



Is visual function affected in severe ocular allergies?

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Purpose of review

The purpose of the present review is to provide an overview on the clinical features and long-term complications of severe ocular allergies, with a special focus on the corneal involvement observed in these diseases, which may impair vision permanently. Furthermore, different treatment options are discussed based on the sight-threatening effects of corticosteroid use.

Recent findings

Recent data on the demographics, clinical and immunologic features of vernal and atopic keratoconjunctivitis are presented and discussed, and the evidence of a lack of literature addressing the issue of visual outcome in allergic diseases is underlined. The efficacy and possible long-term complications of their treatments are described, including visual impairment.

Summary

Diagnosis and treatment of patients with severe ocular allergy is a challenge for ophthalmologists due to the long-term corneal complications and the potential side-effects of topical corticosteroids that may induce cataract formation and glaucoma, and impair vision permanently. The review describes old and new concepts of management and possible complications such as severe, vision-threatening forms of allergic ocular disease. An update on their management and long-term complications may help clinicians to establish a common agreement on treatment options and researchers to design future studies based on similar outcomes, including visual acuity.

Keywords

atopic keratoconjunctivitis, corneal complications ocular allergy, vernal keratoconjunctivitis, visual impairment

INTRODUCTION

Allergic conjunctivitis is often considered an easy-to-treat and self-limiting allergic inflammation of the conjunctiva without long-term complications and potential damage for the visual function. However, the ocular allergic syndromes include a variety of diseases of the ocular surface also affecting lids, cornea, lachrymal gland and tear film, at different levels of severity. Whereas it is true that mild forms with no corneal involvement rarely interfere with visual function – although they can still interfere significantly with patients' quality of life – more severe cases may result in permanent visual damage due to corneal involvement and long-term treatment complications, or either of them.

The mild forms of ocular allergy include seasonal/intermittent allergic conjunctivitis (SAC) and perennial/persistent allergic conjunctivitis (PAC), which are usually well controlled with topical antiallergic drugs and do not result in visual impairment if managed correctly without using

corticosteroids [1[•]]. The more severe and potentially sight-threatening forms include vernal keratoconjunctivitis (VKC) and atopic keratoconjunctivitis (AKC). The former is typical of young boys; the latter can be found in both children and adults. In these two chronic forms of allergic keratoconjunctivitis, a persistent state of mast cell, eosinophil and lymphocyte activation is found, associated with an important corneal involvement, tissue remodelling and fibrosis, resulting in potential scarring and corneal opacities. Therefore, the risk of visual impairment in both VKC and AKC is definitely high. Moreover,

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KEY POINTS

- The risk of visual impairment in VKC and AKC is definitely high.
- Visual loss may be due to corneal complications such as ulcers, scarring, corneal opacities, limbal stem cell deficiency, astigmatism and keratoconus.
- Unsupervised use of topical corticosteroids may induce cataract, glaucoma and infections.
- The clinical approach to atopic patients with keratoconus has not been standardized.

visual loss may be due to other corneal complications, including limbal stem cell deficiency, astigmatism and keratoconus, as well as to complications of the unsupervised use of topically administered corticosteroids, which may induce cataract formation and glaucoma.

SEVERE OCULAR ALLERGIES

Vernal keratoconjunctivitis is a severe ocular allergic disease that occurs predominately in children [2,3]. Most VKC patients complain of symptoms from early spring to fall, with differences among climate zones. Exacerbations of the disease and acute episodes arise, triggered by allergen exposure or, more frequently, by nonspecific stimuli such as wind, light and dust. VKC is an IgE and Th2-mediated disease; however, only 50% of patients present a clearly defined allergic sensitization.

Intense itching, tearing and photophobia are the classic symptoms of these patients. The presence of pain associated with photophobia is indicative of corneal involvement. Foreign body sensation may be caused by mucous hypersecretion, papillae hypertrophy and superficial keratopathy. Various grades of conjunctival hyperemia and chemosis are always present in both forms of the disease. The tarsal form is characterized by irregularly sized hypertrophic papillae, leading to a cobblestone appearance on the upper tarsal plate and abundant mucus that may be incarcerated between them. The limbal form of the disease is characterized by multiple gelatinous, yellow-grey limbal infiltrates and papillae, whose size and location may change over time. The limbus may appear thickened and opacified for 360. The apices of infiltrates may appear as punctiform calcified concretions called Tranta's dots. In the mixed form of the disease, both tarsal and limbal signs are observed to varying degrees. Blepharospasm, tearing and mucus hypersecretion may be present in all VKC forms, whereas

pseudoptosis is usually secondary to the presence of heavy tarsal giant papillae.

