

The Eye

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- Direct action of triggers on the target organ may cause vasodilation, exudation, hypersecretion and nerve endings stimulation without participation of mast cells and basophils.
- Non IgE-mediated release of mediators from mast cells and basophils may explain how triggers other than allergens can induce pseudo-allergic reactions.
- IgE-mediated triggering of mast cells and basophils is not confined - in the eye too - to an immediate reaction, but represents the starting point for a progression to a late-phase reaction with the participation of a network of several cells and mediators.
- Inflammatory changes associated with late-phase reaction in the eye represent the pathophysiological basis for a non-specific hyperreactivity to various triggers.

Key words: Allergic conjunctivitis, vernal and atopic keratoconjunctivitis, red eye

The “red eye”

The participation of the eye in an adverse reaction to food mainly involves the external eye. In fact, there is no convincing evidence up-to-now for the role of food allergy or intolerance in other immunologic or non-immunologic eye diseases.

The more common clinical picture of external

eye reaction to harmful substances are represented by the lid edema and by the red eye. Under this last generic name at least three different forms of conjunctivitis are usually classified by ophthalmologists and allergists on the basis of clinical criteria (Table 1).

Table 1. Clinical forms of “red eye” of allergic origin

Allergic conjunctivitis

The most common allergic eye disease. It can be acute (as in accidental exposure to various “irritants” or animal danders), seasonal (as in hay-fever) or perennial (as in mite allergy). Etiologic diagnosis is usually easy and response to classic anti-allergic treatment is satisfactory. No complications usually occur (Fig 1).

Symptoms

Tearing
Burning
Mild itching

Signs

Mild hyperemia
Mild eczema
Mild papillary reaction
(often absent)

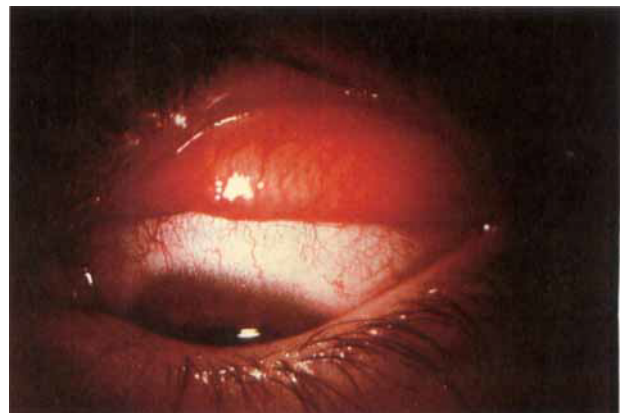


Fig 1. Allergic conjunctivitis

Table 1 continued

Table 1. Clinical forms of “red eye” of allergic origin (cont’d)

Vernal keratoconjunctivitis

Severe bilateral eosinophilic inflammation of the eye which mainly affects young boys in Mediterranean areas. Etiologic diagnosis is not easy (IgE antibodies are detectable in approx. 50% of cases), pathogenesis is still obscure and steroid treatment is often the only effective therapeutic measure. A corneal involvement is frequently present (Fig 2).

Symptoms	Signs
Intense itching	Cobblestone papillae
Tearing	Intense hyperemia
Photophobia	Mucus discharge
Sensation of foreign body	Milky conjunctiva
	Punctate keratopathy
	Tranta’s dots
	Togby’s ulcers

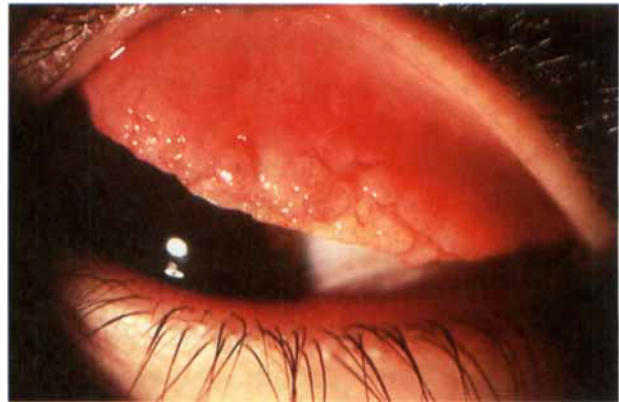


Fig 2. Vernal keratoconjunctivitis

Atopic keratoconjunctivitis

Keratoconjunctivitis associated with eczematous lesions of the lids and skin in both children and adults. Etiopathogenesis is still obscure. Classic anti-allergic treatments are often not effective. Complications are frequent (Fig 3).

