

TITLE PAGE

Ocular allergy as a risk factor for dry eye in adults and children

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Abstract

Purpose of review

To provide an overview of the pathogenic mechanisms underlying the correlation between Ocular Allergy (OA) and Dry Eye Disease (DED), highlighting how the first condition may be a risk factor for the second one.

Recent findings

Recent advances in our comprehension of the pathogenesis of OA and DED allow identifying several pathways of interaction between these 2 conditions. A growing body of evidence supports the role of OA as a risk factor for DED. OA, particularly the severe forms of keratoconjunctivitis, can impact on different key mechanisms of the DED vicious cycle, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities.

Summary

OA and DED are 2 common, relevant, symptomatic, not mutually exclusive conditions affecting the ocular surface. They share some clinical and biochemical features. In order to better understand the complex interactions between these 2 conditions, it's essential to consider the very wide spectrum of clinical conditions included in the term OA and the still largely unexplored peculiarities of the pediatric ocular surface physio-pathology and DED.

Key words

Ocular surface, ocular allergy, dry eye disease, pediatric, inflammation

Introduction

In the daily clinical practice Ocular Allergy (OA) and Dry Eye Disease (DED) are common and growing healthcare problems, with a significant negative impact on quality of life and productivity.

[1*, 2*]

Epidemiological studies, made difficult by heterogeneity and lack of standardization of diseases' definitions and diagnostic algorithms [3*, 4*], report prevalence ranges in the general population of 10%-30% and 5%-50% respectively for OA and DED. [1*, 2*] However, while OA seems to affect more commonly children and adolescents, [1*, 5] DED prevalence increases with age. [2*]

OA and DED are different clinical entities affecting the ocular surface but their clinical manifestations include partly overlapping signs and symptoms. [6] The coexistence of these 2 conditions, hypothesized more than 20 years ago, [7] has been confirmed to be a common circumstance by large cross-sectional studies. [6] Several studies tried to investigate the relationship between OA and DED, suggesting that the first one can predispose to the second one, and the Tear Film and Ocular Surface Society Dry Eye WorkShop II (TFOS DEWS II) recently included Allergic Conjunctivitis among the “probable” (supported by suggestive evidence, implying the existence of either inconclusive information from peer-reviewed publications or inconclusive or limited information but either not published or published somewhere other than in a peer-reviewed journal) risk factors for DED. [2*]

This paper is aimed to provide a critical revision of new insights into the pathogenetic mechanisms of DED and how they can be affected by OA.

Ocular allergy in adults and children

Ocular allergy is a collection of ocular surface disorders, classically classified in two groups: common allergic conjunctivitis, including seasonal and perennial forms (SAC and PAC), and rarer kerato-conjunctivitis, including vernal and atopic forms (VKC and AKC).

SAC and PAC are mild to moderate allergic disease, often associated with rhinitis, involving a type I (immunoglobulin E mediated) hypersensitivity response.

VKC and AKC are severe chronic inflammatory diseases of the ocular surface with a more complex pathogenesis that includes a type IV (T-helper mediated) response.

Ocular itching, swelling and tearing are the most frequent symptoms complained by patients with all forms of OA, while photophobia and pain are typical of the most severe forms, due to the frequent corneal involvement. [3*, 8*]

The different types of OA have different ages of onset and characteristic age-related evolutions. SAC and PAC onset is usually during adolescence and young adulthood (80% of patients are younger than 30 years old), VKC is a paediatric disease, usually subsiding after puberty, while AKC symptoms may appear during childhood but the most frequent onset age ranges from 30 to 50 years old. [3*, 5]

Dry eye in adults and children

“Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological role”. [9**] The newly revised definition of DED, proposed by the TFOS DEWS II, highlights the etio-pathogenetic role of 5 key mechanisms, providing a useful trace to investigate how OA could impact on DED pathogenesis. (Figure 1)

Pediatric dry eye has been historically considered as a rare condition, mainly associated with congenital, autoimmune, and inflammatory disorders, but it has not been investigated as well as in adults and its diagnosis is often overlooked. [10, 11] Recent evidences suggest that the peculiar, not yet fully understood, anatomo-physio-pathology of the pediatric ocular surface, the specific difficulties related to symptoms assessment and interpretation, and the lack of standardized and validated diagnostic strategies, have limited a lot our comprehension of this more neglected than rare disease. [6, 11-14]

OA and tear film instability

A growing number of papers report the association between OA and decreased tear film break-up time (BUT). This phenomenon is more evident in allergic kerato-conjunctivitis and it seems to be correlated with the severity of the ocular surface disease, as suggested by a comprehensive study published by Y. Hu and colleagues which reported a BUT of 3.1 ± 1.6 s vs 4.5 ± 1.0 s vs 11.4 ± 1.0 s ($P < 0.01$) respectively in AKC, VKC and healthy controls.[15]

More recent studies, comparing children affected by SAC, PAC, and even allergic rhinitis to age-matched healthy subjects, demonstrated that also these conditions are able to affect tear film stability. [12-14, 16] These papers provided essential information on this issue but, reporting very heterogeneous BUT values and adopting a threshold value of 10 seconds (validated only in adults), they also indirectly highlighted our current poor knowledge of pediatric dry eye.

