

Ocular manifestations of atopic dermatitis

Abstract

Purpose: A review of the published literature on the history, pathogenesis, and treatment of atopic dermatitis (AD) and its ocular involvement.

Methods: Literature searches were conducted in MEDLINE (Ovid) and Google scholar for AD and ocular AD.

Results: AD is an inflammatory dermatosis that has classic presentations on the skin at different age points. The primary immunological profile is a Th2 profile, releasing an abundance of IL4 and IL10 both systemically and locally. AD can involve the eye and have devastating consequences. Here we review the latest understanding of AD pathogenesis and treatments vis-à-vis the ocular surface.

Conclusion: Ocular AD is a common manifestation of AD. The newest drugs for systemic AD might be deleterious for ocular AD.

Keywords: atopic dermatitis, eczema, ocular eczema, keratoconus, filaggrin, dupilumab

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Introduction

Atopic dermatitis (AD) is referred to as the itch before the rash,¹ and is a chronic skin inflammation that has systemic manifestations. AD constitutes the most common form of inflammatory skin condition.² It commonly presents in childhood before the age of 6 in up to 80% of cases,³ but 7-10% can present in adulthood.⁴ Other than the skin manifestations, AD patients for example have a higher incidence of psychological diagnoses, inflammatory bowel disease and joint inflammation.⁵ AD competes with rosacea as the two common dermatologic conditions with the most ocular and periocular findings. We will review the pertinent elements of ocular AD.

Clinical presentation of ocular atopic dermatitis

AD commonly presents with asthma, hay fever, rhinitis, and allergic conjunctivitis that run-in families, but 20-30% lack such associations.⁶ A systematic review showed that AD patients have more contact sensitivities than the general population.⁷ The most common ocular allergens include aminoglycoside antibiotics, corticosteroids, wool alcohols, thiomersal, and benzalkonium chloride.⁸ Therefore, when topical sensitivity is suspected, a patch test could help in disease management.

AD presents in childhood with red, crusted patches and subsequent lichenification from chronic itching on the flexor surfaces of the extremities, face, eyelids, scalp, and other body parts. AD has a wide spectrum of clinical presentations, from itching in the flexor areas, to erythroderma, a true dermatologic emergency. Eyes can present with chronic blepharitis peri-ocular lichenification, hyperpigmentation (allergic shiners) and excessive skin fold (Dennie-Morgan fold), conjunctivitis, corneal neovascularization, keratoconus, herpes simplex keratitis, and rarely blindness. It has a sinusoidal clinical course, with times of flare and calm, but in some cases, it can be chronic in presentation (Figure 1).⁹

Pathogenesis of ocular atopic dermatitis

Although the dogma of AD pathogenesis was an IgE-mediated

disease, newer data show that IgE involvement is a secondary phenomenon, and not the causative factor of a defective tissue barrier.¹⁰ A faulty epidermal barrier can have multiple causes, one being a lack of filaggrin (*Flg*). Other causes of barrier dysfunction are physical itching secondary to Th2 cytokine release.¹¹ Other factors include elevated lesional skin Ph¹² with increased trans-epidermal water loss (TEWL) and increase permeability to external irritants and allergens.¹³ This process makes AD skin more susceptible to harboring bacteria.¹⁴ Furthermore, there is an imbalance in epidermal protease/protease inhibitor balance;¹⁵ in the epidermal lipid compositions and arrangement;¹⁶ decreased tight junction protein expression;¹⁷ increased release of pro-inflammatory alarmins.¹⁸ Exposure of patients to pre-sensitized antigens can exasperate AD (Figure 2).¹⁹ However, in the barrier enhancement for eczema prevention (BEEP) study, the use of emollients in infancy is protective against AD.²⁰

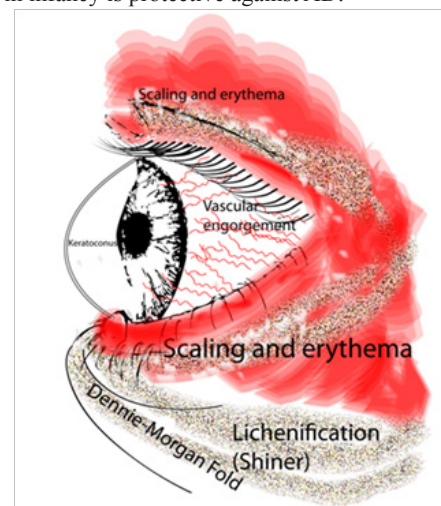


Figure 1 Clinical illustration of ocular atopic dermatitis.