Symptoms	Signs
Itching	Hyperemia
Burning	Eczematous lesions of eyelids
Tearing	Corneal ulcers
	Cataracts
	Pannus
	Keratoconus
	Retinal detachment



Fig 3. Atopic keratoconjunctivitis

The above reported clinical classification of the “red eye” appears to be not satisfactory and should be eventually replaced by a more accurate pathophysiological categorization of allergic eye diseases based on involved mechanisms.

Basic allergic mechanisms in the “red eye”

The three main clinical forms of allergic “red eye” as well as the edema of the lids were ascribed in the past to common Type I hypersensitivity mechanism, according to the classification of immune reactions made by Coombs and Gell. This Type I hypersensitivity requires the presence of IgE antibodies to allergens, the allergen-IgE reaction at mast-cell and basophil membrane, and the subsequent release of mediators causing the pathological changes and symptoms of the allergic reaction (Fig 4).

However, increasing evidence indicates that the “red eye” is an heterogeneous condition, and the different pathological changes occurring in the various form of the allergic “red eye” cannot be explained on the basis of the sole intervention of the classic Type I hypersensitivity reaction.

Among additional mechanisms possibly responsible for a “red eye”, we should like to call attention to the following:

ILs, etc.) is now largely proven. This mechanism might explain how triggers other than allergens (such as food, drugs, bacterial and viral infections) can induce pseudo-allergic reactions (PARs) which are very similar, at clinical level, to typical IgE-mediated immediate hypersensitivity reactions.

3. Late-phase conjunctival response and the role of allergic inflammation

Recently, we were able to show that allergen challenge of human conjunctiva causes persisting inflammatory changes of ocular tissues similar to those previously described in rats. Therefore, the concept of late-phase allergic reaction can be applied to the eye too, as previously shown for the skin, nose and bronchi. In the eye, LPR is characterized, at the clinical level, by redness (with minor itching and tearing) persisting long after allergen provocation, accompanied by a sensation of foreign body. At the cytological level,

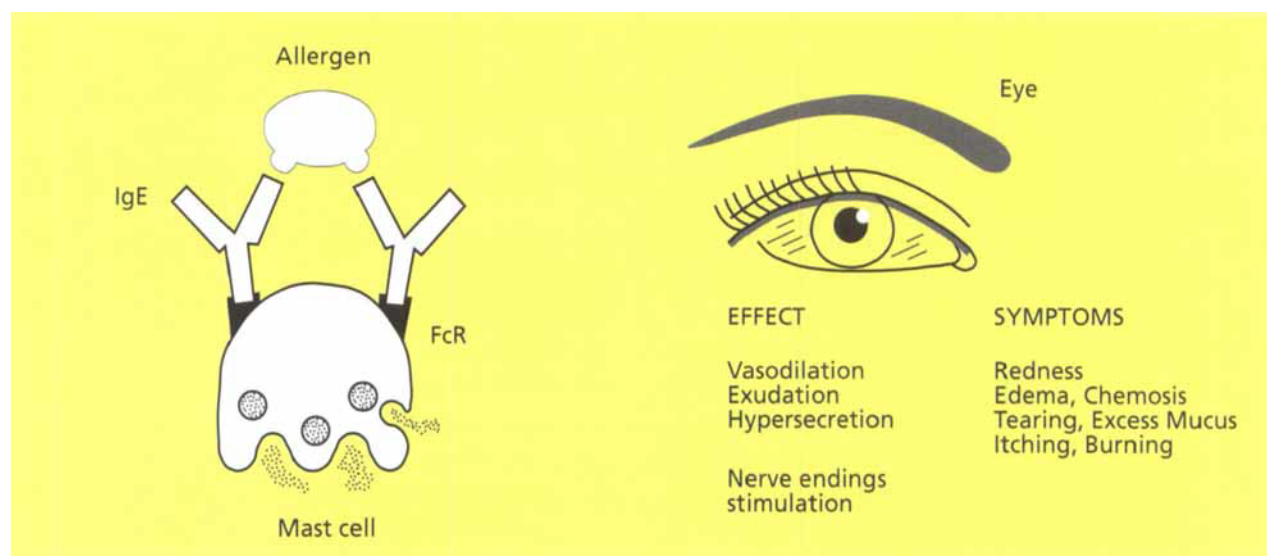


Fig 4. The classical schematic explanation of allergic conjunctivitis, based on Gell and Coombs Type I hypersensitivity.

