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focus

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Chronic Allergic Eye Disease

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It is usual to classify allergic conjunctivitis as acute or chronic disease. Acute allergic conjunctivitis can be seasonal or perennial, depending on whether seasonal (e.g. pollen) or perennial (e.g. house dust mite) allergens are responsible. They can cause distressing symptoms, but sight-threatening complications are unusual. Chronic allergic conjunctivitis is sub-classified as vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). The clinical differences and management of these two phenotypes is the topic of this update.

Definition of disease

VKC has a mean onset of disease of approximately eight years of age with a marked seasonal variation in activity with exacerbations in the spring or summer, but with a strong tendency for eventual remission in late teens or after puberty. Sight-threatening complications are uncommon but can result from a corneal epithelial defect, calcification (vernal plaque), secondary neovascularisation or iatrogenic disease (e.g. steroid-induced cataract or glaucoma). Usually, in temperate regions, VKC and atopic dermatitis (eczema) or allergic asthma appear simultaneously. In contrast, AKC characteristically develops in adulthood, following years or decades of severe facial atopic dermatitis. Symptoms are chronic and perennial, with no expectation of eventual remission for the majority of patients. Sight-threatening complications result from corneal vascularisation, persistent epithelial breakdown, cataract and secondary glaucoma. There is almost always conjunctival scarring that can lead to secondary abnormalities of lid position that may exacerbate the ocular surface disease. A small proportion (5%) of individuals with VKC progress to a phenotype characteristic of AKC in adulthood.

Epidemiology

The prevalence of chronic allergic conjunctivitis is unknown. In temperate regions, VKC has been estimated to affect 2-3 per 10,000 population. It is much more common in equatorial areas, where it is a significant public health problem. VKC is also more common in males than females, especially of South Asian or North African ethnicity. AKC is even rarer, and there is no reliable prevalence data. Whether the prevalence of chronic allergic eye disease has increased in parallel with the increase in other atopic disorders is not known.

System associations

Patients in both groups usually have associated atopic dermatitis and asthma. Patients with VKC are often sensitive to airborne allergens (e.g. pollen, animal dander and house dust mite), while patients with AKC can demonstrate additional sensitivity to moulds and bacterial proteins. Both groups may show impaired delayed-type hypersensitivity with susceptibility to viral infection (herpes simplex, molluscum contagiosum). Patients with AKC may also be at risk of conjunctival squamous cell carcinoma, especially if systemically immunosuppressed.

Lids and periocular skin

Individuals with VKC often have periocular atopic dermatitis, skin pigmentation, excoriation of the skin and angular fissuring. There may also be reactive ptosis if there are giant conjunctival papillae of the upper lid or corneal disease. Similar, but more severe, changes can occur in AKC but with additional lid margin thickening, loss of lashes and lower lid ectropion causing epiphora. The lids of patients with AKC are often heavily colonised with Staphylococcus aureus.

Conjunctival changes

There is a spectrum of conjunctival change in VKC that has resulted in a further sub-classification into predominantly upper lid palpebral change (palpebral VKC) or predominantly limbal papillary change with Tranta dots (limbal VKC). Some individuals demonstrate the features of both. This distinction is valid because corneal complications are more common in patients with the palpebral disease, presumably as the result of the juxtaposition of the inflamed upper lid conjunctiva and the corneal epithelium. In surveys from South Asia and North Africa, the limbal form of the disease is more common than the palpebral form. AKC predominantly involves the upper lid tarsal conjunctiva with characteristic giant papillae early on, but with micropapillae on the lower tarsal conjunctiva and fornix. In chronic AKC, giant papillae may no longer be present, when the tarsal conjunctiva takes on a flat, homogenous, and scarred appearance, even during periods of disease activity.

