Contact Lens Update
CLINICAL INSIGHTS BASED IN CURRENT RESEARCH

Allergy and dry eye disease

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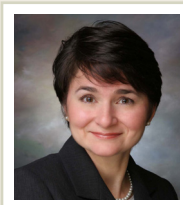

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Almost a decade ago, the ***Annals of Allergy, Asthma & Immunology*** published an article co-authored by optometrist M. Hom and allergist L. Bielory that stated that most patients with "itchy eyes" consistent with allergic conjunctivitis also have dry eyes and redness.[1] Hom and Bielory's study results suggested that some (ocular) symptomatic patients concomitantly have features of allergic conjunctivitis and dry eye syndrome.

Fast forward to 2021, Leonardi *et al*. present a report that can assist us in fine-tuning our clinical thinking and honing our examination skills and treatment options when presented by a patient impacted by either one, or both, of these reciprocal predisposing disease states.[2] This feature article summarizes the most clinically relevant points from the publication

Leonardi A et al. Allergy and Dry Eye Disease, Ocular Immunology and Inflammation. 2021:1-9 DOI: 10.1080/09273948.2020.1841804

Ocular allergy (OA) and dry eye disease (DED) may coexist and have significant clinical overlap. Alterations of the tear film, epithelial barrier and corneal innervation in OA can pave the way to DED. Conversely, as explained below, DED may facilitate or worsen allergic reactions in atopic patients. OA and DED precipitate shared pathogenic pathways to ocular surface inflammation.

The allergy spectrum includes seasonal and perennial allergic conjunctivitis (SAC, PAC) and vernal and atopic keratoconjunctivitis (VKC, AKC). Although these allergy types have associated immune biomarkers, disease symptomatology may exist without a measurable serum or tear allergy biomarker titer, leaving the possibility of an alternate diagnosis.[3] Ocular itching, considered the discriminating symptom of OA, is not specific to an allergic mechanism, just as tear film instability is not to DED: tear film alterations are often observed in patients suffering from OA. Of note, in vivo confocal microscopy (IVCM) in VKC, AKC and DED displays epithelial, stroma and nerve microstructural changes without disease-distinctive features. Similarly, proinflammatory cytokines (IL-1a, IL-1beta, IL-17, TNFalpha, INFgamma), even those considered specific to allergy (IL-4, IL-5 and IL-13) are over-expressed in tears and the ocular surface of patients with both OA and DED, blurring the clinical boundaries between the two diseases.[4-6]

From OA to DED

Multi-mechanism OA induced tear film instability contributes to DED in OA patients. These include atopic-induced changes in the tear film mucin and lipid layer and alterations in the cell and gland activity that controls their production. For example, meibomian gland distortion and dysfunction is associated with OA:[7] obstructed

meibomian glands and altered meibum secretion in OA can result in tear film instability, that may result in DED. Similarly, IVCM shows substantial changes of corneal subepithelial nerve plexus and stromal nerves that may impair neurotrophic and secretagogue functions in atopic patients.[8] Of interest, changes to the tear film mucous layer, a hallmark of DED, have been also been described in atopic patients. Conjunctival-housed goblet cell secreted mucins facilitate tear film spread over the ocular surface, contribute to its stability and provide a barrier to the corneal epithelium. MUC5AC, the principal secreted mucin, exhibits reduced expression in both DED and atopic patients. Additionally, OA induced local inflammation causes histological (squamous cell metaplasia, epithelial cell and goblet cell apoptosis), biochemical (inflammatory cytokines) and gene expression profile changes of the ocular surface.

Not to be forgotten, the anticholinergic properties of oral antihistamines represent an additional contribution to DED in atopic patients.

From DED to OA

DED may facilitate or precipitate the allergic reaction: reduced tear clearance in DED is responsible for reduced allergen and inflammatory mediators' clearance, with consequent collection in the inferior fornix. Reduced tear volume makes it possible for an antigen too weak or insufficient to precipitate a systemic reaction to trigger a local (eye) allergic reaction. DED altered conjunctival and corneal epithelial homeostasis and cell-cycling results in epithelial barrier disruption that can facilitate the penetration of external antigens and exacerbate the local inflammatory reaction to them in predisposed patients. DED ocular surface inflammation precipitated by tear film instability, corneal wetting defects, hyperosmolar stress, increased friction and mechanical irritation combined, along with loss of epithelial immune tolerance may facilitate ocular allergic reactions. Of course, an allergic reaction may also be related to the ocular surface response to the chronic exposure to any preservatives present in topical dry eye treatments.

