Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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REVIEW ARTICLE

OPEN ACCESS

Ocular allergy in children and adolescents

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Received 8 November 2021; Accepted 25 March 2022
Available online 00 XX 2022

KEYWORDS
Ocular Allergy;
Allergic Conjunctivitis;
Rhinoconjunctivitis

Abstract
The association between symptoms of asthma, rhinoconjunctivitis (RC) and allergic conjunctivitis (AC) is frequent, and AC is considered a comorbidity of asthma and allergic rhinitis (AR). Ocular symptoms are often underestimated and undertreated.
Differences according to gender were reported, because girls present symptoms more frequently. The development of RC depends on genetic and environmental factors, and recent studies have indicated that gender, family history of atopy, early sensitization, food allergy, and atopic dermatitis are risk factors for allergic RC. There are six well-defined clinical forms of ocular allergy: seasonal AC, perennial AC, vernal keratoconjunctivitis, atopic keratoconjunctivitis, and contact blepharoconjunctivitis.

Introduction

The association between symptoms of asthma, rhinoconjunctivitis (RC), and allergic conjunctivitis (AC) is frequent. Ocular symptoms such as itching, tearing, and hyperemia can affect 75% of patients with rhinitis and 20% of asthmatics.[1] Although asthma and RC are commonly associated, its prevalence in children and the risk factors for its development have been less studied.[2]

The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline considers AC as a comorbidity of asthma and allergic rhinitis (AR).[2] Most of the available information on AC is contained in studies on allergic RC.

Rhinoconjunctivitis affects approximately 400 million people in the world, mainly in developed countries. Although symptoms of RC are generally not very serious, they are among the 10 most frequent reasons for seeking primary care services, with an increasing prevalence.[3,4] Allergic diseases

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https://doi.org/10.15586/aei.v00i0.000

are often associated, as allergic multimorbidity and IgE polysensitization increase the risk of allergic comorbidity.[5]

Allergic conjunctivitis is a spectrum of clinical conditions that ranges from acute to chronic and severe forms.[6]

Epidemiology

There are few international data on the prevalence of ocular allergy (OA) as a clinical entity independent of AR. The prevalence of AR symptoms is widely known from the numerous epidemiological studies carried out in the field. Most patients have associated ocular symptoms, and majority of data regarding the epidemiology of ocular allergies come from studies on AR.[7] Different terms used, such as rhinoconjunctivitis, seasonal AR, and hay fever, make it difficult to assess epidemiological data from eye symptoms.[8]

In the United States, OA is estimated to affect 15–20% of the general population.[9,10] Eye symptoms occur in 30–70% of patients with AR,[11] and are more commonly triggered by indoor allergens than outdoor.[12] Patients with symptomatic AR present ocular symptoms mostly.[13] Nasal provocation with antigen leads to ipsilateral response and contralateral nasal reflex, reduced on treatment with topical H1 antihistamine, suggesting that ocular symptoms could be induced by nasal reflex-eye.[14]

Allergic conjunctivitis is often underdiagnosed in patients with AR and asthma, as the symptoms are underestimated.[10] A cross-sectional study evaluated a standardized asthma protocol that included symptoms of cutaneous and respiratory allergy. The diagnosis of conjunctivitis was recorded by the attending physician in 16% of 1549 asthmatics (mean age 4.3 years). However, 618 (44%) had at least one ocular symptom that suggested OA, demonstrating the secondary importance that is given to ocular symptoms.[15]

In a nationwide population-based Danish blood donor study with 52,976 participants, an electronic questionnaire including AR, AC, asthma, and allergic predisposition was completed. The second self-reported manifestation of allergy among healthy Danish donors was AC (15%).[16]

The frequency of ocular symptoms was higher in girls than in boys, except in vernal keratoconjunctivitis (VKC). Genetic, hormonal, and cosmetic factors are being investigated as possible causes. Geraldini et al. reported that all OA symptoms surveyed were significantly more prevalent in female adolescents, including ocular itching, tearing, light sensitivity, and feeling of sand in the eyes.[1]

