include tearing, burning sensation, and photophobia. SAC is usually bilateral. The signs consist of mild papillary hypertrophy of the tarsal conjunctiva, redness, lid and/or conjunctival edema, and chemosis. Sometimes there is a mild punctate epithelial keratitis.

It is important to start therapy immediately and continue it sufficiently and long enough until all symptoms have disappeared. The goal is to prevent transformation of SAC to a chronic inflammation. It is also important to treat the concomitant rhinitis or asthma symptoms. However, in the treatment of acute or chronic forms of allergic eye diseases, patient compliance is not always ideal. This manifests as poor efficacy of treatment [18].

In the treatment of SAC, antihistamines are effective. Whereas eyedrops are most effective for ocular symptoms, oral antihistamines are most useful if targeting both nasal and ocular symptoms. There are no major differences in efficacy between different antihistamines, including newer H₁-receptor antagonists [19•, 20]. In the severe acute stage, local corticosteroids are effective for initiating effective treatment for a short period (a few days, maximum of 1 week). Treatment should be continued with mast cell stabilizers, including sodium cromoglycate, nedocromil, pemirolast potassium, or lodoxamide eyedrops (Table 1) [21]. Sometimes there may also be a mild lid eczema that can be treated in the short term with weak corticosteroid ointment.

In most cases, SAC is not serious. However, it may be very disturbing to patients, can affect their quality of life, and can have a significant socioeconomic impact. In cases in which an appropriate local therapy has failed, immunotherapy is a good choice. Until now there has been only subcutaneous immunotherapy with injections [22]. In recent years, a new and comfortable possibility has become available: sublingual immunotherapy [23, 24•, 25]. With both of these forms of immunotherapy, the ocular symptoms usually subside first. The effect of subcutaneous immunotherapy may last 5 to 10 years. New therapeutic modalities, including new

Table 1 Topical treatment schedule for eosinophilic allergic and non-allergic eosinophilic conjunctivitis

Treatment	Allergic (SAC)	Nonallergic (NAEC)
Antibiotics	No	In the beginning
Corticosteroids or corticosteroids-antibiotics	Not usually, or short term	First step/when symptoms persist
Antihistamines	Yes	Not usually, or short term
Mast cell stabilizers	Yes	Yes
Adstringents	Not usually	No
Lubricants	Sometimes	By need
Hyposensitization	In severe cases	No
NSAIDs	Seldom	By need
Immunosuppressants (cyclosporine, tacrolimus)	No	By need
Duration of treatment	Short term	Long term

NAEC nonallergic eosinophilic conjunctivitis; SAC seasonal allergic conjunctivitis

antihistamines, are under investigation, but these are not yet commercially available [26, 27•].

Perennial Allergic Conjunctivitis

PAC is IgE-mediated inflammation that is usually mild. Patients with PAC often show allergy to animals and house dust mites. Symptoms and signs are much the same as in SAC, only milder. This condition affects all age groups, but mostly young and middle-aged people of both sexes.

PAC is often connected to dry eye, which influences therapy. Therapy should be started without delay and be intensive enough and last long enough. Milder cases can be treated with topical mast cell stabilizers, which should not contain preservatives. The most common preservative is benzalkonium chloride, which may occasionally cause ocular allergies. Its toxicity to the inflamed conjunctiva is more harmful, and it may worsen the existing dry eye. Sodium cromoglycate or lodoxamide dropped three or four times daily may be helpful in treating mild dry eye symptoms. Antihistamines are not suitable for long-term use because they can worsen or even cause dry eye. However, they can be used in the short term as an additive medication. Topical steroids may be needed for a few days to 1 week as pulse therapy, especially in more severe cases that do not respond to other medication. Other preexisting allergic symptoms, including rhinitis, asthma, or atopic dermatitis, should be treated appropriately.

Atopic Blepharoconjunctivitis or Keratoconjunctivitis

ABC is a serious and often chronic eye disease. Patients typically have atopic eczema of the face and eyelids. This disease affects boys and men most often. Patients with ABC often have high serum-specific IgE, which may be several thousand IU/mL. These patients are in many cases multi-allergic (ie, they have several positive skin prick tests to common environmental allergens).

