ALLERGIC KERATOCONJUNCTIVITIS – CLINICAL, DIAGNOSTIC AND THERAPEUTIC ENTITIES

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Eye allergy is a hypersensitivity reaction of the eye to specific allergens and the atopy is determined by genetic predisposition to allergic reaction of the eye to a number of allergens. Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common forms of ocular allergies (20% of the population). Vernal keratoconjunctivitis is a disease which tends to appear in warm weather months and also in warm climates. Atopic keratoconjunctivitis (AKC) is a bilateral chronic inflammatory disease of ocular surface and eyelid. Contact allergy (contact dermatitis) is not an IgE mediated allergy and can be considered in a different category than aforementioned allergic conditions. The mainstay of management of ocular allergy involves the use of anti-allergic therapeutic agents such as antihistamine, mast cell stabilizers and multiple action anti-allergic agents. Acta Ophthalmologica 2012;38(1-2):36-41.

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Introduction

Eye allergy is hypersensitivity reaction of the eyes to contact with allergens and the atopy is determined by genetic predisposition to allergic reaction of the eye to a number of allergens. The clinical presentation of various forms of ocular allergy can be classified as: seasonal allergic conjunctivitis, vernal keratoconjunctivitis, atopic keratoconjunctivitis and giant papillary conjunctivitis (1). Vernal keratoconjunctivitis (VKC) is self limiting, chronic inflammatory disease and it mainly affects boys aged 4 -14 years. The patients present the phases characterized by exacerbation of inflammatory symptoms with a consequent decline of the quality of life. The endocrine, genetic, neurogenic, environmental and socioeconomic risk factors have been identified (2). Immunological and clinical profile of patients affected by VKC was defined by family medical history of autoimmune disorders and autoimmunity pattern (Systemic lupus erythematosus, Hashimoto’s thyroiditis, psoriasis, rheumatoid arthritis, etc). Positive analyses of antinuclear antibodies and family history of autoimmune disorders of patients with those diseases may help clinicians to understand association between ocular inflammatory disease, systemic autoimmune disorders and atopic condition (3, 4). It represents a bilateral,
Seasonal allergic conjunctivitis

Seasonal allergic conjunctivitis (SAC) and perennial allergic conjunctivitis (PAC) are the most common forms of ocular allergies (20% of the population). Contact lenses or ocular prosthesis associated with giant papillary conjunctivitis (GPC) are included in the group of ocular allergy. They should not be considered as real allergic diseases, but as chronic ocular micro-trauma related disorders, which need to be managed by ophthalmologists (5, 6). Allergic conjunctivitis is caused by an allergen induced inflammatory response in which allergens interact with IgE bound to sensitized mast cells resulting in clinical ocular allergic expression. The pathogenesis of allergic conjunctivitis is predominantly an IgE mediated hypersensitivity reaction. Activation of mast cells induces enhanced tear levels of histamine, tryptase, prostaglandins, leukotriens and others (early response lasts clinically 20–30 min). Mast cell degranulation induces activation of vascular endothelial cells, which in turn expresses chemokines and adhesion molecules such as intercellular adhesion molecule and vascular cell adhesion molecule. Secreted chemokines include regulations upon activation of normal T-cell expressed chemokines, monocyte chemoattractant protein, interleukin-8, eotaxin, macrophage inflammatory protein-1-alpha, etc (7, 8). Signs and symptoms usually occur in the spring and summer (airborne pollens), and generally abate during the winter months, but can occur throughout the year with exposure to perennial allergens. Diagnostic features of SAC and PAC consist of itching, redness, swelling of the conjunctiva (chemoses). Conjunctival injection tends to be mild to moderate. Corneal involvement is very rare. Itching is a fairly consistent symptom of SAC and PAC (7, 8).

