

Differential diagnosis of severe ocular allergies

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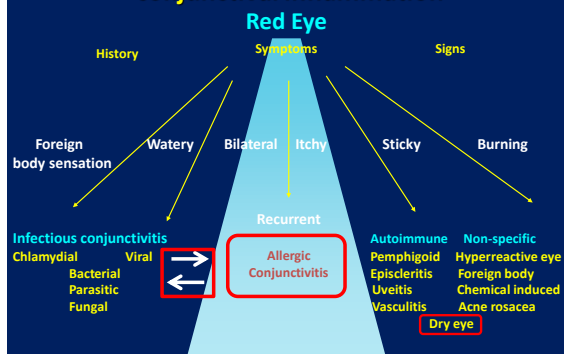
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WISC, Hyderabad
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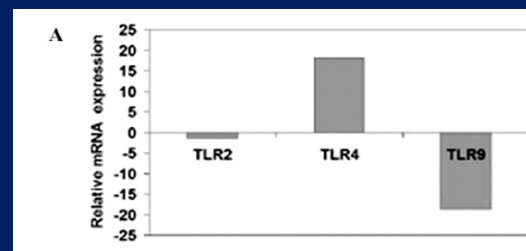
Aim of the lecture

- 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.

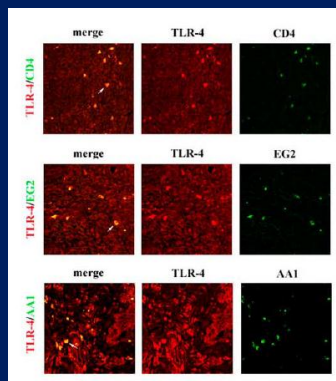
The heterogeneity of conjunctival inflammation



Toll-Like receptors expression in VKC



Micera A et al, 2006



Dry eye

	Aqueous tear deficiency	Melbionian gland disease	Itchy-Dry Eye association (IDEA)	Allergic conjunctivitis
Clinics	Autoimmune diseases	No systemic disease	Polycystic ovaries with hyperandrogenism	Allergy
Treatment	Immunosuppressive agents	Tear substitutes	Anti-androgenic drugs	Anti-allergic drugs
Skin tests	---	---	+/- (25% + ve)	+++ (50-90% + ve)
Schirmer test	↓	→/↓	→	→
Break-up time	→/↓	↓	↓	→
Goblet cells density	↓	→/↓	↑	↑

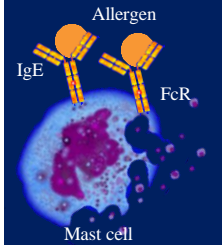
Bonini S et al., Am J Ophthalmol 2007

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)



Red Eye



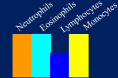
Effects

Vasodilation
Exudation
Hypersecretion
Hyperreactivity of nerve endings

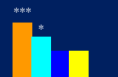
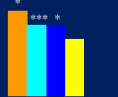
Symptoms

Redness
Oedema, Chemosis
Tearing, Excess Mucus
Itching, Burning

Late-phase allergic reaction in the eye



Histamine

Histamine
TryptaseHistamine
LTs
ECP

Cells

Mediators

Phenotypes of Allergic Conjunctivitis



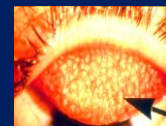
Seasonal or perennial



Vernal



Atopic



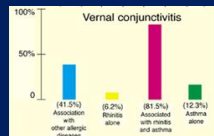
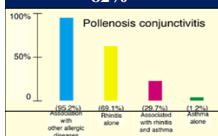
Giant papillary