Using latent class analysis and distinguishing each class through classification and regression tree analysis, the algorithm showed the importance of ocular symptoms in the expression of more severe allergic diseases phenotypes.[17]

Girls have more naso-ocular symptoms; however, they had lower rates of sensitization than boys.[18] Recent studies show a trend toward a change in the prevalence of symptoms of RC and AC in relation to gender which in childhood are more frequent in boys and, after puberty, more frequent in girls.[15,18] An analysis of 4500 Brazilian children aged between 13 and 14 years showed that females had a higher prevalence of not only AR but also allergic RC, asthma, AC, and atopic dermatitis compared to males.[19] In contrast, there was a greater rate of allergic sensitization in boys than in girls. In addition, it was observed that monosensitization was more frequent in females, while polysensitization was more common in males.[20]

Etiology

The development of RC depends upon genetic and environmental factors, and recent studies have indicated that gender, family history of atopy, early sensitization, food allergy, and atopic dermatitis are risk factors for RC.[20-22]

Allergic inflammation of the conjunctiva can be present in many diseases. The term "ocular allergy" refers to diseases that cause conjunctival inflammation mediated by a hypersensitivity mechanism, while the term "allergic conjunctivitis" refers to the two most common ocular allergies, seasonal AC (SAC) and perennial AC (PAC), caused by exposure of the ocular surface to environmental allergens in previously sensitized individuals.[12] Nevertheless, "ocular allergy" and "allergic conjunctivitis" are used as synonyms.

There are five well-defined clinical forms of OA: SAC, PAC, VKC, atopic keratoconjunctivitis (AKC), and contact blepharoconjunctivitis (CBC).[22,23]

The eye is constituted of four layers which are involved in immunological reactions: (1) the anterior portion is composed of the tear film and the conjunctiva which together form the first protective barrier against aeroallergens, chemical substances, and infectious agents; (2) the sclera, which is mainly affected by connective tissue diseases; (3) the richly vascularized uveal tract is the site of production of aqueous humor and is involved in inflammatory reactions associated with the deposition of immune complexes, and; (4) the retina, which is functionally an extension of the central nervous system.[23]

The eyelids are responsible for protecting, moisturizing, and cleaning the ocular surface. The conjunctiva is composed of a thin mucous layer that extends from the limbus to the edge of the eyelids. It is the tissue with the greatest immunological reactivity in the outer part of the eyes and can suffer from lymphoid hyperplasia in response to various stimuli.[23] Anatomically, the conjunctiva is divided into three parts: (1) bulbar conjunctiva, which covers the anterior portion of the sclera; (2) tarsal conjunctiva, which lines the inner surface of the eyelids, and (3) fornix or conjunctival sac, space delimited by the bulbar and tarsal conjunctiva. Histologically, the conjunctiva has two layers: an epithelial layer and the substance itself. Inflammatory cells such as mast cells, eosinophils, and basophils are normally not found in the ocular epithelium but in the substance itself.

In chronic forms of AC, mast cells migrate to the epithelial layer, which start an extensive proinflammatory capacity with the production of several cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and 10 (IL-10), and intercellular adhesion molecules 1 (ICAM-1).[24,25] Tear secretion starts approximately 2–4 weeks after birth. The conjunctiva is bathed with a thin tear film layer, which is composed of an outer lipid part, an intermediate aqueous layer, and an inner mucoprotein layer. Mucin-producing goblet cells are distributed throughout the conjunctiva. Mucin is important in reducing the surface tension of the tear film, keeping the surface of the

cornea hydrophobic and moist. The aqueous layer contains immunologically active proteins such as IgA, IgG, IgM, IgE, tryptase, histamine, and lactoferrin.[23,25,26]