The symptoms of ABC include intense itching, photophobia, epiphora, and occasionally blurred vision. The signs consist of red and swollen lids (often with rhagades), lost eyelashes, and red and swollen tarsal conjunctiva with papillary hypertrophy. There is often punctuate epitheliopathy, and in the most severe cases, a serious corneal ulcer, which may lead to vision-disturbing scars or even ocular penetration. These ulcers are dangerous because in ABC, the skin of the eyelids and the conjunctiva mostly show *Staphylococcus aureus* infection. Serious ABC is often combined with dry eye.

Topical treatment of ABC has consisted of different steroid preparations. However, a new product, calcineurin

inhibitor tacrolimus, which was first used in the treatment of atopic dermatitis, has shown to be very useful in the treatment of ABC. We were among the first to use tacrolimus ointment in the treatment of atopic lid eczema 10 years ago [28]. Since then, we have seen very good results without any serious side effects in this treatment [29].

The treatment of ABC must be divided into two parts: lid care and treatment of conjunctivitis. In short-term lid therapy, weak corticosteroid ointment is a good choice. For long-term treatment, the side effects of corticosteroids are obvious: possible corticosteroid-induced glaucoma and/or cataract or atrophy of the lid skin. By using calcineurin inhibitors tacrolimus (0.03%) or pimecrolimus (1%), the treatment is safe without any serious side effects [29, 30••]. Tacrolimus ointment is usually applied on the lids once daily for 2 weeks or longer until the eczema has healed. When the symptoms have subsided, treatment can be stopped or continued if needed two or three times weekly for a longer period. The remission period is substantially longer than with corticosteroid treatment. Tacrolimus ointment seems to be very safe and can be continued for a longer period regularly or intermittently. At the beginning, weaker pimecrolimus must be applied twice daily, but later, once-daily application is sufficient [30••].

Vernal Keratoconjunctivitis

VKC is a relatively rare chronic disease that mainly affects children and young adolescents. The majority of patients are boys, with a male-to-female ratio of 3:1. The disease usually begins at age 6 to 10 years. Only about 60% of patients are atopic. VKC is often complicated by keratitis and corneal ulcers, which may cause visual disability.

The main symptoms of VKC are intense itching and photophobia. The signs include redness, lid swelling, inflammatory ptosis, ropy discharge, and eosinophilic granulomas as giant papillae on the upper tarsal plate. However, inflammatory infiltrates, which are sometimes called Trantas dots, may occur—in many cases on the bulbar limbal conjunctiva. In these cases, there are no giant papillae on the upper lid. This form is called limbal VKC. Both manifestations can be seen without optical magnification. The incidence of the limbal form may vary in different countries. In northern countries such as Finland, the limbal form accounts for about 50% of all VKC cases. The conjunctival cytology in patients with VKC shows a large number of eosinophils and other inflammatory cells.

Treatment of VKC may last from months to several years, depending on the severity of the disease. VKC has, however, a self-limiting course that begins in puberty or early-adolescence. Before that, long-term therapy is needed. The mainstay of the therapy is mast cell-stabilizing drops.

For relapses, topical corticosteroid pulse therapy is needed. When the need for corticosteroids is almost continuous, cyclosporine eyedrops, 0.05% (Restasis) or 0.1%, are used. Antihistamine eyedrops alone or as additive drops are recommended only for short-term therapy. Cyclosporine eyedrops in these concentrations are very safe and can be used for years in children [31•].

Giant Papillary Conjunctivitis

Giant papillary conjunctivitis (GPC) maybe a real allergic inflammation (against contact lens solutions), and in some instances a consequence of repetitive microtrauma on the upper tarsal conjunctiva generated by a foreign body reaction (eg, against contact lenses [CL] or sutures after cataract or corneal surgery or to plastic ocular prosthesis). Atopy is a well-known risk factor for CL users and increases the risk of GPC fivefold [32, 33]. The symptoms of GPC include itching, redness, discharge, and occasionally photophobia. In soft CL users, the giant papillae are seen on the tarsal conjunctiva of the upper lid or sometimes as limbal infiltrates on the upper part of the limbus. The sutures cause the typical reaction in the tarsal conjunctiva of the upper lid.