1. Direct action of triggers on the target organ

Various trigger factors may directly act at the level of the target organ causing vasodilation, exudation, hypersecretion and nerve ending stimulation without the participation of mast cells and basophils.

2. Non IgE-mediated triggering of mast cell and basophil

The possibility that mast cell and basophil mediator release can be induced by several triggers other than IgE (such as anaphylatoxins C3a and C5a,

the analysis of conjunctival scrapings or tears shows an early accumulation of neutrophils (mainly) during the immediate phase, followed by a prevalent recruitment of eosinophils 6-10 hours after provocation and of lymphocytes and monocytes later on, with persistent inflammatory changes up to 24 hours after challenge.

The recruitment of inflammatory cells during LPR is associated with the detection in tears of mediators released by primary and secondary effector cells. For instance, we were able to detect significant amounts of LTC₄, EPO, ECP and histamine (but not tryptase) during ocular LPR.

This last finding is in agreement with the hypothesis that basophils but not MCs have a role in LPR. Interestingly enough, mediators present in tears (6 hours after allergen challenge) can passively transfer the ocular LPR.

Clinical and cytological changes of conjunctival LPR appear to be a continuous dose-dependent process. When low allergen doses are used for challenge, or when the sensitivity of the patients is low, only cytological changes are observed during the early phase of conjunctival reaction, not associated with clinical symptoms. Increasing the dose of allergen results in a more intense cellular reaction and in a typical clinical immediate response of the conjunctiva. When the dose of allergen is further increased, or when patients with higher sensitivity are challenged, a more intense and prolonged cell recruitment is induced with a clinical LPR when consistent allergen doses are used. Therefore, from our studies in the eye it appears that LPR is a constant outcome of the immediate reaction, provided that large allergen doses are administered to highly sensitized patients.

4. Non-specific conjunctival hyperreactivity

Extensive evidence in target organs other than the eye indicates that allergic patients are hyperreactive to various non-specific substances in addition to the sensitizing allergen. Although close relationships exist between reactivity to allergens and to non allergic substances, specific and non-specific hyperreactivity represent distinct concurrent mechanisms in the pathogenesis of several allergic diseases such as bronchial asthma. We compared the conjunctival responsiveness to histamine diphosphate (0.1-1.0 mg/ml) in patients with VKC and in healthy controls. Both VKC patients and controls reacted to histamine with a dose-dependent conjunctival redness 2 to 5 minutes after allergen challenge. However, at low histamine doses (0.01-0.5 mg/ml) VKC had a significantly ($p<0.05$) more intense reaction than controls. Moreover, the concentration of histamine diphosphate causing a threshold conjunctival redness (provoking concentration of histamine, PC) was significantly lower ($p<0.02$) in patients with VKC than in controls. Similar results were more recently obtained by Ciprandi and co-workers in perennial conjunctivitis and in seasonal conjunctivitis during the season.

The existence of a non-specific conjunctival hyperresponsiveness might be relevant for a better

understanding of some clinical forms of "red eye". For instance, non-specific conjunctival hyperreactivity may play a role in causing the variable course of the conjunctive involvement not correlating with environmental changes of any sensitizing allergen. In fact, sun, wind, dust or other natural agents may represent triggers of a non-specific abnormal reactivity of the conjunctiva.

Summary

In summary, the above reported data strongly suggest that several mechanisms other than the IgE-dependent mast cell mediator release can be operating in different forms of "red eye", including the participation of a complex network of inflammatory cells and mediators, the occurrence of late-phase persistent inflammatory changes, and the presence of an enhanced reactivity of the conjunctiva (Fig 5).

The better knowledge of the immunologic and non immunologic mechanisms involved in allergic conjunctivitis might eventually lead to more accurate investigations about the role of adverse reaction to foods in allergic eye diseases, which up-to-now have been investigated only for the occurrence of IgE antibodies to food allergens.

The "red eye" and the adverse reactions to food

Although it is widely accepted that conjunctivitis and lid edema can be part of the clinical picture of adverse food reactions, the eye involvement is usually considered of minor relevance when compared to other clinical manifestations, and the prevalence of eye symptoms in both immunologic and non-immunologic food reactions is not well defined.