Prevalence of nasal symptoms in allergic conjunctivitis

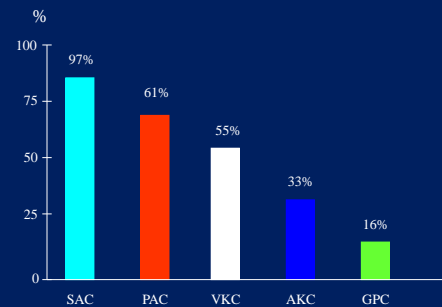
In a study of 898 consecutive allergic patients (Bonini St and Bonini Se Chibret Int J Ophthalmol. 1987; 5: 12-22) 359 (40%) had ocular symptoms

■ Isolated (n=55)

■ Associated with other allergic diseases (n=294)



Prevalence of positive skin tests/RAST in different forms of allergic conjunctivitis



Bonini S et al, 1987; 2002

Vernal Keratoconjunctivitis Revisited

A Case Series of 195 Patients with Long-term Followup

Stefano Bonini, MD,¹ Sergio Bonini, MD,² Alessandro Lambiase, MD,¹ Stefano Marchi, MD,¹ Patrizio Pasqualetti, MD,² Ornella Zaccaro, MD,¹ Paolo Rama, MD,² Laura Magrini, MD,² Tomas Juhos, MD,² Massimo G. Bucci, MD¹

• 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

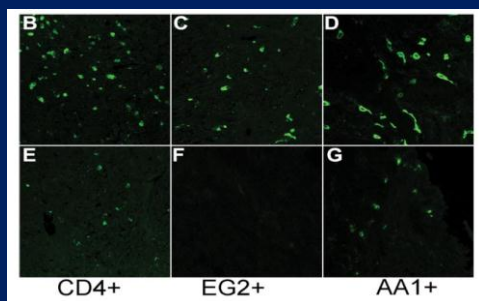
Ophthalmology 2000;107:1157-63

Clinical features of VKC

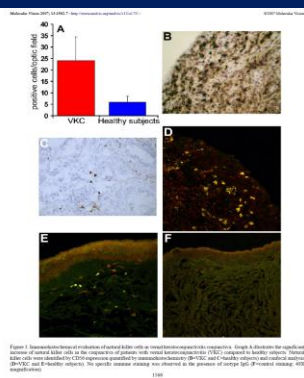
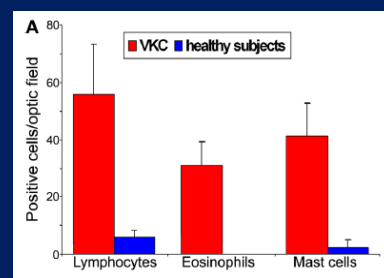
Table 1. Demographic and Clinical Features of Patients with Vernal Keratoconjunctivitis		Table 2. Major (50% Prevalence or Greater) and Minor (Prevalence up to 79%) Clinical Features of Vernal Keratoconjunctivitis (n = 195)	
No. of patients	195	Major clinical features (%)	
Mean age (yr and range)	11.0 ± 5.5 (3-26)	Presentation	Bilateral 98.0
Mean age (yr and range) at onset of symptoms	7.1 ± 4.2 (1-26)	Signs	Age < 20 yr 99.2
Female	51	Presence of papillae	100
Male	144	Bilateral	98.0
MF before age 20	135/11	Conjunctival hyperemia	90.3
MF after age 20	11/0	Superficial keratopathy	90.0
Mean clinical presentation (%)		Itching	96.4
Seasonal	77.4	Conjunctival cytology	Eosinophils in conjunctival scraping 85.1
Perennial	22.6	Minor clinical features (%)	
Chronic evolution after seasonal onset	15.9	Presentation	Seasonal 77.4
Atopic associated conditions (%)		Sex (male)	73.8
Asthma	64.2	Signs	Homer-Taukas dots 15.4
Rhinitis	49.4	Cornel shield ulcer	9.7
Eczema	25.5	Diagn	Diagn 5.1
Urticaria	9.2	Symptoms	Painful eyes 54.4
Family history of atopy (%)		Mucous discharge	53.3
Asthma	48.7	Itching	39.5
Rhinitis	35.8	Burning	8.7
Eczema	50.5	Positive skin test	57.8
Urticaria	4.2	Positive serum radioallergen sorbent test	52.2
Conjunctivitis	20.0	Lab data	IgE serum levels >200 kU/L 41.5
		Anamnestic data	Astma; associated diseases 48.7
			Family history of atopic diseases 48.7

M = males; F = females.