Corneal changes

The presence of central corneal disease is a feature of palpebral VKC. During active inflammation, a mucous layer - demonstrated with Lissamine Green - can adhere to the superior corneal epithelial surface, which is then at risk of breakdown (macro-erosion) with subsequent deposition of calcium to form a vernal plaque. Individuals are then also at risk of secondary neovascularisation and infection. In AKC a diffuse epitheliopathy of the inferior third of the cornea may predominate, a result of the adjacent lid disease or exposure from ectropion. Corneal neovascularisation in AKC may be chronic and unremitting. Chronic inflammation can lead to corneal limbal epithelial stem cell failure or the rapid onset of massive stromal lysis. Both groups are at risk of herpes simplex keratitis, which can assume a geographic pattern even in the absence of topical steroid use. There is a strong association between chronic allergic conjunctivitis and keratoconus. The keratoconus can be severe, and there is an increased risk of acute corneal hydrops. The presence of severe allergic disease can make contact lens wear difficult to tolerate and increase the chances of complications following keratoplasty. Patients with AKC are particularly at risk of delayed epithelialization after keratoplasty as well as microbial infection or reactivation of herpes simplex keratitis.

Corneal plaque and infection

The accumulation of calcium and mucous on the exposed stromal surface following epithelial breakdown can result in a corneal plaque. The calcium physically prevents re-epithelialization, and calcification usually extends significantly peripheral to the epithelial defect. Control the allergic eye disease is essential before attempting to debride a plaque. The epithelium should be reflected to identify the margins of the calcification. If there is a plaque there is a risk of infection and children should be prescribed a prophylactic antibiotic, but due to the concurrent use of topical steroid infectious crystalline keratopathy can still occur. Patients with AKC are also at risk of infection secondary to their severe ocular surface disease and lid colonisation with Staphylococcus aureus, as well as a fungal infection (yeast or mould).

Cataract

Approximately 8% of children with severe VKC develop an anterior cortical cataract, irrespective of the use of topical steroid. Chronic topical steroid can also accelerate the formation of posterior sub-capsular cataract in both groups. In AKC, in particular, there is an increased risk of infectious endophthalmitis following cataract surgery. Chronic, unsupervised topical steroid use can lead to secondary glaucoma and visual loss. Monitoring intra ocular pressure and optic disc appearances, particularly in children who are not co-operative with examination, is mandatory, even if this requires examination under anaesthesia.

Differential diagnosis

The primary differential diagnosis of VKC in children is blepharokeratoconjunctivitis (BKC). However, in BKC the conjunctival change over the upper tarsus is usually relatively minor and micropapillary, although corneal phlyctenules and neovascularisation can cause progressive visual loss. In AKC, the conjunctival cicatrisation can mimic ocular cicatricial pemphigoid. Staphylococcal hypersensitivity and rosacea may coexist with AKC and complicate the clinical picture.

Investigation

The clinical appearance of VKC is characteristic, and further investigation is rarely required to confirm the diagnosed. Total serum IgE does not reflect disease severity, and quantification of specific IgEs in tears or conjunctival challenge is rarely possible outside the setting of research. Similarly, consider referral to an allergist if there are severe associated asthma and atopic dermatitis, but skin or RAST testing to identify potential allergens is rarely helpful in the management of ocular disease.

Pathophysiology

The basis for acute allergic conjunctivitis in an abnormal response to environmental allergens. Studies suggest there is a genetically determined increased epithelial permeability (typically to soluble peptides), that are then processed by dendritic cells and B cells with the formation of specific IgE-coated MAST cells, which show anaphylactic degranulation following re-exposure to the allergen. However, there are likely to be additional abnormalities in both the innate and adaptive responses. In AKC, bacterial colonisation of the ocular surface leads to amplification of the inflammatory response and damage to the ocular surface due to the release of bacterial proteins.

