REVIEW ARTICLE

Ophthalmic Complications Associated with Atopic Dermatitis: A Review

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ABSTRACT

Atopic dermatitis (AD) is a long-lasting dermatological disease that is associated with ophthalmic complications in the long run. Those having AD are more likely at risk of developing comorbidities in eye as compared to normal persons. This review encompasses the clinical manifestations, pathophysiology and treatment of common ophthalmic complications presented with AD i.e., blepharitis, kerato-conjunctivitis, corneal ectasias, glaucomatous eyes, lens opacification, detachment of retina, herpetic eye disease (HED) and dupilumab associated eye toxicities. It is necessary for dermatology colleagues to be vigilant enough not to miss ophthalmic problems associated with AD, as an early detection and management can save the vision.

Key Words: *Atopic Dermatitis, Atopic Keratoconjunctivitis, Blepharitis, Corneal Ectasias, Herpetic Eye Disease.*

Introduction

Atopic dermatitis (AD) is a long-standing dermatitis with a disease burden ranging from 12% to 22% in developed countries.[1] It typically affects the face (cheeks), neck, arms, and legs but usually spares the groin and axillary regions. AD usually starts in early infancy, but it also affects number of adults. AD is commonly associated with elevated levels of immunoglobulin E (Ig-E) resulting in allergic diathesis which may include food allergies, asthmatic events and atopic rhinitis in sequence referred as "atopic march" theory, which suggests that it is a part of progression that may lead to subsequent allergic disease at other epithelial barrier surfaces.[2,3] Any age group can be affected but it predominantly affects adults in their second and third decade manifested as dry skin patches with itching that remits and exacerbates. Primary physical findings include xerosis, lichenification and eczema.[2]

Recently, evidence have shown that AD can present with extra-cutaneous features. Epidemiological surveys have revealed that an enormous proportion of patients develop ocular comorbidities in the course of the disease as compared to normal people, with varying range of severities.[2,3] Notable ocular morbidities include blepharitis, kerato-conjunctivitis, corneal ectasias, glaucomatous eyes, lens opacification, retinal detachments, herpetic eye disease and dupilumab associated eye toxicities.[3]

The pathophysiological basis for these ocular morbidities is myriad and involves multiple mechanisms. Innate immunity dysfunction, excessive eye rubbing due to itching, steroid induced ocular toxicities and genetic susceptibility all have been implicated.[2] Some ocular conditions develop lately in the course of disease, while some presents acutely, however if not picked up early and managed appropriately can result in severe visual impairment. This review encompasses the clinical manifestations, pathophysiology and treatment of common ophthalmic problems associated with AD.

Blepharitis

This inflammatory/infective lid margin disease affects approximately more than 5% of people with AD as compared to normal people.[2] It is divided into an anterior and posterior types, based upon the anatomical landmark of meibomian gland orifices at the lid margins. Patient complains of ocular itching and irritation of the lids, watering of eyes, ocular grittiness or feeling of burning, lid crusts, and light sensitivity.[4] Anterior blepharitis is mostly caused by staphylococci, while posterior one is secondary to meibomian gland dysfunction (MGD).

Though pathophysiology is still unclear, tissue desiccation in atopic patients is accompanied by barrier disruption and trans-epidermal desiccation, causing eyelid dermatitis.[4,5]

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Received: July 07, 2022; Revised: December 01, 2022
Accepted: December 05, 2022

DOI: https://doi.org/10.57234/1396

The conventional therapy of AD associated blepharitis consists of conventional lid-hygiene measures, such as warm compresses and gentle scrubbing of the lid margins to remove crust and debris, which can be done with non-prescription cleansers, lid-scrubs, and baby shampoos. Acute flare needs topical antibiotics, topical calcineurin inhibitors (i.e., cyclosporine 0.05%), or low-strength topical steroids.[5] Due to possible toxicities of medication especially topical steroids, ophthalmic consultation is mandatory for early diagnosis and treatment.

Kerato-conjunctivitis

Atopic kerato-conjunctivitis (AKC) is a non-infectious inflammatory condition involving the corneal and conjunctival tissues with a prevalence ranging from 23% to 43% of patients with AD.[6,7] Mostly present in the late teens and peaks from the third to fifth decade.[8] The symptoms of AKC include itching, red eyes, stringy mucous secretion, burning sensation, light sensitivity and decrease vision. Long standing disease can cause corneal vascularization, punctate epithelial erosions and secondary bacterial keratitis, repeated corneal trauma can lead to scarring and corneal blindness.[7]