Interestingly, a few researches on tear film stability in intermittent forms of OA reported that VKC patients seem to show a shortened BUT even in the quiet phases of the disease, [11] while SAC patients don't have decreased tear film stability outside the pollen season. [17]

In the Vicious Circle of DED, tear film instability may be due to different mechanisms, including Meibomian glands (MGs) and lipid layer changes on the one hand and mucins alterations on the other. [18**, 19*]

A few imaging studies assessed MGs in different forms of OA, [20*] including AKC, VKC and PAC. They showed morphological changes, probably related partly to ocular surface inflammation and partly to continuous mechanical stress to the tarsal tissue by eye rubbing. Functional implications of these morphological changes have been suggested, but they need to be further investigated. Only one study, published more than 10 years ago by S Suzuki and colleagues, [21] assessed the alterations of the tear film lipid layer in OA. This research showed increased lipid layer thickness in patients with SAC and reported a surprising negative correlation between lipid layer thickness and BUT.

The impact of OA on secreted and membrane-associated mucins has been studied a bit more in depth, at least in severe forms.

Preclinical studies on mouse models suggested that histamine, leukotrienes, and prostaglandins directly stimulate goblet cell secretion, while inflammatory cytokines as IL-13, TNF α , and IFN γ have opposing effects on the regulation of secretion, proliferation, and apoptosis of these cells. [22] Several in vivo studies from the Keio University reported a depletion of MUC5AC in patients with AKC and VKC, [15, 23] particularly in eyes with corneal shield ulcers. [24] The decreased tear concentration of this gel-forming mucin is widely accepted as a feature of all forms of DED. [18**]

OA and tear film hyperosmolarity

Hyperosmolarity of the tear film is a core mechanism of DED [18] and, thanks to the existence of a validated point-of-care tear film osmometer, it has been recently incorporated in the diagnostic algorithm proposed by the TFOS DEWS II. [4*]

The previously discussed impact of OA on tear film stability provides a strong rationale to hypothesize an effect of these conditions on tear film osmolarity, mediated by increased evaporation. However, at the moment, this issue has been investigated by a single uncontrolled study (level IV of evidence), [25] which reported in eyes with Acute Allergic Rhinoconjunctivitis mean values of tear osmolarity ranging from 318 and 324 mOsm/L, therefore higher than threshold adopted for diagnosis of DED (308 mOsm/L). [26]

OA and ocular surface inflammation

Inflammation, including both innate immune response and adaptive response, is a key element of the DED Vicious Cycle. The acute response involves the MAP kinases and NF κ B signaling pathways, the generation of inflammatory cytokines as IL-1 and TNF- α , and the up-regulation of matrix metalloproteinases (MMP) production by epithelial cells. The adaptive response is initiated by the activation and migration of resident APCs toward the regional draining lymphnodes, where they stimulate naïve T cells (Th0), leading to the expansion of IL-17- and IFN-gamma-secreting Th17 (Th17/1) cells. [18**, 27**]

The conjunctival allergic inflammatory response is associated with IgE-mediated mast cell activation leading to the release of preformed mediators including histamine and proteases (acute

phase). The subsequent de novo formation of chemokines and cytokines triggers a cascade of cellular and molecular events leading to the recruitment and activation of eosinophils and of Th2 and Th1 lymphocytes (late phase). [28**]

The role of Th17 in ocular allergy is controversial. Some researches reported preliminary data suggesting increased tear levels of IL-17 in VKC [29] and in SAC and PAC [30]. However this does not directly point to a role for Th17 cells as other cells, innate immune cells, are also IL-17 producers. [31] Moreover, Fukushima and colleagues, in an experiment conducted on an animal model of allergic conjunctivitis, showed that WT and IL-17^{-/-} mice did not differ in conjunctival eosinophil infiltration. [32]

MMPs deserve a brief additional comment. These proteolytic enzymes, particularly MMP-9, play a key role in DED pathogenesis by disrupting intercellular epithelial tight junctions, leading to a breakdown of the ocular surface epithelial barrier. [18] MMP-9 has recently been proposed as one of the best DED severity biomarkers [33**] and, thanks to the availability of a point-of-care immunoassay, [34] as a diagnostic biomarker.