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis is a disease which tends to appear in warm weather months and also in warm climates. The prevalence of VKC in Europe ranges from 1.2 to 10.6 cases per 10,000 population, although the prevalence of associated corneal complications is 0.3 - 2.3 per 10,000 population. VKC has three clinical forms: palpebral, limbal and mixed (with preponderance in males) (9). It is a chronic allergic inflammation of the ocular surface mediated mainly by Th2 lymphocyte; in a complex pathogenesis have a role of the over-expression of mast cells, eosinophils, neutrophils, Th2 derived cytokines, chemokines, adhesion molecules, growth factors, fibroblast and lymphocytes. IL-4 and IL-13 are involved in the formation of giant papillae by inducing the production of extra-cellular matrix and the proliferation of conjunctival fibroblasts (9, 10). Symptoms include ocular itching, redness, swelling and discharge. Itching may be quite severe, and even incapacitating. The most characteristic sign is giant papillae on the upper tarsal conjunctiva. These “cobblestone-like” swellings can measure several millimeters in diameter, and 10–20 of them are found on tarsal conjunctiva and they can be seen easily by “flipping” the upper eyelid. The giant papillae are filled with inflammatory cells, edema and mucous. Neutrophils, plasma cells, mononuclear cells and eosinophils are found in abundance. Mast cells may also be found in the conjunctiva epithelium. The tears of VKC patients contain high levels of IgE and mast cell mediators (10). A punctate keratitis, known as keratitis epithelialis vernalis of El Tobgy, may begin in the central cornea. Vernal plaques may interfere with vision and lead to central scarring of the cornea. Plaques may interfere with vision and lead to central scarring of the cornea. Plaques can be removed by superficial keratectomy, but they rarely resolve without surgical therapy. Histologically, plaques are consisted of mucin and epithelial cells, which are literally ground into the central cornea. Tranta’s dots consist of clumps of necrotic eosinophils, neutrophils and epithelial cells. The dots represent almost pure collections of eosinophils. Trantas dots tend to appear when VKC is active, and disappear when symptoms abate (10). Shield ulcers can occur in the superior sectors of the cornea; these are noninfectious, oval-shaped circumscribed epithelial ulcers with underlying stromal opacification. Corneal epithelial punctate keratitis may evolve to macroerosion, ulcers and plaques, which are all expressions of epithelial toxicity.
extricated by epitheliotoxic factors released by activated eosinophils (11).

**Atopic keratoconjunctivitis**

Atopic keratoconjunctivitis (AKC) is a bilateral chronic inflammatory disease of ocular surface and eyelid. Its pathomechanism involves both a chronic degranulation of mast cell mediated by IgE and immune mechanisms mediated by Th1 and Th2 lymphocyte derived cytokines. It is considered to be the ocular counterpart of atopic dermatitis or atopic eczema, etc (12). Over time, AKC can lead to loss of vision due to corneal complications. The classification, histology, ocular examination findings and complications of AKC are described herein, as well as the roles and interactions of inflammatory cells involved (13). Eczematous lesions are itchy, and scratching them makes them itchier. The eyelid skin may be chomotic with fine sandpaper like texture. AKC patients may develop atopic cataracts. Typically, these are anterior, shield like cataracts, but nuclear, cortical and posterior subcapsular cataracts may develop.

VKC resolves by age of 20 years, whereas AKC can persist throughout life. Many patients with AKC (45%) have skin test or allergic sorbent test negative to common allergens (13).