Corneal involvement is common in VKC, and is more frequent in tarsal than limbal patients, taking the form of a superficial punctate keratitis, epithelial macroerosion or ulcers, plaque, neovascularization, subepithelial scarring or pseudogerontoxon. Ulcer formation is preceded by a progressive deterioration of the corneal epithelium, which appears irregularly stained and covered with fine filaments.

Atopic keratoconjunctivitis is a rare disease that comprises less than 1% of all ocular allergies. Generally, it emerges in children with active atopic dermatitis or in young adults, and continues through the fifth decade of life, reaching its peak incidence between the ages of 30 and 50 [4]. A family history of allergic conditions is common, whereas 95% of patients have a history of eczema and 87% have a history of asthma. AKC presents as a chronic bilateral conjunctivitis with seasonal exacerbations corresponding to the offending allergen/s or food exposure. The common presenting symptoms are bilateral ocular itching, burning, tearing and mucous discharge. The hallmark sign of AKC is erythematous, exudative lesions of the lids [1,5]. Eyelids tend to be thickened, indurated, erythematous and fissured, due to eczema, and is often associated with chronic blepharitis, meibomian gland dysfunction and staphylococcal infection. The lids of about 90% of atopic patients are colonized with *Staphylococcus aureus* rather than the usual staphylococcal flora; however, their presence does not correlate with the incidence or severity of keratopathy [6]. The limbus may present Tranta's dots and the tarsal conjunctiva may present giant papillae similar to those observed in VKC patients. Cicatrizing conjunctivitis, subepithelial fibrosis and symblepharon have also been reported, with the lower fornix possibly shrinking subsequent to scarring. Reduced tear function and tear volume may also be observed. Punctate keratitis, persistent epithelial defects and ulcer with plaque formation are possible complications. Keratoconus is also often associated with AKC (see later). Herpes keratitis and microbial infections may complicate the disease, particularly if chronic topical steroid therapy is required. Severe keratopathy with corneal neovascularization, pannus formation and stromal keratitis may develop as a consequence of repeated corneal inflammation.

VISUAL IMPAIRMENT AND LOSS IN SEVERE OCULAR ALLERGIES

Several of the above mentioned clinical signs or ocular complications may induce permanent or

fluctuant visual impairment in VKC. We found a decreased visual function in 2% of patients with VKC in a long-term follow-up study [3]. Possibly, central corneal scars, cataract or steroid-induced glaucoma are the main causes of the visual function impairment. In addition, keratoconus or an irregular astigmatism greater than 2 diopters was found more than six times higher in VKC patients than in controls. These patients are not tolerant to contact lenses due to giant papillae and severe inflammation.

In one study [7] of 58 consecutive VKC patients, 12 (21%) had a best corrected visual acuity in one or both eyes of 20/200 or less, 20 (34%) had 20/50 to 20/200 vision and 26 (45%) had 20/20 to 20/50 vision. The ocular complications that led to visual loss among these 32 patients included steroid-induced cataract (8 patients), steroid-induced glaucoma (4), central corneal scars (7), irregular astigmatism (4), keratoconus (3) and limbal tissue hyperplasia (3). Of the 32 patients, 12 had dry eye syndrome, which may have contributed to the visual loss. In addition to possible permanent vision loss, the longer the shield ulcer persists, the greater the likelihood of sterile ulceration, corneal scars, bacterial keratitis, amblyopia and globe perforation [7]. Fungal keratitis may be associated with VKC.

Children with VKC in Rwanda had more than six times higher risk to have corneal astigmatism greater than 2 diopters in their worse eye [odds ratio (OR) 6.31, 95% confidence interval (CI) 3.26–12.26, $P < 0.001$] than controls [8^{*}]. Eight affected eyes had astigmatism greater than 4 diopters or irregular astigmatism incompatible with keratometry. In the same study, although four eyes (1.7%) had uncorrected low vision from VKC-induced corneal astigmatism or keratoconus, only one child was visually impaired in both eyes.

Visual impairment is mainly due to involvement of cornea in a cohort of 220 patients in Nepal [9]. A best corrected visual acuity of more than 6/9 was found in 96.4% of patients, whereas 2.3% had a visual acuity less than 6/12. Corneal superficial keratopathy was reported in 9.5% of patients, whereas shield ulcer, pannus, corneal scar and keratoconus were reported in 8.3% of the whole VKC population. In a cross-sectional survey including 1144 primary and secondary school students in Nigeria, VKC was found in 7.4% of this population and was a cause of blindness in 0.08% of the whole population [10].

