Pathophysiology of Ocular Allergy

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Disclosure Statement
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I participate in the following Speaker’s Bureau and/or Advisory Boards:

- TEVA
- Myland Labs
- Sunovian
- Sanofi
Learning Objectives

At the end of this lecture, the attendee should be able to:

• List the 5 major types of ocular allergy
• Describe the major signs and symptoms for each major type of ocular allergy
• Discuss the differences in pathophysiology between the major types of ocular allergy
Transverse view of L eyeball
Ocular Allergy

- Allergic Conjunctivitis
  - Season Allergic Conjunctivitis
  - Perennial Allergic Conjunctivitis
- Vernal Keratoconjunctivitis
- Atopic Keratoconjunctivitis
- Giant Papillary Conjunctivitis
- Contact Ocular Dermatitis
Ocular Allergy Classification

- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)
- Atopic Keratoconjunctivitis (AKC)
- Keratoconjunctivitis
- Vernal Keratoconjunctivitis (VKC)
- Acute allergic conjunctivitis (AAC)
- Giant Papillary Conjunctivitis (GPC)
- Contact dermatococonjunctivitis
Ocular Allergy & Pathophysiology

- Ocular Allergy Mechanisms

- **Adaptive immunity**
  - IgE-mast cell-mediated
  - T-lymphocyte-mediated
    - T cell-mediated cytotoxicity
  - Th1: IFN-gamma recruits/activates macrophages (*contact dermatitis*)
  - Th2: IL-5 recruits/activates eosinophils (*most important in most ocular allergy*)
Ocular Allergy & Pathophysiology

- Ocular Allergy Mechanisms
  - **Innate immunity** (new research)
  - New evidence of innate/adaptive cross-talk in ocular allergy
  - Toll like receptor expression found in cornea and conjunctiva
  - Commensal flora which helps to maintain epithelial mucosal homeostasis may help protect against allergy
- Ocular allergy (all types) may differ more in quantity than quality of cytokines in tears, with both Th1 and Th2 profiles
Ocular Allergy & Pathophysiology

- Eye structures involved
  - Conjunctiva
  - Cornea
  - Limbus
  - Eyelid
Ocular Allergy - Anatomy

Eyelid

Accessory lacrimal glands:
- Glands of Krause
- Glands of Wolfring

- Bulbar conjunctiva
- Conjunctival fornix
- Palpebral conjunctiva
- Surface of the cornea (functions as a part of the conjunctival sac)
- Meibomian gland
Ocular Allergy & Pathophysiology

- **Eye structures involved**
  - Conjunctiva
  - Cornea
  - Limbus
  - Eyelid

- **Cells & mediators responsible**
  - B lymphocytes
  - T lymphocytes
  - Cytokines
  - Chemokines
  - Allergen presenting cells
Seasonal allergic conjunctivitis with moderate injection
Persistent intermittent allergic conjunctivitis
Allergic Shiners
Allergic Conjunctivitis

Affects approximately 20% population

Symptoms
- Red, itchy, burning, watery
- Dryness/irritation
- Discomfort
- Mucoid discharge

Signs
- Bulbar conjunctival hyperemia and edema
- Eyelid chemosis and edema
- Mild watery discharge
- Papillary hypertrophy of upper palpebral conjunctiva
- Cornea rarely involved
Chemosis
Allergic Conjunctivitis

Pathophysiology

- Mast cell-IgE immediate reaction (major immunological process)
- Eosinophil-Th2 delayed reaction (relatively minor immunological process)
- Cell-mediated cytotoxicity (if prolonged and severe)
- H1 is main mediator
- Mast cells are of mucosal type (TC$_T$)
- Conjunctiva is main affected tissue
- sIgE elevated serum/tears
- **Mast cell** in main cell in this disease
Allergic Conjunctivitis
Pathophysiology

- Mast cells
- H1 & H2 lymphocytic receptors important
- Eosinophils (esp. in substantia propria)
- Tears have
  - Histamine
  - Tryptase
  - Leukotriene C4
  - Eosinophilic peroxidase
  - Cationic protein
  - IgE
Mediators of IgE-related reactions producing Allergic Conjunctivitis symptoms