**Contact allergy and giant papillary conjunctivitis**

Contact allergy (contact dermatitis) is not an IgE mediated allergy and can be considered in a different category than the aforementioned allergic conditions. It is a type-IV delayed hypersensitivity response that occurs through interaction of antigens with Th1 and Th2 cell subsets followed by release of cytokines. It consists of two phases: sensitization (at the first exposition to allergen, with production of memory T-lymphocytes) and elicitation of the inflammatory response (at the re-exposure to antigen, mediated by the activation of memory allergen-specific T-lymphocytes). In the sensitization phase, antigen presenting cells processed antigen - MHC-II complex and memory T-cells stimulates the proliferation of T-cells. The memory T-lymphocytes during proliferation release cytokines. Th2 derived cytokine, such as IL-4 and IL-5, participates in the activation and chemotaxis of eosinophils. Two novel Th cell subsets, IL-17-producing Th cells (Th17 cells) and regulatory T cells (Treg cells) are also found to be contributors in the pathogenesis of conjunctivitis (14). Contact allergy involves the ocular surface, eyelids and periocular skin. Examples of allergens include poison ivy, poison oak, neomycin, nickel, latex, atropine, etc. The delay in development of the reaction is due to the slow migration of lymphocytes to the antigen depot. Contact allergic reactions are generally associated with itching. Treatment consists of withdrawing and avoiding contact with allergen. Severe reactions can be treated with topical or systemic corticosteroids (14).

Giant papillary conjunctivitis (GPC) is an inflammatory disease characterized by papillary hypertrophy of the superior tarsal conjunctiva, but there is no significant corneal involvement. GPC is not an allergic disease; the incidence of systemic allergy in patients is similar to that of general population, and the stimuli for papillary conjunctiva changes are inert substances rather than allergens. GPC may be caused by limbal sutures, contact lenses, ocular prostheses, limbal dermoids, etc (14). The conjunctival tissues may contain mast cells, basophils, or eosinophils, but not to extent of an allergic reaction. There is no increase of IgE or histamine in the tears of patients. It appears that protein build-up on the surface of contact lenses, and irregular edges were the main reason for close association between contact lenses and GPC, by immune or mechanical mechanisms: in particular protein deposits on the surface of contact lens could become antigenic and stimulate the production of IgE; mechanical trauma and chronic irritation can determine release of some mediators (CXCL8 and TNF-α) from injured conjunctival epithelial cells (14).

**About diagnoses**

The diagnosis of ocular allergy is primarily clinical, but there are laboratory
tests that can be useful in supporting the diagnosis. Allergists can perform skin testing for specific allergens by scratch tests or intradermal injections of allergen. In-vitro tests for IgE antibodies to specific allergens are widely used. Allergic tests would help in differentiating intrinsic and extrinsic forms and would, therefore, be helpful in the treatments.

In the single dose allergen provocation examination, the patients responded with a typical IgE mediated allergic reaction. Signs and symptoms from both eyes were graded at baseline and at 10 min, 8 and 48 h after conjunctiva provocation. Tear fluid was collected from both eyes for cytokine analyses at baseline and at 8 and 48 h. A significant change in clinical symptoms and signs (redness, chemosis) was evident 10 min after provocation compared with baseline and compared with the unprovoked eye in allergic patients. A significant increase for IFN-\(\gamma\) and IL-6 and a near significant increase for IL-10 were noticed in tear fluid of challenged eye at 48 h after provocation vs. baseline and vs. the control eye for IFN-\(\gamma\), IL-6 and IL-10 in allergic patients (15,16).

About therapy

The mainstay of management of ocular allergy involves the use of anti-allergic therapeutic agents such as antihistamine, mast cell stabilizers and multiple action anti-allergic agents. Topical antihistamines competitively and reversibly block histamine receptors and relieve itching and redness but only for a short time. A limited duration of action requires frequent dosing of up to 4 times per day, and topical antihistamines may be irritating to the eye, especially with prolonged use. Combination treatments using decongestants with antihistamines have been shown to be more effective, and are administered to the eye as drops up to 4 times daily. Decongestants act primarily as vasoconstrictors and are effective in reducing erythema, however, adverse effects include burning and stinging on instillation, mydriasis, and rebound hyperemia or conjunctivitis medicamentosa with chronic use (17).