More information is available about the role of food allergy in allergic conjunctivitis. In a survey carried out in 363 patients with a "red eye" the prevalence of a positive RAST to one or more food allergens was 5%. However, several patients had positive skin tests and/or RAST to other allergens too and even in subjects with sensitization to food allergens only it was very difficult to establish a cause-effect relationship between the food sensitivity and the clinical symptoms.

With reference to the different clinical pictures of the "red eye", food allergy seems to have a limited importance in allergic conjunctivitis and appears to be confined to episodic cases of acute reactions for accidental contact of the sensitizing

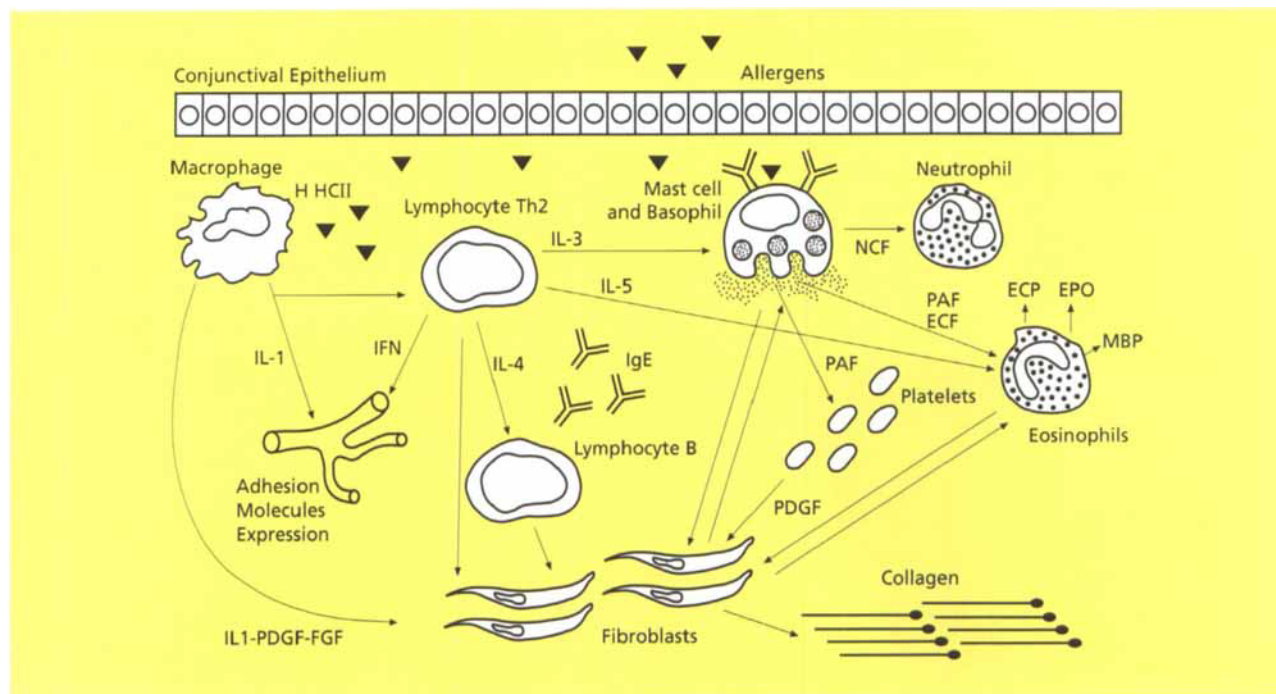


Fig 5. A new more complex and in part hypothetical schematic explanation of "allergic conjunctivitis" (see text for details).

food with the eye or to mild forms of perennial conjunctivitis almost always associated with rhinitis.

The frequency of positive skin tests and/or RAST in vernal keratoconjunctivitis is controversial. It has been reported to be high by Frankland and Easty, while it was 10% in our personal experience. Atopic keratoconjunctivitis appears to be the type of conjunctivitis more frequently associated to food allergy. The significance of this association is not peculiar and all the questions not answered for atopic eczema should also apply to atopic eczema with ocular participation to the clinical picture.

The relationship between the eye and food intolerance or other non immunologic mechanisms of adverse reactions to food is even less documented than food allergy. The periorbital and eyelid localization of the edema in urticaria-angioedema is quite frequent. However, it is quite transient and does not require specific therapeutic measures. Of course, all the problems still existing, about pathogenesis, diagnosis and treatment of the systemic disease also apply to the ocular localization.