Immunopathological mechanisms in the conjunctiva incorporate Gell and Coombs hypersensitivity reactions. The most frequent type I reaction occurs when a genetically predisposed individual produces specific IgE against an allergen. IgE has a strong affinity for mast cells and basophils, and the cross-linking of two adjacent IgE molecules, caused by the allergens, results in mast cell degranulation and release of chemical mediators such as histamine, tryptase, leukotrienes, and prostaglandins in the tear film. Biological agents that cause itching, edema, lacrimation, and hyperemia are characteristic of ocular allergies.[25,27] The relationship between total tear IgE, specific serum IgE, and total serum IgE levels in patients with pollen-induced AC showed that tear IgE was positive in 69% of patients clinically diagnosed with SAC. The higher the score of the positive class value of each pollen-specific IgE antibody, the higher the positive rate of tear-specific IgE. These findings suggest that pollen-induced conjunctivitis is very likely caused by pollen sensitization of the conjunctiva.[2]

Local type I reaction has been described in patients without specific serum IgE. There are several cases in which the results of tear IgE and serum IgE are divergent, suggesting the concept of local AC.[28]

Type II hypersensitivity reactions are mediated by IgG and IgM class antibodies bound to specific cells or tissues, differing from type III reactions where antigen–antibody binding occurs in serum. The fourth type of hypersensitivity is the T-cell mediated. This delayed reaction usually starts 48 h after the initial event. Examples of conjunctivitis involving this type of reaction include ocular pemphigoid, corneal allograft rejection reaction, and drug hypersensitivity.[25,27]

Mast cell degranulation and histamine release are the main mechanisms in the common forms of SAC and PAC, whereas patients with AKC and VKC have a conjunctival cell infiltrate composed of Th2 lymphocytes, activated mast cells, and eosinophils. Individuals with AKC and VKC often have tear film dysfunction. Patients with PAC and SAC have elevated serum and tear film IgE levels. Eosinophilic infiltrate is present in approximately 25% of those affected with SAC. Elevated serum and tear IgE levels can be demonstrated in approximately 78 and 96% of patients with SAC, respectively.[29] Elevated mite-specific serum IgE levels can be demonstrated in 89% of patients with PAC and 43% of patients with SAC. In tear film, mite-specific IgE can be detected in 78% of patients with PAC, but it is rarely present in those with SAC. Eosinophils are found in conjunctival scrapings in up to 84% of patients with PAC and 43% of patients with SAC, and in chronic forms one can observe eosinophil nodules and Horner–Trantas nodules[30] (Figure 1).

Late-phase reactions have been described in patients with PAC and SAC, and histological evaluations of the conjunctiva revealed a noneosinophilic cellular infiltrate, consisting of neutrophils and basophils. Histopathological findings of AKC demonstrate infiltrates of eosinophils, mast cells, and lymphocytes in the conjunctival epithelium. Changes in the conjunctival and corneal epithelium can be caused by several factors, for example, the direct effect of mediators released by eosinophils, presence of exotoxins derived from *Staphylococcus aureus*, and reduced concentration of secretory IgA.[23,27]

The demonstration of cytokines such as IL-2 and IFN-γ supports the hypothesis that AKC results from a pathological interaction between several cell types, with a lower participation of IgE[10] antibodies. Innate immunity may contribute to etiology of AKC. Keratoconjunctival resident cells have also been involved in the production of chemokines. Eotaxin and thymus and activation-regulated chemokine (TARC) stimulate migration of eosinophil and Th2 cell from the circulation, respectively.[29,31]

Patients with OA present with ocular and periocular pruritus, hyperemia, lacrimation, ocular foreign body sensation, sensitivity to light, and ocular secretions. Most of the time, symptoms are bilateral. Recurrent eye itching is the most characteristic symptom, and the diagnosis of AC is unlikely in its absence.[2,10] Although it is mild in most individuals, eye itching can be severe and even disabling for some activities. Many of the symptoms of eye allergy are nonspecific, such as tearing and light sensitivity. Photophobia, burning, pain, dry eye, and unilateral symptoms not associated with rhinitis suggest an alternative diagnosis to AC.[32] In the study by Chong et al., itching, lacrimation, and hyperemia were reported by 38, 20, and 25% of patients with PAC, respectively.[15]

Figure 1 Conjunctival hyperemia, limbal edema and Horner-Trantas nodules.