CORNEAL ECTASIA AND ALLERGIC CONJUNCTIVITIS

The hypothesis that allergy, itching and continuous prolonged rubbing are relevant to the pathogenesis

of keratoconus is still unclear. The association between atopy and keratoconus has been reported; however, there was no statistically significant difference between the group of keratoconus patients and the control group with respect to the presence of atopy [11]. Nevertheless, it has been reported that, in a healthy population, 3% of individuals had eczema, whereas in patients with keratoconus, 32% of patients had eczema and itchy eyes [11]. In another study [12], the prevalence of asthma in the control group was 1%, whereas it was 17.9% in keratoconus patients. In a recent cohort study [13], asthma, eczema and hay fever were associated to keratoconus in 23, 14 and 30%, respectively, and 48% reported significant eye rubbing. It has also been reported that in keratoconus patients with atopy, the progression of keratoconus takes place more rapidly, the need for keratoplasty surgery appears earlier, and both refractive and immunologic complications are seen more frequently [14]. These findings have led to the concern of whether atopic keratoconus patients should be evaluated as a separate entity in keratoconus disease.

Children with VKC have a high incidence of keratoconus if investigated by videokeratographic maps and have more abnormal topography patterns than expected compared with normal eyes [15]. A recent study [16] showed that atopic keratoconus eyes have steeper cones that appear to be thinner centrally, and both the thinnest point on the cornea and the cone are more peripherally located. In a separate study [17], unlike in axial curvature maps, most apices in elevation maps were clustered in the infero-temporal quadrant. Corneal topography characteristics in keratoconal eyes with atopy are different from those in keratoconal eyes without atopy; thus atopic keratoconus patients may indeed be a separate entity in this disease. The clinical approach to patients with keratoconus and some form of allergy has not been standardized.

Keratoglobus is characterized by global corneal thinning and ectasia of the cornea, and has been reported in patients with vernal keratoconjunctivitis [18]. Severe microbial keratitis in a patient with corneal hydrops in keratoglobus-associated vernal keratoconjunctivitis and atopic dermatitis has been described [19]. This rare comorbidity can impair corneal integrity and immunity, and may allow rapid penetration of infectious organisms. These patients are at high risk for developing a severe sight-threatening ocular infection that may respond poorly to intensive medical management.

Several studies have shown that penetrating keratoplasty in eyes with keratoconus and VKC has an excellent visual outcome and low complication rate. Graft rejection episodes occurred in

13.3% eyes, with irreversible graft failure occurring in 4.4% eyes. Bacterial keratitis occurred in 7.7% eyes, 2.2% of which developed irreversible graft failure [20]. In another study, the clinical outcome of penetrating keratoplasty (PK) in eyes with keratoconus and VKC was comparable to that in eyes with keratoconus alone. However, because complications such as prematurely loosened sutures and steroid-induced cataract were more common in the coexistence of VKC, closer monitoring in these cases was recommended [21].

Postkeratoplasty atopic sclerokeratitis (PKAS) is a potentially severe complication in atopic patients undergoing keratoplasty [22]. Principal recommendations for these patients include the use of interrupted sutures and early immunosuppression with high-dose oral steroids at the onset of the inflammatory condition, together with control of risk factors for microbial keratitis. Systemic immunosuppression should be considered before PK in patients with active atopic blepharitis and corneal neovascularization [23].

VISUAL OUTCOME IN ALLERGIC CONJUNCTIVITIS

In spite of the abundant literature describing the possible sight-threatening complications of severe ocular allergies, the analysis of clinical trials performed to evaluate safety and efficacy of medical treatments for allergic conjunctivitis, including both VKC and AKC patients, clearly demonstrates that visual outcome has been, to date, a neglected issue [24,25^{*}]. Moreover, a recent systematic review of clinical trials in allergic conjunctivitis has demonstrated that only a limited number of trials fulfill all criteria of proper clinical trial design: this appears to be especially true for the severe forms of allergic conjunctivitis [25^{*}]. In fact, masked, placebo-controlled studies are not always feasible for ethical reasons in severe diseases with corneal involvement, which can result in long-term complications and sight loss if not properly treated. However, it must be underlined that even in open uncontrolled trials, visual acuity unfortunately never represents a primary outcome and endpoint of treatment, and is only rarely evaluated as a secondary outcome of treatment efficacy.

CONCLUSION

In this review, we have described the more severe forms of allergic conjunctivitis and their possible long-term complications. Among them, we put a special focus on the possible development of corneal disease, which may range from corneal

opacification and scarring, to corneal ectasia such as keratoconus, invariably leading to permanent sight loss and the possible need of surgical interventions.

We also showed that evidence coming out of clinical trials on medical treatments for severe ocular allergy is limited, and does not properly address the issue of vision impairment. As a result, the strength of recommendations to ophthalmologists for optimal management of these conditions is quite limited and may result in an inadequate use of topical corticosteroids, which carry the risk of long-term complications, including cataract formation and glaucoma. Therefore, we underline the need of considering visual acuity as a primary outcome of future clinical trials on ocular allergies affecting the cornea.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 584–585).

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