How Do We Differentiate OA and DED?

First, an exhaustive ocular and systemic history guides the differential diagnosis pathway. Age and sex of the patient, reaction description (itching, foreign body sensation, redness, tearing, pain), frequency (seasonal recurrences or perennial symptoms, worsening at end of day, etc.) laterality (uni- or bilateral) of ocular symptoms, associated extraocular symptoms (rhinitis, dermatitis, skin dryness, itchiness in the ears or throat), positive family/or personal history of atopy and/or DED, type of job and environment, and review of topical and systemic ongoing therapies. Fundamental information includes the use of any oral drugs. These include oral antihistamines, diuretics, antidepressants, antiparkinsonians, anticholinergics (for example those used in overactive bladder control medications), oral contraceptives, hormonal replacement therapies, among others, as these have all been associated with the development of DED.

Clinical examination for diagnostic clues includes examination for abnormalities of the facial skin (atopic dermatitis, rosacea), eyelids (edema, eczema, blepharitis, tone), conjunctiva (redness, papillae, subepithelial fibrosis, scleral show, conjunctivochalasis, type of discharge), the cornea (Horner-Trantas dots, ocular surface staining, shield ulcer, neovascular vessels), and the tear film (tear break up time (TBUT), quality, tear prism). Keep in mind that patients can also report ocular itching in other pathologies such as bacterial conjunctivitis, giant papillary conjunctivitis and floppy eyelid syndrome.

In vivo and in vitro methods exist to detect allergen-specific IgE, the skin prick test being the gold standard. Although not routinely performed in clinical practice, the conjunctival allergen provocation test is reserved for situations in which the relationship between exposure to suspected allergens and ocular signs and symptoms is not clear or when local symptoms occur without evidence of systemic sensitization or when systemic sensitization occurs without clinical allergy.

DED diagnosis is primarily clinical, supported by results from biomarkers of ocular surface homeostasis that can include TBUT, Schirmer test and/or tear osmolality.

OA and DED Main Therapeutic Options

Inflammation is the underlying pathogenic mechanism of OA and DED and hence therapeutic management strategies for the two can overlap.

In OA, avoiding or limiting exposure to causative allergens and nonspecific triggers (e.g., sun, warm climates, wind, flowers and plants) and increased hygiene procedures (frequent hand, face and hair washing) are effective measures to dampen the allergic reaction. Similarly, but not addressed in this paper, environmental modifications such as avoiding desiccating air currents, e.g. fans or air conditioners, humidifying the ambient air, modifying positions of visual targets, and limited application of sensitizing creams, cosmetics and other products in and around the eye as well as their complete removal, are helpful in tempering the impact of DED.[9] Lid abnormalities that cause ocular surface exposure or irritation such as ectropion or entropion, lid inflammation or blepharitis should be addressed.

Pharmacologic measures in OA are general employed in a stepwise fashion, with topical mast cell stabilizers and histamine H1 receptor antagonists being considered first-line drugs for symptomatic relief in OA.[10] Systemic antihistamines in combination with local therapy can dampen allergic flare ups, keeping in mind surface drying induced by oral antihistamine therapy. Low-penetrance topical steroids are the most effective drugs to address inflammation of the ocular surface. Topical cyclosporine or tacrolimus are viable options for OA treatment. With severe systemic allergic involvement, biologic medications are indicated.

DED, likewise, can be treated initially with tear replacement therapy targeted at one or more of the layers of the tear film. As inflammation is core to both the development and propagation of DED, as in OA treatment, topical steroids, cyclosporine, tacrolimus and lifitegrast (not discussed in this article) are included in advanced DED care therapies.

Conclusion

This article reminds us that inflammation is a common pathogenic pathway of OA and DED and that both entities should be considered in the symptomatic patient. Included is a sophisticated review of the immunology of OA and DED. The authors suggest that IVCM is proving to be a useful tool during treatment to monitor and correlate microscopic changes in inflammation in the cornea, conjunctiva and meibomian glands to clinical observation. Added are clinical images and a very useful table of systemic and topical medications potentially responsible for OA and DED. Finally, a simple, yet eloquent graphic outlining the “vicious cycle of allergy and dry eye disease” can easily be committed to memory to keep the points reviewed in this monograph top-of-mind.

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