Inflammatory cells in the conjunctiva of VKC (B,C,D) and healthy subjects (E,F,G)

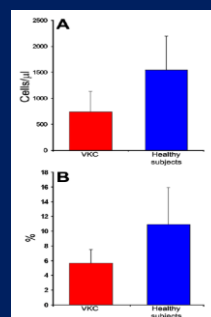


Inflammatory cells in VKC



CD 56 +ve cells in VKC

Immunohistochemistry and confocal analysis of conjunctival tissues of VKC (B and D) and healthy controls (C and E). F anti-IgG Ab.



Total and % of CD3 circulating NK cells (CD56/CD16 +ve) in VKC

mRNA expression for IL-2 and IL-5 in VKC

Metz D, Bonini S, Lightman S. *Invest Ophthalmol Vis Sci* 1993; 34: 857

- 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)
(Lambiase A. et al *Invest Ophthalmol Vis Sci* 1995; 36: 2127-32)

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

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

Invest Ophthalmol Vis Sci 1995; 36: 2127-32

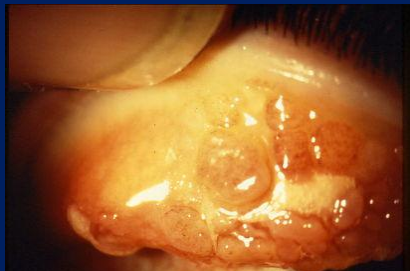
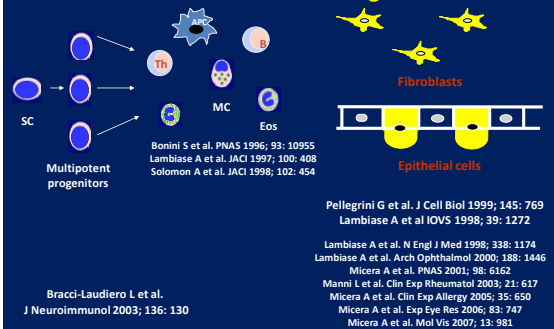
Circulating nerve growth factor levels are increased in humans with allergic diseases and asthma