Especially young (<20 years of age) atopic CL users need regular controls at least two times per year. Therapy is needed if complications follow the CL use. CL use is restricted until the eyes are calm; the lens type may need to be changed to 1-day lenses or to another type, and use must be reduced. During CL use, preservative-free mast cell-stabilizing agents can be used. In a worst-case scenario, CL use must be ceased.

Nonallergic Eosinophilic Conjunctivitis

NAEC seems to be poorly known in clinical practice, as the presence of eosinophils is usually regarded as a sign of allergy [7, 8•, 34]. The condition may be analogous to nonallergic eosinophilic rhinitis and nonallergic eosinophilic asthma [7, 35, 36]. The majority of patients are middle-aged or older women. Their skin prick tests are negative, serum IgE is normal, and they have no atopic eczema. However, these patients often have dry eye.

The symptoms of NAEC include itching, foreign body sensation, lacrimation, slight discharge, and minimal lid swelling. Signs consist of eosinophilia in conjunctival cytology, at least one on the semiquantitative scale [37]. The diagnosis requires conjunctival cytology. The incidence of NAEC is about 5% to 10% of patients seen in the ambulatory department of ocular allergology.

In the treatment of NAEC, we have successfully used hydrocortisone-containing eyedrops for 1 to 2 weeks and continued with topical mast cell stabilizers, including

cromoglycate, nedocromil, or lodoxamide, or with NSAIDs, including topical diclofenac. Because of the common coexisting dry eye, preservative-free mast cell-stabilizing agents are recommended. Long-term use of topical or systemic antihistamines should be avoided because of their drying effects. Additive short-term use of corticosteroids is often needed. By need, moistening drops are added. In severe cases, cyclosporine (0.05%–0.1%) eyedrops can be used (Table 1). Due to the chronicity of NAEC, the duration of therapy varies from months to years. Regular controls two or three times per year are necessary if the cyclosporine treatment continues for years.

Contact Allergic Blepharoconjunctivitis

Contact allergic blepharitis and contact allergic blepharoconjunctivitis (CABC) are common. In a German study, the predominant causes were allergic contact dermatitis (44%), atopic eczema (25%), airborne contact dermatitis (10%), and irritant contact dermatitis (9%) [38]. The eyelids are exposed to both airborne allergens and contact allergens. The skin of the eyelids is thin and reacts easily. Therefore, in patients with CABC, the eczema can occur alone in the eyelids.

Immediate Allergy

Immediate type of allergy is an IgE-mediated rapid (in minutes) allergic reaction. Besides the usual protein allergens (eg, pollen, molds, animal dander, house dust, mites), many industrial chemicals may cause immediate allergy whose prodrome in the skin may be blepharitis. The provoking components are many artificial resins (epoxy and its hardeners, acryl resins and their hardeners, aziridine in water-soluble two-component lacquers and paints). Because the immediate ocular allergy always occurs in connection with the symptoms of mucus membranes, the diagnosis of blepharoconjunctivitis is connected to the diagnosis of the other mucus membranes.

Delayed (Cell-Mediated) Allergy

Contact dermatitis is a typical contact T-cell-mediated delayed hypersensitivity reaction to haptens, which become immunogenic only after they bind to tissue protein. Typical delayed-type allergens, the symptoms of which may be only in the eyelids, are nail lacquer and mascara and the components of eyedrops and ointments. Nail lacquer may affect the eyelids alone. The sensitizer is often the toluenesulfonamide-formaldehyde resin. The main allergen in mascara is natural resin, which is used in most mascara as an adhesive. Mascara often contains nickel and cobalt (blue color), which may cause lid eczema in those who are already sensitized, and mascara itself may also sensitize the users.

