Allergic conjunctivitis: presentation, diagnosis, and management

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Abstract

Allergic conjunctivitis is a common ocular eye disease in Hong Kong. Severe allergic eye disease can cause permanent visual impairment if it is not managed appropriately. In this overview of the condition, the clinical presentation, diagnosis, and current management strategy will be discussed.

Key words: Allergy and immunology, Conjunctivitis, allergic, Diagnosis, Therapeutics

Introduction

Allergic conjunctivitis is a common ocular eye disease in Hong Kong. Many patients are young children and adolescents. A significant proportion of patients also have other atopic diseases such as allergic rhinitis, eczema, dermatitis, or asthma. Although patients with allergic conjunctivitis often have a similar presentation, careful ocular examinations can differentiate the condition into different subcategories, requiring different management strategies. Some patients may have severe allergic eye disease, and permanent visual impairment can result if this is not managed appropriately.

Incidence

The incidence of ocular allergy varies in different geographical regions and tends to be more common in countries with warm climates such as Italy and Japan. A recently published prevalence study in Japan showed that, of 1079 patients with allergic ocular disease, 90% was due to seasonal and perennial allergic conjunctivitis.1 The mean age was older than 50 years. Seasonal and perennial allergic conjunctivitis was found to be less severe than vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). An Italian study of 406 patients with chronic allergic conjunctivitis found that the overall prevalence was approximately 7.8/100,000 population, with a higher rate in young men (57.0/100,000 population) than in young women (22.0/100,000 population), and lower rates among people older than 16 years (3.8/100,000 population for men, 1.0/100,000 population for women).2 Epidemiological studies have been performed in Europe3 and the USA,3 but no studies have yet been performed to study the local epidemiology of allergic eye diseases in Hong Kong.

Classification

According to the severity and chronicity of the presentation, allergic eye diseases can be divided into acute and chronic disease. Chronic allergic conjunctivitis includes both VKC and AKC. Each of these subtypes has its own disease pattern, chronicity, and presentation. In this review, each of these subtypes will be discussed and some of the current treatment strategies will be outlined.

Acute allergic conjunctivitis

Acute allergic conjunctivitis is one of the most common forms of allergic eye disease. The condition can be classified as seasonal or perennial allergic conjunctivitis. In most patients, the causative allergens can be identified. Patients usually present with acute ocular symptoms of itchiness, tearing, ocular irritation, and discomfort. Classical signs include redness, injection, lid swelling, and chemosis. Allergens that can initiate these symptoms include dust mites, pollens, and fungi, the presence of which suggests a seasonal variation pattern. Patients usually have a history of atopy and previous allergies. A proportion of these patients will also have a history of asthma and allergic rhinitis.

Vernal keratoconjunctivitis

VKC is a rare disease, that usually affects boys around the age of puberty. According to a large case series performed in Italy, the average age at presentation is approximately 11 years.4 The disease usually waxes and wanes over its course.
and the severity will usually subside towards the end of puberty. VKC is clinically more severe and chronic than other types of allergic conjunctivitis, and patients have regular exacerbations during the course of the disease. Some patients also experience a climacteric pattern, with exacerbations in spring and autumn being more common.

Classically, these patients have itching, tearing, redness, and ocular discharge, which is similar to acute allergic conjunctivitis. Clinical signs include conjunctival injection, giant papillae in the tarsal conjunctiva (Figures 1 and 2), Trantas’ dots (Figure 3), and corneal complications of punctate epitheliopathy. Giant papillae are one of the hallmarks of the disease. Giant papillae consist of a papillary conjunctival mass >1 mm in size on the tarsal conjunctiva, with a proliferation of collagen underneath the conjunctival epithelium. The presence of giant papillae signifies prolonged chronic inflammation, and conjunctival fibrosis can occur in the long term.

The presence of giant papillae indicates poor prognosis of the disease. Trantas’ dots are round gelatinous white elevations over the superior limbal area, made up of collections of eosinophils. Corneal complications are secondary to the breakdown of corneal epithelium, with subsequent plaque formation with fibrin and mucus deposits on the ocular surface. These deposits lead to delayed corneal healing and formation of shield ulcers (Figure 4). Shield ulcers only occur in 3% to 11% of patients with VKC, but they can lead to permanent visual disability in 6% of patients with VKC.\(^4\)

**Atopic keratoconjunctivitis**

AKC differs from VKC, in that the presentation is more chronic and signs and symptoms can continue into adult life. AKC is rare, and is only seen infrequently by ophthalmologists. Patients experience the different sequelae of chronic allergic inflammation, and can present with severe excoriations, pigmentation, and scarring of the lids, due to prolonged eye rubbing. The tarsal conjunctiva no longer has signs of giant papillae, as in VKC, but is featureless with scarring formation. The eye could be itchy and red at times, but patients often have exacerbations that taper in severity, partly because they are getting used to the symptoms. However, patients can present with serious corneal complications, which include microerosions and punctate
epitheliopathy, macroerosion, shield ulcers, and plagues forming on the macroerosions secondary to prolonged delayed healing of the corneal epithelium and deposition of calcium on the de-epithelialised cornea. Patients often have complications of cataract (usually anterior subcapsular) and glaucoma. Some of these complications may be secondary to the disease, but may also be secondary to the prolonged use of topical steroids.