Mast cell stabilizers have a mechanism of action that is unclear. They may increase calcium influx into the cell preventing membrane changes and/or they may reduce membrane fluidity prior to mast cell degranulation. Final result is a decrease in degranulation of mast cells, which prevents release of histamine and other chemotactic factors that are present in the preformed and newly formed state. Mast cell stabilizers do not relieve existing symptoms and they can be used on a prophylactic basis to prevent mast cell degranulation with subsequent exposure to allergen. Mast-cell stabilizing medications can also be applied topically to the eye, and may be suitable for more severe forms of conjunctivitis. They require a loading period during which they must be applied before the antigen exposure. Therefore, poor compliance should be taken into account as a possible drawback (18). In recent years several multimodal anti-allergic agents have been introduced, such as olopatadine, ketotifen, azelastine and epinastine that exert multiple pharmacological effects such as histamine receptor antagonist action, stabilize mast-cell degranulation and suppress activation and infiltration of eosinophils (19).

Non-steroidal anti-inflammatory drugs (NSAIDs) can be used as additive drugs, in order to reduce the conjunctiva hyperemia and the pruritus, related in particular to prostaglandin D2 and prostaglandin E2 (20).

Corticosteroids used in the more severe variants of ocular allergy are also effective in the treatment of acute and chronic clinic forms. Corticosteroids possess immunosuppressive and anti-proliferative properties since they can hinder transcription factor that regulates the transcription of Th2-derived cytokine genes and differentiation of activated T-lymphocytes into Th2-lymphocytes. But, these agents are appropriate for short courses (2 weeks); if needed for longer durations, an eye examination should be carried out, including baseline assessment of cataracts and intraocular pressure measurement (21).

The efficacy of immunotherapy against ocular symptoms precipitated by conjunctiva antigen challenges was originally demonstrated at the beginning of the 20th century and this well-established method may be considered for the long-term control of ocular allergy (22). Traditionally, immunotherapy is delivered via subcutaneous injections. Sublingual (oral) immunotherapy (SLIT) is gaining momentum among allergists. SLIT requires
further evaluation for ocular allergy relief. It has been shown to control ocular signs and symptoms, although ocular symptoms may respond less well than nasal symptoms.

Oral antihistamines are commonly used for the therapy of nasal and ocular allergy symptoms. Second-generation antihistamines can, however, induce ocular drying, which may impair the protective barrier provided by the ocular tear film and thus actually worsen allergic symptoms. Intranasal corticosteroids are highly effective for treating nasal symptoms of allergic rhinitis, but there is no consistent evidence that they may also be effective for the treatment of ocular symptoms (22).

Current evidence supports the use of cyclosporin A, topically or systemically, as well tolerated and effective steroid sparing agent.

Seasonal atopic conjunctivitis is treated with antihistamines, cromoglycate and short courses of corticosteroids, in severe cases with subcutaneous or sublingual immunotherapy. Chronic conjunctivitis requires year-round treatment with mast cell stabilizers, antihistamines or topical corticosteroids. For atopic keratoconjunctivitis corticosteroid and, if necessary, cyclosporine eye drops are needed. First-line therapy of vernal conjunctivitis involves mast cell stabilizers and, if necessary, corticosteroid eye drops. Treatment of non-allergic eosinophilic conjunctivitis involves mast cell stabilizers, corticosteroid and cyclosporine eye drops (21). Other modes of treatment include acetylcysteine (mucus, plaque), surface excimer laser - keratectomy, tarsal steroid injections (dexa, triamcinolon), cryotherapy, excision of giant papillae, amniotic membrane transplantation, etc. Treatment is symptomatic and causal, with the use of artificial tears, cold compresses, dark glasses, treatment of associated blepharitis, etc (22).

Understanding the immune-pathogenesis of atopic disease has already influenced therapy and is essential to the development of future immune-modulating treatments. The current challenge is to find more specific topical and systemic immune-modulating therapies with a better side effect profile. Ocular allergy represents one of the most common ocular conditions encountered in clinical work, diagnoses and therapy, and represents the common conditions encountered by ophthalmologists, allergists and other causal specialists.

Literature


ALERGIJSKI KERATOKONJUNKTIVITIS- KLINIČKI, DIJAGNOSTIČKI I TERAPIJSKI ENTITETI

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