Management

Topical or oral antihistamines and topical mast cell stabilisers are the first options for the control of symptoms of acute allergic conjunctivitis. In chronic allergic conjunctivitis, it is usually necessary to add topical or systemic steroid or immunosuppression (ciclosporin, tacrolimus). Realistic goals should be identified, particularly in young patients with VKC, aiming to control symptoms while minimising absence from school and iatrogenic disease. Emphasise the high expectation for the eventual resolution of VKC. Monitoring activity of disease in VKC can be problematic and usually relies on an objective assessment of conjunctival redness, mucous production and corneal epithelial disease. Limbal papillae reflect disease activity, but giant tarsal papillae only reduce in size slowly with treatment. A step-wise approach can be helpful. Aim for long-term management with lubricating drops, topical cromones (e.g. cromoglycate), MAST cell stabilisers or topical antihistamines. An oral antihistamine may help with sleep and help prevent nocturnal eye rubbing. Discuss the role of allergen avoidance (hypo-allergenic bedwear). For more severe disease topical steroid is often required, and topical calcineurin inhibitors (ciclosporin, tacrolimus) can be helpful to reduce reliance on corticosteroid. In acute exacerbations, or before surgery to remove corneal plaque, a short course of intensive topical steroid can be useful bring symptoms and signs under control. In severe cases, who are at risk of visual loss, consider systemic immunosuppression under the supervision of a paediatrician. Montelukast can be helpful in the sub-group with severe allergic asthma. The role of biological IgE-blocking molecules such as Omalizumab should be thoroughly evaluated. Unfortunately, some of the newer biologics for asthma and eczema can exacerbate rather than improve the eye disease (e.g. Dupilumab-related conjunctivitis). In children undergoing surgery to remove a plaque, there is an opportunity for a depot supra-tarsal injection of triamcinolone.

We recommend a similar step-wise approach to the management of AKC. However, in these individuals, more attention should be directed to any associated ocular surface disease, including trichiasis, ectropion and corneal exposure. Treatment of secondary lid margin infection and angular fissuring with a topical antibiotic such mupirocin can be helpful. Bacterial colonisation may have a significant role in AKC, and topical Azithromycin or oral Doxycycline may reduce the bacterial load of the lid margin and reduce inflammation. Before cataract or graft surgery patients with AKC may require systemic immunosuppression to control their ocular surface inflammation, which should then be continued for some months or at least until there is stable re-epithelization. Cover surgery with an oral antiviral agent, e.g. Aciclovir 400 mg bd.

Summary

Both VKC and AKC are uncommon diseases, and both can have severe implications for patients and their families. The prognosis and management of the two conditions are not identical, and a tailored approach is required. With a step-wise approach to management, it is possible to control the majority of symptoms to enable a reasonable quality of life. Unfortunately, secondary complications of treatment and uncontrolled disease still occur. The relative rarity of these conditions and poor reporting of outcomes in controlled trials has made interpretation of clinical studies of comparative therapies difficult.

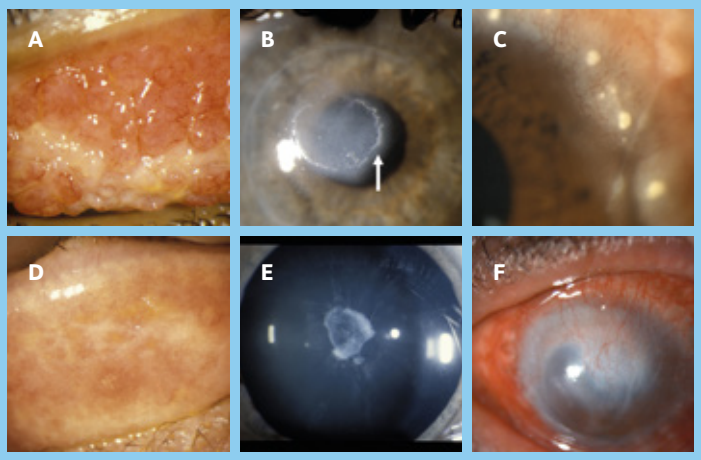

Figure 1

Palpebral vernal keratoconjunctivitis (VKC) showing giant papillae >1mm diameter and mucous production indicating active disease (A). Calcified corneal plaque (B) with calcium extending peripherally to the epithelial defect (arrow). Limbal VKC with papillae and white Tranta dots (C). Everted upper lid of individual with atopic keratoconjunctivitis (AKC) showing dense scarring and flattened giant papillae (D). Anterior polar cataract unrelated to corticosteroid use in an individual with VKC (E). Peripheral corneal vascularisation and opacity in AKC that can progress to limbal epithelial stem cell failure (F).

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