**Mechanisms of allergic eye disease**

In all forms of allergic eye diseases, the clinical response is caused by mast-cell activation due to either an antigen–mast-cell linkage or T-cell activation of mast cells. The activation of conjunctival mast cells leads to the release of histamine, prostaglandin D\_2, leukotriene C\_4, tryptase, chymase, platelet activating factor, and other chemo-attractants. This further attracts eosinophils and neutrophils.\(^5_8\) VKC and AKC are traditionally seen as type I immunoglobulin (Ig) E–mediated hypersensitivity reactions. However, current evidence shows that eosinophils and their major basic proteins are also important in the chronic allergic process of ocular surface inflammation and epithelial damage.\(^9\)

Chronic allergic conjunctivitis is associated with increased concentrations of T helper–1 (Th1) and Th2 cells, which stimulate the migration and proliferation of conjunctival fibroblasts, as well as protecting these cells from apoptotic cell death, effects that likely underlie the hyperplasia of fibroblasts, contributing to the formation of giant papillae. Stimulation of fibroblasts in the corneal stroma with the combination of a proinflammatory cytokine and either interleukin (IL)-4 or IL-13 results in upregulation of the expression of the chemokine eotaxin and thymus- and activation-regulated chemokines, as well as vascular cell adhesion molecule-1, which together mediate the infiltration and activation of eosinophils and Th2 cells.\(^10\) Fibroblasts therefore appear to play a central role in the induction and amplification of ocular allergic inflammation and the consequent development of giant papillae and corneal disorders in individuals with VKC.

**Treatment**

The treatment regimen for allergic conjunctivitis is multidisciplinary. Many patients may have associated atopic diseases of asthma and rhinitis, which necessitates a multidisciplinary approach, involving paediatricians, medical physicians, general practitioners, and clinical immunologists. Avoidance of allergens is an important strategy. For the ocular involvement, the mainstay of treatment includes topical medications. Oral medications are only indicated for severe disease.

Current topical medications for allergic conjunctivitis include topical antihistamines, mast-cell stabilizers, eosinophil deactivators, and lubricants (Table 1). Anti-inflammatory drugs, including topical steroids and non-steroidal anti-inflammatory drugs (NSAIDs), are usually required for more severe disease. The most useful medications for rapid relief of symptoms include topical antihistamines (antazoline, levocabastine, and emedastine). Through their immediate histamine receptor antagonist effect, these antihistamines can reduce the itching, redness, and swelling commonly seen in acute allergic blepharoconjunctivitis. The onset of action of topical medication is faster than for oral antihistamines. These agents can be used on an as needed basis for patients with occasional allergic eye symptoms and can offer great relief. Oral H\_1-receptor antagonists (astemizole, terfanidine, and loratadine) have also been shown to be effective for alleviating ocular symptoms.

These agents are excellent choices for control of multiple early-phase and some late-phase allergic symptoms in the eyes, nose, and pharynx.\(^10,11\) However, the clinical effect is offset by the longer time of action and accompanying systemic side effects of sedation and dry mouth. Hence oral medications are not generally selected for allergic eye disease.\(^11\) The newer second-generation antihistamines (cetirizine, fexofenadine, loratadine, and desloratadine) are preferred to the older first-generation antihistamines as they have fewer sedative and anticholinergic side effects.\(^10,11\)

Mast-cell stabilizers are useful during the quiescent phase to prevent exacerbations. The most commonly used medication is sodium cromoglycate eye drops. The philosophy behind these mast-cell stabilizers is that they can prevent mast cells becoming degranulated, stopping initiation of the allergic and inflammatory cascade. Therefore, this medication is especially useful if patients can start a course several days before an expected exposure to allergens. Symptom relief may be less effective for an acute allergic attack.\(^3,11\)

Topical vasoconstrictor agents provide rapid relief of symptoms, especially redness. However, the relief is often short-lived, and overuse of vasoconstrictors may lead to rebound hyperemia and irritation.

Recently, new medications with a combination of antihistamines, mast-cell stabilizers, and eosinophil deactivators

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<th>Table 1. Medications for allergic conjunctivitis.</th>
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<td>Medication</td>
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<tr>
<td>Topical or oral antihistamine (antazoline, levocabastine and emedastine)</td>
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<tr>
<td>Topical mast-cell stabilizer (sodium cromoglycate)</td>
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<td>Topical combined agents (olopatidine, ketotifen)</td>
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<td>Topical non-steroidal anti-inflammatory drugs (ketorolac)</td>
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<td>Topical steroids</td>
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<td>Topical cyclosporine</td>
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in one formulation with superior clinical effects have been developed. These combination medications include olopatadine (Patanol®), ketotifen (Zaditen®), and epinastine (Elastar®), which have been found to provide a superior clinical response to the traditional antihistamines alone and have now become the medications of choice. The twice daily dosing regimen for most of these medications is also a potential benefit for patients compared with some of the older antihistamines.