Increased tears levels of MMP-1, MMP-2 and MMP-9, and increased ratio of MMPs to their tissue inhibitor have been well demonstrated in VKC and in a minority of patients with allergic conjunctivitis. [35, 36] Interestingly, in OA as in DED, MMP-9 showed a significant correlation with corneal epithelial damage.

OA and ocular surface damage

Epithelial cells death, loss of goblet cells, and squamous cell metaplasia are well-known key components of the DED vicious cycle, especially in advanced forms. This type of ocular surface damage is due to several concomitant elements, including frictional damage, hyper-osmolar environment, and chronic inflammation with IFN-gamma over-expression. [18**]

Several studies, using conjunctival impression and brush cytology to investigate the grade of metaplasia, the density of goblet cells and the level of secretory mucins (mainly MUC5AC) expression, clearly demonstrated squamous metaplasia in AKC and VKC. The ocular surface

damage was correlated to severity and duration of the allergic inflammation and it was negatively correlated to the tear film stability, probably because of a “mucin deficient dry eye state”. The over-expression of some membrane-associated mucins might be interpreted as a manifestation of an ocular surface defence response. [15, 22-24, 37]

Mild forms of allergic conjunctivitis don't seem to induce this type of ocular surface damage. [38]

OA and neurosensory abnormalities

The crucial role of neurosensory abnormalities in DED has been recently highlighted including them in the definition of the disease. [9**] Tear film hyper-osmolality and instability and ocular surface inflammation are able to change the behavior of the different classes of corneal sensory receptors, inducing peripheral sensitization and, in the long term, inducing nerves damage. The peripheral ocular surface neuropathy can impact on several components of the morpho-functional unit, including tear secretion, blink rate, epithelial and goblet cells trophism, and the behaviour of the corneal immune cells. Perpetuation of the vicious cycle can ultimately lead to central sensitization. [18**, 39**]

In DED patients, several clinical studies, using mechanical esthesiometry and in vivo confocal microscopy, showed a reduction of corneal sensitivity and corneal sub-basal nerves density, and increased nerves tortuosity and sub-basal immune cells density. [39**, 40]

Similar researches reported similar results, with a few qualitative differences, also in AKC and VKC patients. [40, 41] Interesting findings in severe OA included a good correlation between corneal sensitivity and sub-basal nerves quantitative and morphological changes, the correlation between corneal sensitivity and conjunctival goblet cells density, and the confocal demonstration of the presence of stromal nerves morphological abnormalities. [15, 23, 40, 41]

Anti-allergic treatment and iatrogenic dry eye

Dry eye can be caused by a variety of iatrogenic interventions, including topical or systemic drugs, the use of contact lenses, and ophthalmic surgical and non-surgical procedures.

Large population-based studies showed that systemic antihistamines are a risk factor for DED (OR: 1.6). These drugs have anticholinergic activity and can affect G-protein coupled muscarinic receptors in the lacrimal gland acini and conjunctival secreting cells. [42**]

Topical drugs may affect the ocular surface determining allergic, toxic and inflammatory effects by interaction with the tear film components, by tension-active effects, by reducing tear secretion, or by damaging goblet cells, epithelial cells, corneal nerves and MGs.

Several studies reported correlations between different topical anti-allergic drugs, mainly epinestina and olopatadine, and DED. However, specific data on the active compounds are difficult to obtain because of the possible confounding role of preservatives and excipients. [42**]

About preservatives, the role of benzalkonium chloride in damaging the ocular surface has been largely studied [43].

Conclusion

In conclusion, OA and DED are 2 common, relevant, symptomatic, not mutually exclusive conditions affecting the ocular surface. They share some clinical and biochemical features.

If DED is a comprehensive term, including different types of patients, OA include a very wide spectrum of clinical conditions, ranging from mild SAC to severe and sight-threatening keratoconjunctivitis.

Recent advances in the comprehension of DED pathogenic mechanisms allow identifying several pathways of interaction between these 2 conditions, providing a strong rationale to consider OA as a risk factor for DED. (Figure 1)

OA have peculiar implications and manifestations in children. Further studies on this topic will help to better understand the several outstanding issues relating to pediatric ocular surface and DED.

Key points

- OA and DED are common and growing healthcare problems, with a significant negative impact on quality of life both in adults and children
- OA include a very wide spectrum of clinical conditions, ranging from mild SAC to severe and sight-threatening keratoconjunctivitis
- A growing body of evidence support the role of OA as a risk factor for DED
- OA can impact on different key mechanisms of the DED vicious cycle, including tear film instability, ocular surface inflammation and damage, and neurosensory abnormalities
- The peculiarities of the pediatric ocular surface physio-pathology, including OA and DED features, are still largely unexplored

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Figure legend

Figure 1. Scheme of the main pathways of impact of OA on DED vicious cycle.

SAC and PAC sub-set is under-represented in the OA set because of the lower impact of these forms on the DED pathogenic mechanisms.