- **Histamine**: Itching, redness, edema
- **Prostaglandins**: Sensitized nerves, enhanced pain, edema, redness
- **Leukotrienes**: Chemotaxis, edema, & vascular permeability
- **Chemotactic factors**: Recruitment of eosinophils and neutrophils leading to tissue destruction
Conjunctival Epithelium
IgE Allergic Sensitization
First exposure to allergen
Mast cell-IgE Immediate Reaction

Early Allergic Response
(Second Exposure)

Antigen in tears → Conjunctival epithelium

Histamine, ECF-A

Pre-Formed Heparin

Activated mast cell

Synthesis

Phospholipids → Arachidonic Acid

Leukotrienes, Prostaglandins, Thromboxines

Newly-Formed Platelet Activating Factor
Pathophysiology of an immediate allergic reaction

DUST MITE

HISTAMINE

pharmacological effects
blood vessels, airways etc.
cell infiltration and accumulation
(see Figs 23.14 and 23.20)

clinical effects
hay fever
asthma
eczema
anaphylaxis

antigen presentation → IgE production → mast-cell activation → mediator release → clinical effects
Eosinophil-Th2 Delayed Reaction
Tarsal vernal keratoconjunctivitis
Limbal Vernal conjunctivitis
Vernal Keratoconjunctivitis

- In US and temperate climates peaks in childhood 11-13 y/o (3-25yr)
- Lasts 4-11 yrs
- Males > females
- Worse spring and summer
- sIgE to pollen and perennial allergens in most patients
- Some patients lack sIgE
- Elevated serum/tear total and sIgE
- Cornea, limbus, conjunctiva involved
### Vernal Keratoconjunctivitis

<table>
<thead>
<tr>
<th>SYMPTOMS</th>
<th>SIGNS</th>
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</thead>
<tbody>
<tr>
<td>Intense itching</td>
<td>Giant papillae</td>
</tr>
<tr>
<td>Intense tearing</td>
<td>Horner-Trantas dots</td>
</tr>
<tr>
<td>Severe photophobia</td>
<td>Shield Ulcers (corneal plaque)</td>
</tr>
<tr>
<td>Intense foreign body sensation</td>
<td>Epithelial plaques</td>
</tr>
<tr>
<td>Thick ropy discharge</td>
<td>Corneal ulceration</td>
</tr>
<tr>
<td>Ocular pain (cornea is involved)</td>
<td>Superficial punctate keratitis</td>
</tr>
</tbody>
</table>
Fluorescein staining of the papillary conjunctivitis
Horner-Trantas dots
Shield Ulcer
Corneal Ulcer
Corneal ulcer staining with fluorescein
Superficial Punctate Keratitis
Vernal Keratoconjunctivitis

• May represent over-expression of chromosome 5q which regulates:
  • IL-3, IL-4, IL-5, and GM-CSF
  • Nerve growth factor, Substance P, IL-9, IL-13, eotaxin

• 2 major forms
  • Giant Papillae- upper tarsal conj.
  • Limbal- gelatinous infiltrates
Vernal Keratoconjunctivitis

- Late phase eosinophil-Th2 response is major immune response
- IgE-mast cell response is minor. Mast cells are $\text{TC}_{\text{TC}}$ (connective tissue type)
- Corneal fibroblasts play key role in $\uparrow$ eotaxin
- Eosinophil is main cell in this disease
Atopic keratoconjunctivitis
Atopic Keratoconjunctivitis

- Presents in atopic individuals in late adolescents/young adults
- Males > females
- Childhood hx of atopic dermatitis
- Perennial symptoms but worse in winter/dryer climates
- Conjunctiva, eyelids, periorbital area, cornea, limbus involved
- Severe patients may develop keratoconus
Keratoconus
Atopic Keratoconjunctivitis