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



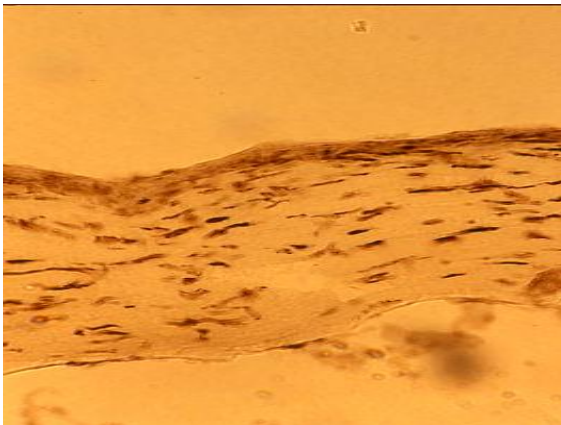
NGF in Allergic Diseases

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

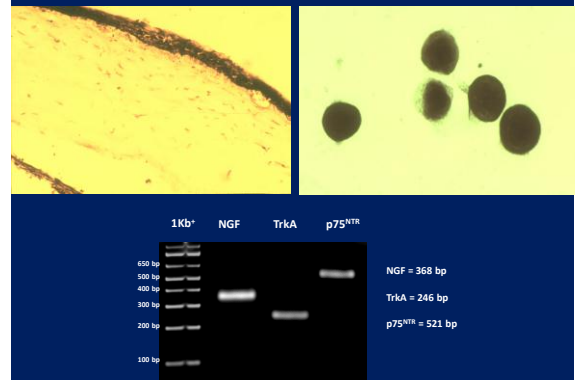
Study models

- 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

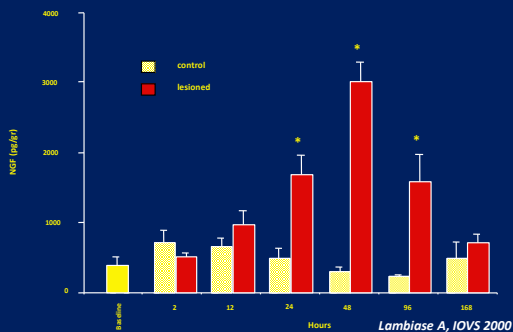
Epithelial cells produce, store, release and respond to NGF



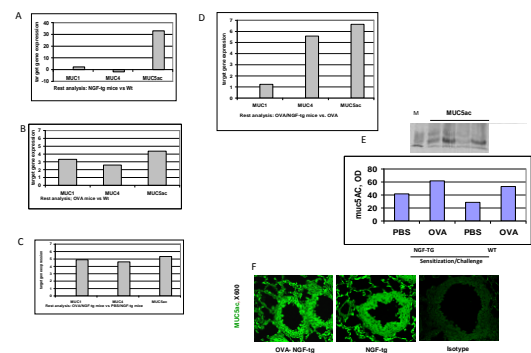
NGF production by human corneal epithelial cells



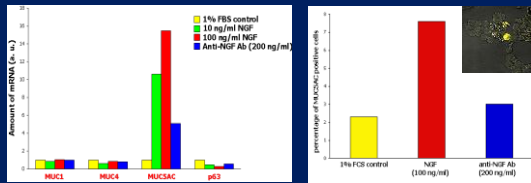
NGF CORNEAL LEVELS FOLLOWING EPITHELIAL DEBRIDEMENT



Mucins expression in NGF transgenic mice



NGF increases goblet cells in primary culture of human conjunctival epithelium



AN INCREASE IN MUC5AC mRNA WAS OBSERVED AFTER THE ADDITION OF NGF IN CULTURE (100 ng/ml)

NGF INDUCES AN INCREASE OF THE GOBLET CELL NUMBER

Lambiase et al. Invest Ophthalmol Vis Sci. 2009;50:4622-30.

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.

Atopic keratoconjunctivitis

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

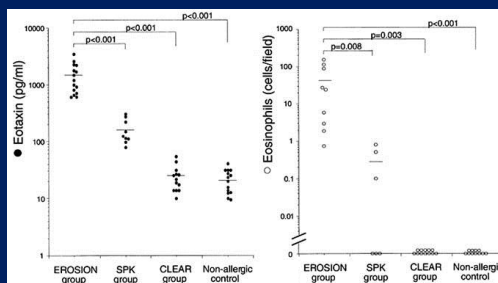
Complications include: higher prevalence of Staphylococcus and Herpes simplex infections, keratoconus, cataracts.

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

Complications of Atopic keratoconjunctivitis



Eotaxin and eosinophils in AKC

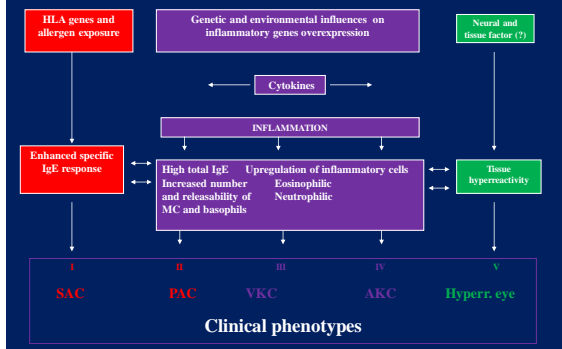


Fukagawa K et al. J Allergy Clin Immunol 1999; 103: 1220-21

Atopic and Vernal Keratoconjunctivitis (AKC and VKC) vs Seasonal and Perennial Conjunctivitis (SAC and PAC)