All eyedrops and ointments contain potential allergens (eg, antibiotics, including neomycin, framycetin, sulfa, chloramphenicol, and (oxy)tetracycline; glaucoma medication, including pilocarpine, β -blockers, brimonidine, apraclonidine, dorzolamide, and prostaglandin derivatives; local anesthetics; antihistamines; anticholinergics; preservatives benzalkonium chloride and thimerosal; and mydriatics, including scopolamine, atropine, tropicamide, phenylephrine hydrochloride, and cyclopentolate hydrochloride). These agents can cause very angry allergic reactions that may last a long time and cause, especially in glaucoma therapy, a common intolerance to all topical glaucoma medication. Therefore an early diagnosis is mandatory. CL care solutions (eg, chlorhexidine and papain) can also cause allergic reactions. These allergic reactions almost always manifest as blepharoconjunctivitis, which means that besides lid eczema, there is also conjunctivitis. It is important to know that steroids can also cause contact allergy. In rare cases, the lanolin/wool fats in ointments cause allergy.

Many different substances can cause symptoms in the eyelids and in other skin parts of the body, but the thin skin of the eyelids is most sensitive to react. Nickel, rubber chemicals, fragrances, preservatives in ointments and detergents, hair colors, and some plants (eg, the houseplant *Primula obconica*) are the most common allergens. Frames of eyeglasses that contain plastics and metal may cause lid and face eczema in the contact area.

Delayed-type hypersensitivity is caused by many components that are spread as aeroallergens and can cause lid or face eczema. Those allergens include rubber chemicals, some green houseplants, and the lactones of composites.

Diagnosis of Responsible Agent

Skin prick tests and epicutaneous tests are used in the diagnosis of lid eczema. It is important to test with the patient's own cosmetics and medicaments because the standard test series do not cover all the allergens that cause lid eczema. Atopic and seborrheic lid eczema may resemble each other. Skin tests are the only way to make the correct diagnosis. Most lid eczemas are of atopic origin, and then all the tests may be negative. The organic solvent vapors and other chemicals cause toxic reactions that are often very difficult to distinguish from allergic symptoms.

Treatment

In the treatment of CABC, it is most important to clarify the causing agent and eliminate it. Allergic lid eczema heals without therapy when the allergen is avoided. The healing process may speed up with use of mild corticosteroid ointment on the lids for a few days.

Atopic blepharitis is often chronic and requires therapy of a longer duration. In treatment, corticosteroid ointments can be used for a short time. In chronic atopic blepharitis, we can now use a very effective and safe corticosteroid-replacing therapy: tacrolimus ointment (Protopic). It has two concentrations: 0.1% and 0.03%. We have used during the past 10 years tacrolimus (0.03%) ointment on the lids, and also in children for about 10 years without any serious side effects. It does not cause skin atrophy, cataracts, or glaucoma the way long-term corticosteroid treatment does [29, 30•]. Pimecrolimus in 1% concentration is another corticosteroid-replacing therapy for lid eczema.

Work-Related Ocular Allergies

Occupational health and safety legislation varies in different countries. In many countries, obviously strong allergenic exposure factors are almost eliminated [10, 39, 40]. However, industry annually produces thousands of new chemicals that may include new allergenic exposure factors. When there is a suspicion of work-related ocular allergy, it must be confirmed that the worsening of symptoms in the workplace is valid [41].

An ophthalmological examination is needed to rule out other causes, including dry eye, CL use, refractive surgery, other ocular operations, and inflammatory and other ocular diseases. When this is done, the next step is a careful surveying of the workplace.

Diagnosis requires elucidation of cause. Basic examination includes a brush cytologic examination from the upper and lower lid conjunctiva, which helps in differentiating the inflammation, whether it is allergic or another type [37]. An eosinophilic inflammation is strong evidence of allergy. In contact allergy, the cytologic examination reveals more lymphocytes and a low degree of eosinophilia.