Immune System in atopic dermatitis

Dermal infiltrates in AD lesions constitute CD4+ T cells and dendritic antigen presenting cells.²¹ Specifically, Th2 products, IL-4,

IL-10 and IL-13 are upregulated; moreover, Th22 secreting IL-22²² and Th17 secreting IL17 are upregulated.²³ Most AD patients have IgE to air-borne allergens, food allergens, microbial proteins²⁴ and keratinocyte specific antigens.²⁵ Even non-affected skin in AD patients show inflammation that is analogous to lesional inflammation.²² As AD waxes and wanes, there is an increased infiltration of Th2, Th17, and Th22 cells in the lesional skin.²³ The Th2 and Th22 cytokines induce barrier dysfunction.²⁶ Upon epithelial barrier disruption, alarmins become abundant. Langerhans cells and Th2 cells induce abundant IL-4 and IL-13. This cytokine profile induces immunoglobulin switching to antigen-specific IgE through the signal transducer and activator of transcription (STAT) and the IL-13 induces itch.

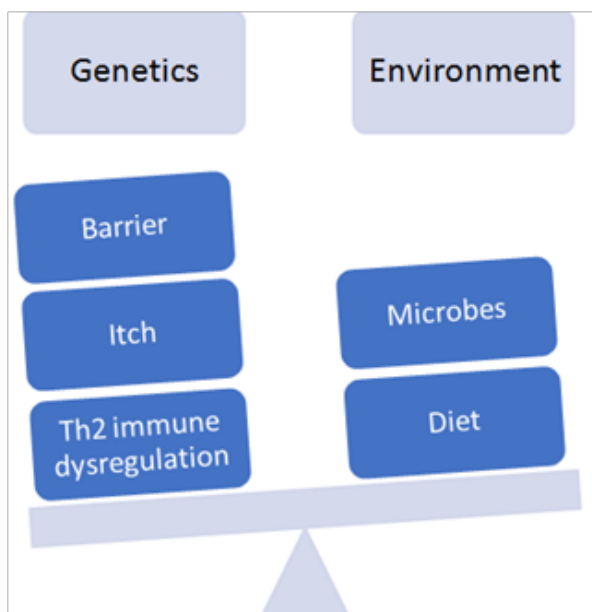


Figure 2 Pathogenic elements of ocular atopic dermatitis.

Genetics of atopy

The most common predisposing factor to acquiring AD is family history. If one parent has atopy, the offspring risk of AD is 3-fold, and if both parents have atopy, the offspring's risk is of AD is 5-fold.²⁷ Studies of identical twins place genetic causality at 75%.²⁸ Filaggrin (*FLG*) mutation resulting in reduced expression of *FLG* is seen in 20% of AD patients, and constitutes the greatest genetic association with AD.²⁹ However, in the general population, more than 50% have *FLG* mutations without any atopy.³⁰ This indicates other needed factors in the development of AD. However, *FLG* is a complex protein of the stratum corneum and epidermal barrier with multiple variants. Its part of the AD manifestation, but not the whole story.³¹ Another genetic association is on chromosome 5, at a stretch that controls Th2 cytokines, itch, and Th switching.³²

Itch

The itch from AD is conducted by slow-conducting and fast conducting myelinated fibers,³³ and can be heightened by emotional stress.³⁴ Fibroblasts and keratinocytes in AD patients produce artemin, which induces greater innervation and hypersensitivity.³⁵ One known inducer of artemin production is air pollution via stimulation of keratinocyte aryl hydrocarbon receptors.³⁶ Thymic stromal lymphopoietin (TSLP) is a keratinocyte-derived cytokine that contributes to itch in AD. However, the most common itch-

causing agent is histamine from mast cells and basophils,³⁷ followed by endothelin-1, IL-4, IL-13 and IL-31, but IL-31 is the predominant itch-inducing cytokine in AD (Figure 3).³⁸