Pathophysiology of kerato-conjunctivitis involves inflammatory involvement of the conjunctiva by eosinophil, mast cells and other inflammatory cells. It has been reported in studies that patients having peri-orbital AD is linked with the development of severe form of atopic kerato-conjunctivitis, which in the long run can turn into development of entropion if not properly mananged.[7] Eye consultation is very important in AKC for its proper management in order to avoid ocular complications ultimately leading to visual impairment.[7,8] Conservative measures include cool compresses and treatment with ophthalmic eye drops containing antihistamines (i.e., ketotifen 0.025%) and mast-cell inhibitors (i.e. olopatadine 0.2% drops).[8] Atopic kerato-conjunctivitis flare ups may require short-term use of topical steroids or calcineurin inhibitors, or systemic steroids/ immune-suppressants for refractory cases.[6] In the long run patients with AKC needs maintenance therapy with long acting anti-inflammatory agents in the form of calcineurin inhibitors which controls the inflammatory component of the disease without having steroid induced complications.[8] Corneal involvement resulting from chronic inflammation requires steroids, calcineurin inhibitors, amniotic membrane grafting and in severe cases may need limbal stem cell transplantation.[7]

Keratoconus

Keratoconus (KC) is a non-inflammatory ectatic corneal disease characterized by slowly advancing ectasia and cone-like bulging of the cornea. Corneal topography reveals changes in the thickness profile characteristic of KC along with irregular astigmatism depending upon the severity of condition clinically manifested as diminished vision with distorted images.[2,9] Numerous studies have shown positive link between KC and AKC.[10,11]

The exact mechanism of KC development in AKC is ambiguous and thought to be multi-factorial. Excessive eye rubbing from peri-ocular itch and irritation has been shown to be responsible for KC.[12] Furthermore, immune deregulation and altered synthesis of inflammatory mediators have also been implicated in the causation of KC.[13]

KC is dynamic in its course with significant effect on visual acuity, making it imperative to detect it earlier on before its lead to severe visual impairment. Certain risks predisposes the person to develop KC includes, AKC, AD involving the lids, excessive eye rubbing and familial KC. Any of these conditions make it prudent to seek ophthalmic consultation for screening and visual assessment.[10,11,12]

Early management of KC includes spectacles and rigid gas permeable (RGP) contact lenses for refractive correction. For severe KC, specially designed contact lenses are used. The RGP contacts are custom made lenses to vault over the ectatic corneal surface.[9]

For moderate cases of KC without apical corneal scarring, a technique developed to strengthen the bond between the corneal collagen fibers to prevent its progressive thinning by using riboflavin and UV-A irradiation to make firm bonds between collagens in the corneal tissue, this is known as corneal cross linking. Studies have shown its efficacy and safety in halting the progression of KC, especially if undertaken earlier in the disease, and has been given FDA approval in 2015.[9,10,11]

Glaucoma

Glaucoma development is common during the therapy of AD and can cause irreversible damage to

DOI: https://doi.org/10.57234/1396

the nerve fiber layer of the retina and optic discs. Steroids used in the treatment of AD is mainly responsible for its causation.[14]

Numerous case reports have attributed glaucomatous risk to chronic use of high potency topical steroids in the peri-ocular areas, which is mainly responsible for it to direct absorption by ocular tissues, as glaucoma seldom develops with topical steroid application anywhere else in the body.[15-17] Oral steroids (i.e. betamethasone) taken for more than 2 months is also associated with very high intra-ocular pressure (IOP).[18]

Predisposing factors for raised IOP, includes preexisting glaucoma, diabetes, connective tissue disorders, and high myopes.[15,19] Steroid responders and younger lot also shows hypersensitivity to steroids.[20]

As glaucoma progresses silently until advanced, earlier diagnosis is important from the management point of view. Patients who are showing exaggerated clinical response (raised IOP) to optimal dose of steroids as compared to normal individuals, patients on long standing steroids via different routes for their medical conditions and those having positive family history of glaucoma should be screened for glaucoma assessment.[17] In addition to that, individuals having simultaneous glaucoma and AD should seek consultation from both the Ophthalmologist and Dermatologist for their management, and preferably steroid sparing agents should be used in such cases to avoid steroid induced complications.[21,22,23]

Cataracts

Prevalence of cataract ranges from 6% to 23% with AD.[21,24] Pre-senile cataracts are quite common in patients of AD, which can be attributed to both steroids use and disease process itself. Cataract development can sometimes become abrupt and number of evidences from studies have shown it to be associated with flare ups of AD.[25,26]

Sub-capsular variants of cataract are quite common in AD, in contrast to nuclear and cortical ones, which mostly effect normal elderly population.[27,28] Anterior sub-capsular cataract is more specific to AD, whereas posterior sub-capsular ones are specific to long-standing steroids use in AD.[27] Younger age group are more prone to steroid induced cataract development with short duration of therapy and even less potent ones as compared to elderly people.[29]