The ocular challenge test is the most reliable way to prove work-related ocular allergy. A direct challenge test is made by dropping with a small syringe through a special thin needle onto the eye one drop of a known commercial and standardized water-soluble allergen solution. At the same time, one drop of the diluents (usually balanced salt solution) is dropped as a control onto the other eye. This is a safe and reliable way to prove ocular allergy [16, 42].

It is not always possible to conduct a direct challenge test. In such cases, an indirect challenge can be made in a special challenge chamber in which the individual handles suspected matter for 20 to 30 min. If this individual shows an allergic reaction, the allergy diagnosis is clear. Sometimes the reaction first appears after several hours, and we speak then about a late-phase reaction. In such cases, the patient is usually no longer in the testing place; therefore, the reaction should be shown to a physician to confirm that the reaction is true.

The third possibility is to put an individual on sick leave for 2 weeks. Before and after the sick leave, when the person is again at work, a control examination is made. It is possible to take before and after the sick leave a brush cytologic sample from the lower and upper lid conjunctiva of one eye. When comparing these examination results, we can determine the possible existence of occupational allergy.

Common causes of work-related allergic conjunctivitis are proteins (eg, enzymes, animal dander, and flour dust). In industry, the most commonly used enzymes are proteases, amylases, and cellulases. These can cause allergies in those who prepare them or who use enzyme-containing products. The enzymes can sensitize those who are working in the food and feed industry or in the pharmaceutical and detergent industry. Tiny amounts can sensitize laboratory workers or people working in health care. Amylases can sensitize workers in bakeries or larvae in flour.

Small molecules, including phthalic acid anhydrides, penicillin, ethylene oxide, chloramine-T, metals, isocyanides, acid anhydrides, amines, acrylates, formaldehyde, and reagent colors, can sometimes cause allergy. Foundry workers who were exposed to isocyanic acid, methyl isocyanate, and formaldehyde have demonstrated an increased prevalence of nasal and ocular symptoms [43].

The amount of occupational allergens is increasing all the time, causing new problems. An example is the production of food mushrooms that can sensitize workers. The professional mushroom agriculture can sensitize the workers through spores and molds. The ocular symptoms can appear as allergic conjunctivitis. Hospital workers in operating rooms may have allergic conjunctivitis caused by latex dust from surgical gloves.

When it is impossible to avoid an occupational allergen or to change the workplace, it becomes necessary to treat the work-related allergic conjunctivitis and blepharitis. This is, however, a temporary solution, leading in many cases to worsening of the symptoms, rhinitis, and even asthma. Typically, the symptoms flow in the course of time from upper parts to lower parts (ie, to the lungs). In dusty working conditions and tasks, it is recommended to use protective glasses that are sufficiently sealed, or a special fresh air helmet.

Differential Diagnosis of Ocular Allergies

Infectious conjunctivitis is mostly caused by bacteria or viruses. Conjunctival swabs for the culture or polymerase chain reaction techniques may show infectious etiology. Conjunctival cytology, if available, is a good and practical tool in making the diagnosis.

Dry eye is a common symptom and should be taken into account, especially in chronic forms of conjunctivitis. It may

occur alone or in connection with chronic allergic conjunctivitis. In many dry eye patients, a slight eosinophilia can be found in conjunctival cytology [8••].

Follicular conjunctivitis is a common differential diagnostic eye disease in children and young adults. In most cases, it is an asymptomatic or mild disease and may not require treatment. Molluscum contagiosum in the lid margin may cause chronic follicular conjunctivitis, which can be treated erroneously as an allergic blepharoconjunctivitis.

Superior limbic keratoconjunctivitis is a chronic conjunctivitis that usually manifests in both eyes in the upper limbal area. It has some features of allergic conjunctivitis and can be seen as a complication of soft CL use.

Conclusions

In short, we can conclude that we already have good clinical experience, results, and design in using the new drugs and effective modalities for the treatment of ocular allergies. The treatment must start early and be effective and last long enough to avoid the chronicity of the allergic disease. However, a need still exists for further randomized controlled clinical trials to confirm the efficacy and safety of our currently available therapies.

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- Of major importance

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