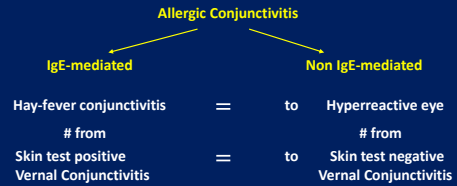
	SAC, PAC	AKC, VKC
Symptoms	+	+++
Signs	+	+++
	(vasodilation and edema)	(proliferative events)
Corneal involvement	-	+
Allergic disease more frequently associated	Rhinitis	Eczema, Asthma
Total IgE	+	++/+++
Skin tests serum specific IgE	+	+/-
Eosinophils	-/+	++/+++
Conjunctival non-specific hyperreactivity	+/-	++/+++
Anti-allergic treatment	++/+++	-/+

The spectrum of allergic conjunctivitis



Current Nomenclature. I

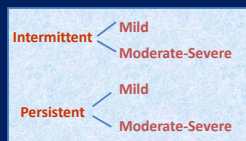
EAACI Task Force. Allergy 2001;56:816-824



The Allergy Nomenclature on the basis of IgE testing accommodates patients with diseases of different severity and separates subjects with similar diseases.



Current Nomenclature. II (ARIA and GLORIA classification)



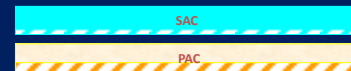
Intermittent: Less than 4 days a week or less than 4 weeks
Persistent: At least 4 days a week or more than 4 weeks

The ARIA classification, valuable for allergic rhinoconjunctivitis, does not allow to distinguish between AAC/SAC/PAC and VKC/AKC/GPC where corneal involvement can cause irreversible changes, severe complications and visual loss.



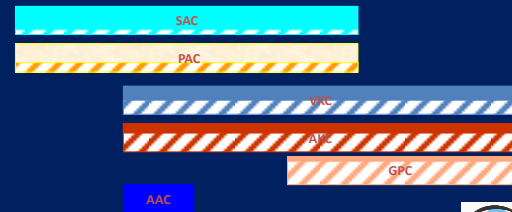
Intermittent

Mild Moderate-Severe



Persistent

Mild Moderate-Severe

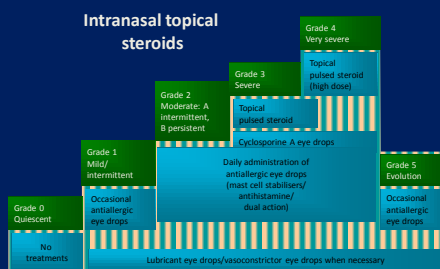


IgE-mediated

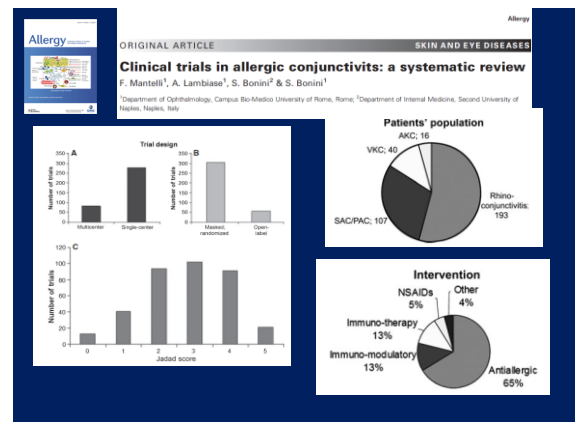
Non IgE-mediated



A Step-Wise Approach in the Treatment of Allergic Conjunctivitis



Bonini et al. Curr Opin Allergy Clin Immunol. 2007;7:436.



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