The patho-physiology of cataract development in AD is multi-factorial. Evidence based scientific reports have shown that patients with AD have breached blood retinal barrier and high levels of free radicals in the lens suggestive of oxidative damage.[30,31] Steroids in any form can cause cataract formation but mostly the oral form are strongly associated with cataractous changes in the lens, however steroids in the form of inhalers and topical creams/ointments are also responsible for cataract development.[26,32]

Patients with early onset peri-orbital AD, long standing steroids use, and positive family history need to be reviewed periodically. Anterior and posterior sub-capsular lens opacities are detected with red-reflex assessment that can readily be performed by the optometrists or ophthalmologist.[33]

Retinal Detachment

Retinal detachment (RD) is a vision threatening ocular comorbidity of atopic dermatitis that hits younger people more than 5 years old. The prevalence of RD in patients with AD is in the range from 3% to 7%.[34] Patients with RD presents with loss of vision, photopsia, floaters and curtain like field defects.[35,36]

Many studies have reported that involvement of peri-orbital region by AD along with long standing history of eye rubbing is strongly associated with retinal detachment. RD is also accompanied with other ocular pathologies such as proliferative vitreo-retinopathy, ectopia lentis, and lens opacifications.[34-38] The underlying development of RD is thought to be due to ocular distortions from forceful ocular rubbings, also the morphological appearance of RD in AD-associated RD versus traumatic RD both are characterized by retinal breaks at vitreous base.[37]

Avoiding eye-rubbing and optimal therapy for peri-orbital AD can reduce the risk of developing RD. In addition to that, all patients with symptoms of RD should seek ophthalmic consultation.

Herpetic Eye Disease

Herpetic eye disease (HED) presents with potential ocular morbidity, as recurrent attacks can lead to corneal scarring and neo-vascularization. Individuals with atopic dermatitis are more prone to develop severe herpetic ocular infection and mostly of atypical variants with more complication and refractory to conventional therapy as compared to

DOI: https://doi.org/10.57234/1396

normal indivisuals.[38,39] Additionally, atopic disorders are associated with frequent herpetic recurrences leading to neurotropic keratitis .[38,39,40]

These observations suggests that Atopic dermatitis patients with a prior HED should be carefully observed and treated with anti-virals and topical steroids in case of dendritic keratitis or topical steroids only in disciform keratitis, while for recurrences prophylaxis with acyclovir is needed for few months.[39,40] Addionally, active HED warrants urgent ophthalmic consultation.

Dupilumab associated Ocular Complications

Dupilumab, is a monoclonal antibody that inhibits IL-6 and IL-12 transduction pathways. It is one of the first biologics given approval for treatment of moderate to severe AD. Some studies have reported a higher incidence of anterior conjunctivitis in dupilumab treated AD patients (6%–26%) compared to placebo (1%–9%).[41] Surprisingly, the incidence may go as high as 68%, reported in some literature.[42] However, in some other studies it has been found that dupilumab given in asthmatics, nasal polyposis and eosinophilic-granulomas didn't show any rise in the incidence of dupilumab associated conjunctivitis in dupilumab treated patients when compared with control group, emphasizing upon an AD-specific mechanism.[43]

Main findings of dupilumab associated conjunctivitis includes conjunctival congestion and limbal hyperemia, along with eye symptoms such as watering, itching and blurring of vision. Its use has been associated with reduced goblet cell density in conjunctiva on histological and spectroscopic specimens.[44] Blepharo-conjunctivitis is also reported in some literature due to dupilumab therapy.[45]

Standard treatment protocol for dupilumab associated ocular complications hasn't yet been established. It is noteworthy that anti-histamine eye-drops are ineffective in the treatment of dupilumab associated conjunctivitis.[42] But, topical less potent steroids and tacrolimus ointment 0.03% has shown some promising results in its management.[41] Lifitegrast, an immunosuppressant agent has been granted approval in the treatment of kerato-conjunctivitis sicca, in patients who are resistant to topical steroids.[45] As a last resort, stopping of the therapy is the only way to get rid of therapy induced ocular toxicities in AD patients.[43,44] Those taking dupilumab, who develop eye problems should seek ophthalmic consultation.

Recommendations

Dermatologists who are dealing with AD should be made aware of possible ocular comorbidities that develops in due course of time. They should be educated via conducting joint clinco-pathological sessions by increasing their knowledge with inputs from both the ophthalmologists and dermatologists, mutual clinical rotations of the postgraduate residents of both specialties, interdisciplinary and multidisciplinary approach towards managing such patients and making joint protocols/ guidelines for AD patients with liaison between both specialties.

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DOI: https://doi.org/10.57234/1396

CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

GRANT SUPPORT AND FINANCIAL DISCLOSURE

Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

DOI: https://doi.org/10.57234/1396