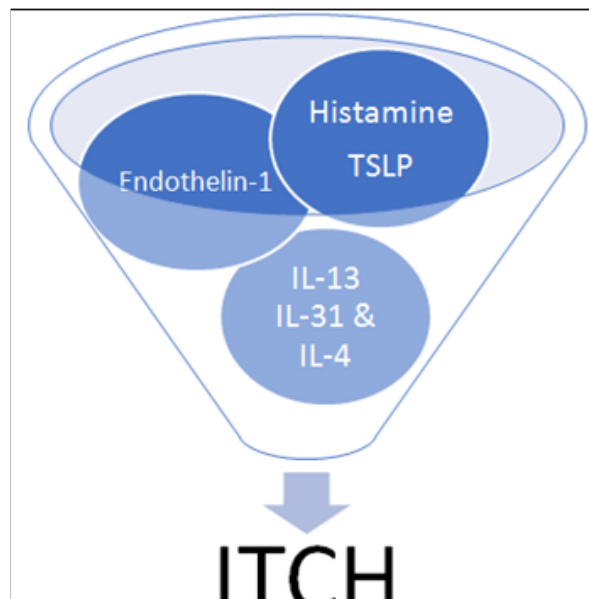


Figure 3 Itch causing endogenous agents in AD.

Microbes

Patients with AD have an altered innate immune system that allows for an overgrowth of bacteria, especially *Staph*.³⁹ Staph and other microbes, release multiple enzymes that degrade tissue and disrupt barrier. The different elements that exacerbate AD can interplay. In one study, food allergy was linked to Staph colonization in children with AD.⁴⁰ This bacterial enzymatic phenomenon of AD extends to ocular AD, especially in cases of chronic AD blepharitis.⁴¹ However, “good” GI and bacteria have some beneficial effects. During pregnancy, ingestion of probiotics has mild protection for the fetus.⁴²

Diet

Thirty seven percent of infants suffering from AD have a concomitant food allergy, while 10% of adults with AD have food allergies.⁴³ AD tends to precede food allergies in most cases,⁴⁴ and early introduction of allergy-inducing foods can cause tolerance to the food.⁴⁵ However, peanut allergy can remain after childhood, while egg and milk allergies tend to be transient in childhood.⁴⁶ Other associations with AD include diets rich in simple sugars, diets rich in polyunsaturated fats. Food allergy test, in the form of RAST or skin prick testing, is not indicated in the workup of AD, except in recalcitrant forms in patients <5years of age or in patients with immediate food-related flares. There is no evidence that delaying solid food to infants, or avoiding early use of antibiotics, or the consumption of fish oil protects against AD.

Environmental elements

Asthma and rhinitis and the most common occurrences with AD.⁴⁷ Any air-borne allergen exposure occurs post-infancy. This exposure can flare AD.⁴⁸ Other associations with AD include proximity to urban or inner-city environment, areas with low ultraviolet light, multiple courses of antibiotics prior to age 5, climates with low humidity, small families, and higher educated families. Furthermore, tobacco smoke

increases AD risk, and should be avoided. There is no evidence that avoiding farm animals protects against AD.

Systemic Associations with atopic dermatitis

AD is most commonly associated with systemic findings in the form of psychological diagnoses and autoimmune diseases. Attention deficit disorder, depression and autism have been linked to childhood AD.⁴⁹ The association of AD with depression extends into adulthood.⁵⁰ There is some association with inflammatory bowel disease, rheumatoid arthritis,⁵¹ alopecia areata and vitiligo.⁵² Cutaneous T cell lymphoma could be a risk factor in AD.⁵³ The association of AD and cardiovascular disease is an ongoing debate,⁵⁴ but a recent study identified a notable association of AD with heart disease.⁵⁵

Treatment of ocular atopic dermatitis and conclusion

The treatment of ocular atopic dermatitis includes establishing hydration, eliminating bacterial colonization, treating any herpetic infection, and reducing the overall inflammation. Atopic dermatitis has periods of activity and periods of inactivity. A regimen is required to suppress the activity in its height, and prevent an active spike during the calm period. Ocular AD can have severe manifestations, and with the proper management and treatment, the severe manifestation of AD can be avoided (Figure 4).