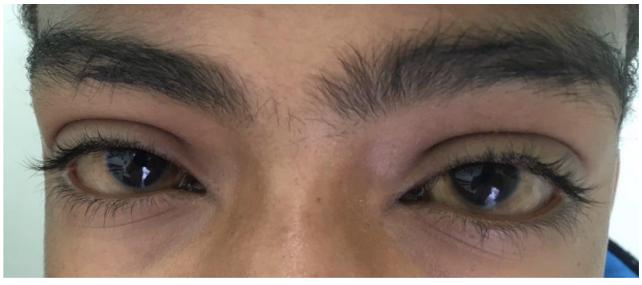

Figure 2 Conjunctival hyperemia in a patient with ocular allergy.

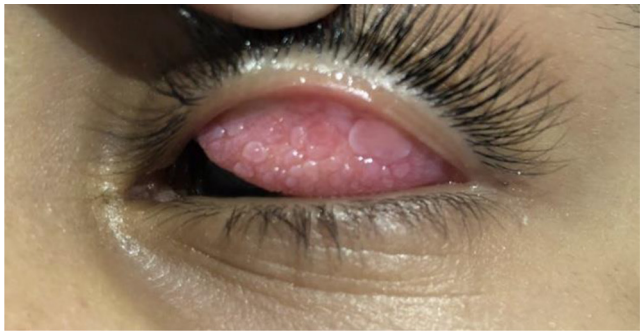

Figure 3 Clinical examination of a patient with ocular allergy demonstrating the presence of giant papillae in the tarsal conjunctiva.

Conjunctival hyperemia is usually present in OA (Figure 2). Although it is a nonspecific symptom, it is frequent and has a wide differential diagnosis ("red eye syndrome"). Hyperemia occurs due to inflammation of the conjunctiva and can be caused by exposure to allergens, irritation from nonspecific environmental factors (wind, air pollution), infectious agents, tear film dysfunction (dry eye disease), topical medications, autoimmunity, and several other systemic diseases.[32]

The presence of conjunctival papillae (Figure 3), conjunctival secretion, corneal involvement, and symptoms such as pruritus, photophobia, lacrimation, and xerophthalmia helps in the differential diagnosis of red eye. Clinical examination of the eye should include assessment of periorbital tissues. The eyelids and eyelashes should be examined for the presence of erythema of the lid margin, telangiectasia, edema, thickening, and lichenification.[10,11,32]

Treatment

Every patient, no matter the severity of the allergy, should reduce environmental exposure to the triggers of symptoms. Cold compress and refrigerated topical medication are ancillary. Lubricants help to remove and dilute allergens that come in contact with the ocular surface.

Most patients with ocular allergies start treatment with self-medication, usually with over-the-counter eye drops.[33] Consultation with an allergy specialist is important for the identification of possible triggering agents (through allergy tests, serum-specific IgE determination, and/or conjunctival provocation tests), which allows for the guidance of environmental hygiene, a part of the treatment[5,9] and for the management of other types of allergic conditions, such as AR. In addition, knowledge of the sensitizing allergen can guide in the treatment for allergen-specific sublingual (SLIT) or subcutaneous immunotherapy (SCIT), both of which improve the quality of life of patients with OA. In some studies with SLIT, it was necessary to use topical medications to control symptoms.[34,35] The efficacy of immunotherapy is better established for the treatment of AR than for ocular symptoms; however, studies show a reduction in ocular symptom scores and in the use of topical medications, both in seasonal and perennial forms, in addition to increasing the allergen exposure necessary to provoke a reaction in conjunctival provocation tests.[10,36] There is suppression of type 2 immunity accompanied by early induction of regulatory T cells and type 2 innate lymphoid cells, immune deviation in favor of TH1 responses, and induction of local and systemic IgG, IgG4, and IgA antibodies.[37,38]

Aeroallergen polysensitization is common among patients with AC, and allergen immunotherapy is a safe and effective treatment option. Either SLIT or SCIT achieves clinical and immunologic improvement of ocular symptoms, and patient preference may determine the route of allergen administration.[39,40]

The pharmacological treatment of ocular allergies comprises topical and oral medications, including antihistamines, mast cell membrane stabilizers, corticosteroids, and immunomodulators[33,41–45] (Table 1).