- Late phase Type 1 IgE-mast cell mediated immune response if most important
- T-lymphocyte-mediated hypersensitivity
  - Th2 eosinophil triggered is moderately important
  - Th1 cell-mediated is involved
    - Eosinophils in serum and tears
    - IgE in serum
    - TNF-α, IL-4, IL-13 in tears
    - IFNγ, a TH1 cytokine
# Atopic Keratoconjunctivitis

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<th>SYMPTOMS</th>
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<tr>
<td>Intense itching of eyes, lids, periorbital area</td>
<td>Tylosis</td>
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<td>Intense tearing</td>
<td>Swollen eyelids</td>
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<td>Severe photophobia</td>
<td>Scaly, indurated lids</td>
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<td>Blurred vision</td>
<td>Hyperemic conjunctiva</td>
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<tr>
<td>Stringy, rope-like mucous</td>
<td>Edematous conjunctiva</td>
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<tr>
<td>Burning</td>
<td>Tarsal conjunctival papillae</td>
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<tr>
<td>Dry sebssation</td>
<td>Meibomian gland dysfunction</td>
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<td></td>
<td>Dry eye</td>
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<td>Keratoconus</td>
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Giant Papillary Conjunctivitis
Giant Papillary Conjunctivitis

- Pathogenesis involves **mechanical** and **immunologic** mechanisms
- Combination of **Type 1 and Type 4** (Gell and Coombs) immune response
- Response to foreign substance, e.g. contact lens surface debris, exposed sutures, prosthesis
- Mechanical trauma can provide port of entry of allergens or irritants
- Characteristic large papillae (>0.3mm) on the superior palpebral conjunctiva
- Usually resolves when **contact lens are removed**
Giant Papillary Conjunctivitis

- Increased lymphocytes
- Increased numbers of mast cells, eosinophils, and basophils but lower than in other forms of ocular allergy
- Tears have increased IgE, IgG, IgM (made to contact lens allergenic materials/contaminants)
- ↑ Leukotriene C4, IL-4, IL-6, eotaxin, CD4 T cells, mucosal-associated M cells
- Papillary formation, fibroblast proliferation, and collagen production is noted
Ocular Contact Dermatitis
Contact Ocular Dermatitis
Reactions noted almost exclusively at site of exposure of the putative antigen

- Direct contact
- Indirect contact with hands
- Aerogenic exposure

- Small molecular weight molecules/haptens conjugate with proteins in skin to become immunogenic

- Atopic contact dermatitis causes > 50% eyelid dermatitis
- Responsible for 5% of all contact dermatitis
- 25% develop secondary irritant dermatitis
Ocular Contact Dermatitis

- Contact dermatitis can be from allergens or irritants
- Involves eyelids, periocular skin, ocular surface
- Erythema, itching, edema, vesciculation, and scaling
- Initial sensitization following allergen exposure takes 10-14 days
- Upon subsequent exposure, symptoms starts hours to days after exposure to the allergen
8 Main causative agents in eyelid Contact Dermatitis

• 1) Gold sodium thiosulfaate (8.2%)
• 2) Fragrance mix (7.1%)
• 3) Balsam of Peru (6.3%)
• 4) Nickel sulfate (6%)
• 5) neomycin (3.3%)
• 6) methyldibromoglutaronitrile (3%)
• 7) Quaternium-15 (3%)
• 8) Methylchloroisothiazolinone/methylisothiazolinone (2.2%).
Ocular Contact Dermatitis
Pathophysiology

• Th1 lymphocyte mediated delayed hypersensitivity
• Allergens and irritants can bind to the Langerhan cells (allergen presenting cell) found within the suprabasilar layer of the epidermis
• Langerhan cells migrate to the regional lymph nodes to complete the sensitization process
• Allergens (not irritants) induce CD1a+CD83+ Langerhans cell migration
Ocular Contact Dermatitis
Pathophysiology

- Increase in basophils, eosinophils, Th1 lymphocytes, dendritic cells
- Increase of IL-1, IL-6, IL-8, GM-CSF, RANTES, Interferon-inducible protein 10
- IL-8 seems to be present only in allergic contact dermatitis
- CD4+ CCR10+ memory cells remain in the dermis
- Filaggrin barrier defects likely predispose to allergic contact dermatitis