Conclusions

In conclusion, the paucity of consistent data, the lack of specific diagnostic procedures (apart from some sporadic reports on the use of conjunctival provocation with food allergens), as well as the

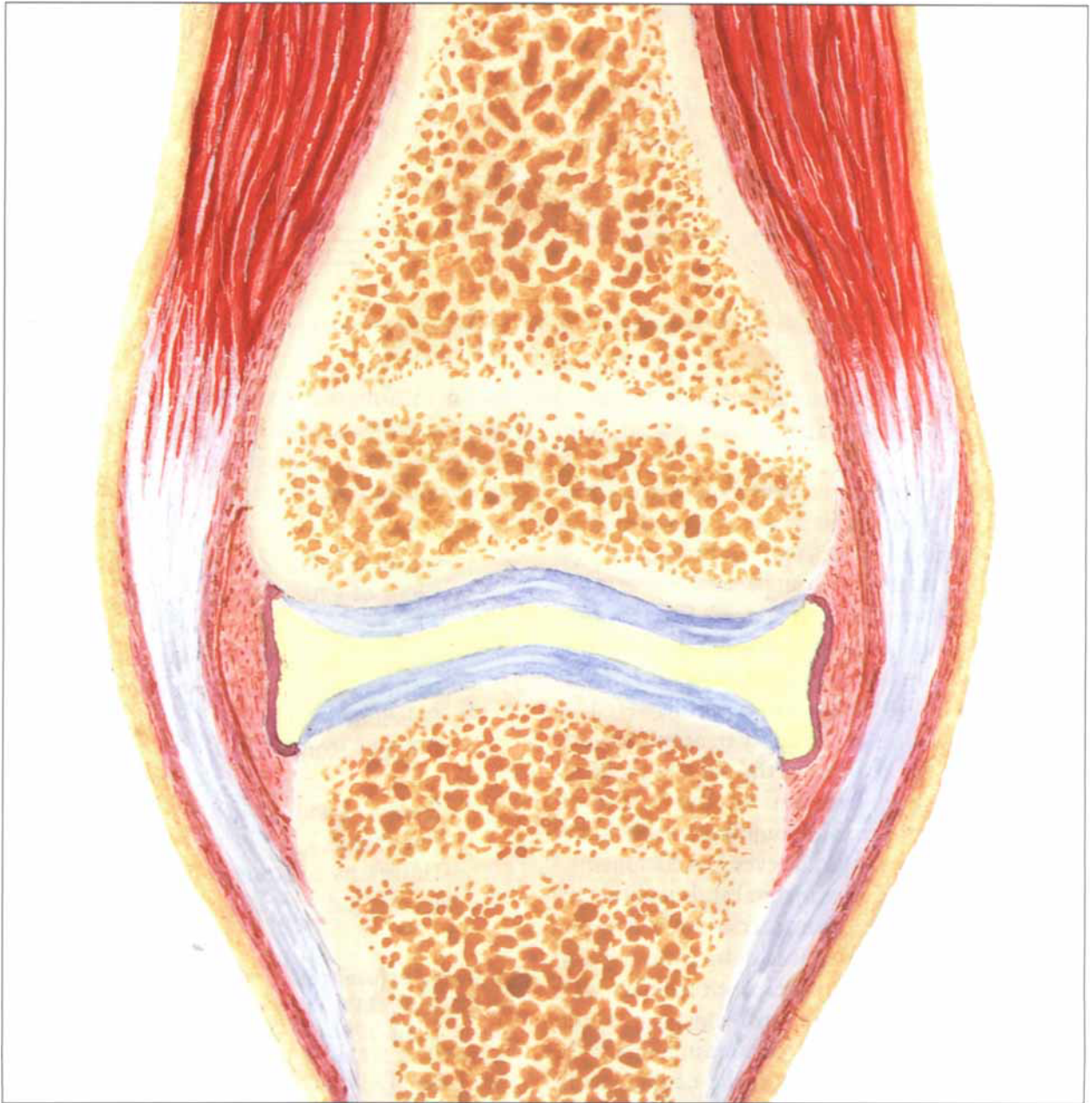
lack of information about the effect of elimination diets in subjects with a red eye or eyelid edema, make the eye as a minor problem in the maze of adverse reactions to food.

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