Irrigation of the ocular surface helps to dilute and remove allergens, produce a barrier against allergens and irritants minimizing their effect on the conjunctiva. Artificial tears can provide immediate symptom relief, although they do not treat the underlying allergic response or modify the activity of inflammation mediators.[6,10,41]

Topical dual-acting agents (e.g., olopatadine, ketotifen, and alcaftadine), with antihistamines and mast cell–stabilizing properties, are first-line treatment in AC and are preferred for SAC and PAC.[43]

Oral antihistamines may provide some relief from OA symptoms but have a prolonged onset time. Second-generation H1 antagonists cause less sedation and less anticholinergic effects (dry eye) than first-generation ones.[6,13]

Because patients with AR or AC often have symptoms of both diseases, intranasal corticosteroids can have positive effects in controlling ocular symptoms.[40,41]

The effects of long-term chronic use of nasal corticosteroids on ocular symptoms have not been well studied, so they should not be used for the treatment of OA in the absence of nasal symptoms.[10]

Leukotriene receptor antagonists are useful in the treatment of AR, and although they have been shown to decrease levels of nitric oxide in the conjunctiva, their effect on OA is limited.[37,38,47]

Topical decongestants reduce some signs and symptoms of OA by vasoconstriction induced by α-adrenergic stimulation. This results in the improvement of chemosis and hyperemia, but they do not antagonize any of the mediators of allergic inflammation. Prolonged use and discontinuation of these agents can cause rebound hyperemia ("drug-induced conjunctivitis"), so they should be avoided. The combination of decongestants with topical antihistamines has different, but complementary and synergistic, mechanisms of action, and has better efficacy than either one alone.[6,10,37,48] Side effects like those described for the single drugs can be expected.

Mast cell membrane stabilizers prevent mast cell degranulation, release of preformed mediators, and synthesis of additional mediators.[4,40] They block the early and late phases of the ocular surface allergic response and are more effective when used prior to triggering the allergic reaction (prophylactic use). Because they need a longer period of use for optimal benefit and have a late onset of action, adherence to treatment with mast cell stabilizers can be troublesome. They are generally safe and have

Table 1 Pediatric ocular allergy treatment overview. Modified from Bielory et al.[46]

Therapeutic intervention	Clinical rationale	Pharmaceutical agents	Comments
Primary	Effective, simple		>30% symptom improvement
Avoidance			
Cold compresses	Decrease nerve stimulation, reduce vasodilation		Effective for mild to moderate symptoms
Preservative-free tears	Lubrication	Artificial tears	Highly recommended, comfortable, and safe
Secondary	Simple	Emedastine	Acute symptoms
Topical antihistamines			
Topical antihistamines and mast cell stabilizers	Relieve itching and prevent recurrence	Olopatadine Ketotifen Alcaftadine Epinastine	Safe, dual action
Topical mast cell stabilizers	Relieve mild to moderate symptoms	Cromolyn	Safe and effective
Nonsteroidal anti-inflammatory drugs	Improvement of symptoms	Ketorolac	Ocular side effects, often not tolerated
Tertiary	Relieve all facets of inflammatory response, including erythema, edema, and itching	Loteprednol Prednisolone Dexamethasone Fluorometholone	Short-term use only
Topical corticosteroids			
Topical immunomodulators	Improve symptoms	Cyclosporine Tacrolimus	Steroid-sparing effect
Oral immunosuppressants or immunomodulators	Relieve all symptoms. Severe refractory symptoms		Potential side effects
Immunotherapy	Identify and modulate allergen sensitivity	Subcutaneous or sublingual	Adjunctive to allergic rhinitis treatment
Ancillary	Improve itching	Second-generation antihistamines	Used if nasal symptoms are present; late onset action
Oral antihistamines			

minimal ocular adverse effects, although they may cause a burning sensation upon application. When combined with topical antihistamines (dual action), it has a faster onset of action (usually 30 minutes) and greater adherence.[6,10,48]