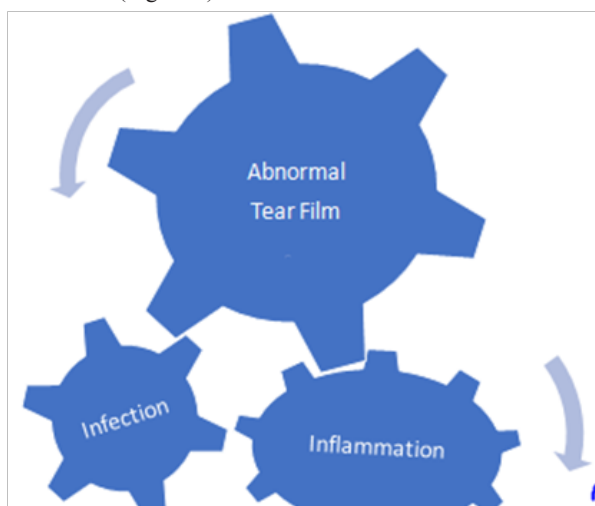


Figure 4 The main elements of ocular atopic dermatitis.

Hydration of the tear film is accomplished by regaining meibomian and lacrimal glandular health (Figure 4). In the meantime, hydrating eye drops are needed to protect the ocular surface, such as over-the-counter drops (preferably preservative free) can be used 4-5 x per day. Hydrating eye drops can be used less frequently during the inactive period of ocular atopic dermatitis. Topical anti-histamine + mast cell stabilizers are also used routinely in ocular AD patients.

Staph and other bacteria tend to colonize skin and mucosa, including the ocular lash line. Their presence is accompanied with stimulation of the innate immune system and their toxins can activate the adaptive immune system. This causes pro-inflammatory cytokine release, swelling, and angiogenesis on the ocular surface. Furthermore, herpes simplex virus can be reactivated in severe cases, i.e., eczema herpeticum. A lytic virus on the ocular surface is quite devastating. Therefore, it is imperative to identify pathogens that occupy lesional tissue. For bacteria, ocular erythromycin ointment is both antibacterial,

anti-angiogenic, endothelin-1-blocking,⁵⁶ and helps trap moisture. In more severe cases, oral antibiotics, like amoxicillin with clavulanate is recommended for a period of 10 days. If there are signs of a herpetic reactivation, then topical/oral antivirals are recommended.

The most important aspect of AD is inflammation. The tissue integrity and barrier repair are contingent on an appropriate anti-inflammatory regimen. Topical steroids, like prednisolone eye drops, are a first line drug, but should not be used for extended periods. Therefore, with the steroid, a steroid-sparing agent, like ocular cyclosporin (or tacrolimus), make for a good combination. After the a few weeks, the steroids are tapered off, and the cyclosporin is continued. If the symptoms are more severe, a short course of oral methylprednisolone taper for 5 days is effective. Anti-histamines are commonly used; however, their anti-cholinergic effect can exacerbate the tear film dysfunction. Recently, a new biologic targeting the IL-4 receptor, dupilumab, has been FDA approved for moderate-to-severe atopic dermatitis. However, dupilumab has been associated with drug-induced conjunctivitis. This makes us cautious in recommending it for severe AD with ocular manifestations.⁵⁷ Latest though on AD is that there is an imbalance of the skin flora, and potentially the periocular flora. When virulent strains of *Staph* dominate the flora, disease occurs, and when non-virulent microbes dominate, skin barrier is protected. The establishment of a healthy microbiome will be the next exciting approach to AD, and possibly ocular AD.⁵⁸

Acknowledgments

None

Conflicts of interest

The authors declare no conflicts of interest.

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