Differential diagnosis of severe ocular allergies

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Aim of the lecture

• Ocular allergy is usually considered of minor clinical relevance, just as a symptom or a “complication” of “rhino-conjunctivitis”
• However, some allergic eye diseases are very severe and may lead to loss of vision
• This lecture aims at discussing symptoms, signs and co-morbidities that may help in identifying the most severe ocular allergies, to be adequately jointly faced by allergists and ophthalmologists.

The heterogeneity of conjunctival inflammation

Red Eye

History

Watery

Water

Bilateral

Itchy

Sticky

Burning

Foreign body sensation

Infectious conjunctivitis

Viral

Chlamydial

Bacterial

Parasitic

Fungal

Recurrent

Autoimmune

Pemphigoid

Epidermolysis

Uversitatis

Non-specific

Hyperreactive eye

Foreign body

Chemical induced

Acne rosacea

Dry eye

Allergic Conjunctivitis

Toll-Like receptors expression in VKC

Micsa A et al. 2006

Dry eye

<table>
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<tr>
<th></th>
<th>Aquous tear deficiency</th>
<th>Meibomian gland disease</th>
<th>Iris-Grey Eye association (IDEA)</th>
<th>Allergic conjunctivitis</th>
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<td>Clinics</td>
<td>Autoimmune diseases</td>
<td>No systemic disease</td>
<td>Polycystic ovaries with hyperandrogenism</td>
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<td>Treatment</td>
<td>Immunosuppressive agents</td>
<td>Tear substitutes</td>
<td>Anti-androgenic drugs</td>
<td>Anti-allergic drugs</td>
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<td>Skin tests</td>
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<td>++ (25% + ve)</td>
<td>+++ (50-90% + ve)</td>
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<td>Schirmer test</td>
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<td>Break-up time</td>
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<td>Goblet cells density</td>
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Clinical forms of Allergic Conjunctivitis

- Acute allergic conjunctivitis (AAC)
- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (VKC)
- Atopic keratoconjunctivitis (AKC)
- Giant-papillary conjunctivitis (GPC)

Late-phase allergic reaction in the eye

- Histamine
- Histamine Tryptase
- Histamine LTs
- ECP

Phenotypes of Allergic Conjunctivitis

- Seasonal or perennial
- Vernal
- Atopic
- Giant papillary

Prevalence of nasal symptoms in allergic conjunctivitis

In a study of 898 consecutive allergic patients (Bonini St and Bonini Se Chibret Int J Ophthalmol. 1987; 5: 12-22) 359 (40%) had ocular symptoms

Prevalence of positive skin tests/RAST in different forms of allergic conjunctivitis
VKC is a bilateral inflammatory disease of the bulbar and/or tarsal conjunctiva, affecting mainly boys before puberty.

The frequent corneal involvement may lead to severe complications and loss of vision.

_Orthamology 2000;107:1157-63_
mRNA expression for IL-2 and IL-5 in VKC


- Signal for IL-5 in 5/7 VKC and in 0/8 controls
- No difference in IL-2 gene expression

Additional cytokines in VKC

- Thymosin beta-4
  (Micera A et al, Mol Vis 2006;12:1594-600)

- Nerve Growth Factor (NGF)

Increased plasma levels of Nerve Growth Factor in vernal keratoconjunctivitis and relationships to conjunctival mast cells

Lambiase A, Bonini S, Bonini S, Micera A, Magrini L, Bracci Laudiero L, Aloe L

Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma

Bonini S, Lambiase A, Bonini S, Angelucci F, Magrini L, Manni L, Aloe L
PNAS 1996; 93: 10955-10960

- Increased NGF circulating levels in allergic diseases
- Relationship to tissue mast cells and plasma Substance P
- Relationship to severity of disease

NGF and NGF receptors in allergic inflammation and tissue remodelling

NGF in Allergic Diseases

A novel function of NGF: a regulatory role in mucus production
Study models

- Epithelial expression and release of NGF
- Functional effects of NGF
- Transgenic mice overexpressing NGF
- Effects of NGF on differentiation and mucus production in epithelial cell lines and primary human epithelial cell cultures
- Mucin genes expression

Epithelial cells produce, store, release and respond to NGF

NGF production by human corneal epithelial cells

Mucins expression in NGF transgenic mice
**Atopic keratoconjunctivitis**

AKC is a bilateral chronic allergic inflammatory disease of the external eye associated with atopic dermatitis.

Symptoms of AKC include: itching, burning, tearing, and photophobia. Major signs of AKC are represented by eyelid eczema, redness, hypersecretion, and fine papillary hypertrophy.

**Complications of Atopic keratoconjunctivitis**

Conjunctival inflammation is more severe and persistent than in SAC and PAC, possibly causing subepithelial fibrosis, fornix shortening, and symblepharon formation.

Complications include: higher prevalence of Staphilococcus and Herpes simplex infections, keratoconus, cataracts.

Corneal involvement is frequent, from superficial punctate keratopathy to more diffuse limbal infiltration with Horner’s point, Trantas’ dots, and erosions. Corneal scarring and neovascularization may result in blindness.

**Eotaxin and eosinophils in AKC**

Fukagawa K et al. / Allergy Clin Immunol 1999; 103: 1220-21
The spectrum of allergic conjunctivitis

Current Nomenclature. I
EAACI Task Force. Allergy 2001;56:816-824

IgE-mediated Non IgE-mediated
Hay-fever conjunctivitis = to Hyperreactive eye
Skin test positive = to Skin test negative
Vernal Conjunctivitis

Clinical phenotypes

Current Nomenclature. II
(ARIA and GLORIA classification)

Intermittent
Persistent

Mild
Moderate-Severe
Mild
Moderate-Severe

Intermittent: Less than 4 days a week or less than 4 weeks
Persistent: At least 4 days a week or more than 4 weeks

A Step-Wise Approach in the Treatment of Allergic Conjunctivitis

Intranasal topical steroids

Major bias of clinical trials in allergic eye diseases

- Small number of subjects
- Inadequate study design
- Subjective or surrogate outcomes (CAC)
- Selection of subjects with reference to:
  - diagnosis
  - severity of the disease

Allergic Patient

- Always ask for ocular symptoms

Ocular symptoms 70%  
No ocular symptoms 30%

Optometrist

- Association with asthma or eczema
- Contact lenses
- Severe symptoms (giant papillae, intense photophobia, eye pain)
- High total IgE, polysensitization
- Eosinophils in tears or conjunctival scrapings

If associated with rhinitis:
- treat rhinitis and symptomatically

No effect on ocular symptoms

Efficacy on ocular symptoms