Olopatadine is a selective H₁-receptor antagonist and has mast–cell membrane stabilizing properties, inhibiting the release of the inflammatory lipid mediators leukotrienes and thromboxanes from polymorphonuclear leucocytes and eosinophils. 12,13 Ketotifen is a similar medication, which blocks the H₁ receptors, stabilizes mast cells, and inhibits chemotaxis and activation of eosinophils. 14,15 Epinastine is another potent H₁-receptor antagonist that showed good in vivo and in vitro evidence of antiallergic and anti-inflammatory effects in addition to antihistaminergic properties. 16

A randomized double-blind controlled trial to study the effect of olopatadine 0.1% versus placebo by Abelson and Turner has shown a decrease in symptoms and signs scores for seasonal allergic conjunctivitis with olopatadine. 17 A double-masked environmental study of patients with seasonal and perennial allergic conjunctivitis showed that olopatadine achieves better efficacy and comfort scores than ketotifen. 18 However, another randomized double-masked study comparing ketotifen and olopatadine showed no difference in clinical effects and improvement in inflammatory markers on conjunctival impression cytology. 19

A recent randomized double-blind placebo-controlled trial comparing the effect of topical olopatadine, ketotifen fumarate, epinastine, emedastine, and fluorometholone acetate found that all the medications except for fluorometholone were equally effective for reducing itching and redness. There were no clinical differences in terms of reducing tearing, chemosis, and swelling amongst the medications studied. 20 Compared with olopatadine, some studies have revealed that ketotifen and epinastine can have higher degranulation-inducing effects on corneal epithelial cells and mast cells, and may be less comfortable to use than olopatadine. 15,21 Further clinical trials are necessary to further investigate the side-effect profiles and tolerability.

NSAIDs, with their effect of inhibiting prostaglandin synthesis, including prostaglandins D₂ and E₂, have had clinical effects for patients with seasonal allergic conjunctivitis. Ketorolac (Acural®) has been approved by the FDA for this indication. Studies of ketorolac have shown a superior effect to placebo for control of allergic symptoms. 22 A comparative study of ketorolac and olopatadine by Yaylali et al found an equally effective profile for alleviating symptoms and signs of seasonal allergic conjunctivitis in 40 patients. 23 However, olopatadine reduced ocular itching significantly more than ketorolac. Therefore, topical NSAIDS are generally inferior for relief of allergic conjunctivitis than olopatadine and emedastine.

Topical corticosteroids may be considered for symptoms of severe seasonal ocular allergy, although long-term use should be avoided because of the risks of ocular adverse effects, including glaucoma and cataract formation.

Topical cyclosporine (Restasis®) has received much interest in recent years. Treatment benefits have been noted for patients with keratoconjunctivitis sicca and chronic dry eye. 24 The evidence shows that this medication is also helpful for treating allergic eye diseases. Studies by Hingorani et al 25 and Akpek et al 26 have shown clinical improvement for both the 2.00% and 0.05% concentrations. However, studies have had conflicting results. 25-28 The most effective concentration and dosing regimen for this medication have yet to be confirmed.

Studies have shown that topical cyclosporine could lead to a reduction of epithelial and stromal class II major histocompatibility complex cells, T-helper cells, and IgA and IgG plasma cells in patients with VKC, highlighting an immunomodulating effect on cell-mediated and humoral immune responses. The effects on mast cells and IgE-mediated allergic responses are not significant. 29 Since VKC and AKC involve both IgE and non-IgE mechanisms, cyclosporine should have some clinical effect on VKC. However, the clinical effects and improvement of signs need to be further quantified.

Patients with asthma and VKC now have more choice for their medications. Montelukast, a leukotriene-receptor antagonist has demonstrated a clinical effect in patients with asthma. Its efficacy for the treatment of allergic rhinitis, atopic dermatitis, and allergic eye disease is now being recognized. 30-31 A recent study by Lambiase et al showed significant improvement in physician-rated hyperemia, secretion, and chemosis, as well as patient-rated burning, tearing, photophobia, secretion, and redness for patients with VKC. 30 The clinical effect persisted for 15 days after discontinuation of treatment. It is yet to be seen whether this medication will be useful for chronic allergic eye disease in the long term.

Measures such as cold compresses, eyewashes with tear substitutes, and avoidance of allergens are also helpful ways to alleviate symptoms of allergic eye disease.

Conclusions

As many patients with allergic eye disease are young, they may not be able to provide a full clinical history. It is important that the clinician is cautious when managing young patients with red eyes, so as not to miss the important symptoms and signs of chronic allergic eye disease. Patients who are not treated appropriately are at risk for permanent visual complications. Therefore, young patients who present with itchy red eyes should be investigated. Patients with symptoms that cannot be alleviated with traditional antihistamines should be referred for specialist management.
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