Nonhormonal anti-inflammatory drugs block the enzyme cyclooxygenase and arachidonic acid production of prostaglandins. They reduce ocular symptoms; however, they can cause systemic reactions, and local side effects, in particular an intolerable burning or stinging sensation during instillation and, occasionally, corneal perforation; therefore, their use must be monitored. Ketorolac is a formulation available for ocular topical use.[6,13,37]

Topical corticosteroids are the most effective therapy, as they reduce signs and symptoms of all phases and forms of OA due to nonspecific anti-inflammatory effects.[37] However, its use should be cautious and judicious due to the frequent occurrence of side effects, such as cataract, increased intraocular pressure, and greater susceptibility to infections.[42] More recent formulations, such as loteprednol, may not increase intraocular pressure.[39]

Immunomodulatory agents, such as topical cyclosporine 0.1% is commercially available in Europe, USA, Canada, and Asia.[49] Tacrolimus is commercially available only in Japan for the treatment of VKC. Tacrolimus ointments and creams are widely used to treat eyelid dermatitis and can improve conjunctival symptoms; however, they can irritate the conjunctival surface.[10,34,36]

Systemic corticosteroids may be prescribed for severe refractory cases, usually in short courses to avoid side effects. Systemic immunosuppression is an alternative for severe refractory and potentially vision-threatening allergy, and the most frequently prescribed immunosuppressant is cyclosporine, although micofenolate and azathyoprin may be used.[50,51]

New treatments are being studied for severe allergic keratoconjunctivitis, including biologicals such as dupilumab and omalizumab. Omalizumab, an approved antisystemic IgE antibody for asthma, has been used on an off-label regime in refractory VKC and AKC and reported in case series. Disease control was partial or complete in most patients, but a poor response was observed in some with very intense presentation.[37,51] There was a description of a patient with AKC who fully responded to the single application of 300 mg omalizumab.[52]

Dupilumab (anti-IL-4Rα) is a licensed and promising intervention in atopic dermatitis and asthma; however, ocular inflammation associated with dupilumab leading to cicatricial ectropion has been reported, suggesting that this

medication may not be ideal for the treatment of AKC with eyelid eczema.[53]

Biologicals are highly efficient and expensive.[54] Thus, they are usually justified only in severe and chronic illnesses. Omalizumab, dupilumab, and mepolizumab are approved in some countries for children aged 6 years and older, but not for isolated OA but eventually as comorbidities. Even though they theoretically look ideal for the treatment of severe T2 inflammation with local eosinophilia, the lesson from dupilumab teach us that the ocular system may function in a different way.[55]

In severe nonrespondent cases, giant papillae excision, local steroid injection, and amniotic membrane transplantation are surgical options for specialized ophthalmologists.

Conclusion

Ocular allergy is often associated with other atopic diseases such as asthma, rhinitis, and atopic dermatitis and is often underdiagnosed or misdiagnosed, and undertreated. The most common symptoms of eye allergy are itching, hyperemia, and tearing. Allergy tests can help in the diagnosis, for identifying possible triggering agents.

Topical dual-acting agents are the main medications used to treat ocular allergies. The use of topical corticosteroids is reserved for acute crisis of keratoconjunctivitis patients with severe and refractory symptoms, under the supervision of an allergist and ophthalmologist for potential local sight-threatening complications. Specific immunotherapy can increase the concentration of the allergen by up to 10–100 times in studies with conjunctival provocation, therefore, it is recommended in moderate and severe forms when the allergen is appropriately identified.

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