ORIGINAL ARTICLE

Ocular co-morbidities in patients with atopic dermatitis - a cross-sectional study from a tertiary referral hospital, Malaysia

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin disease that commonly occurs among children as well as adults. AD patients were reported to have high prevalence of ocular manifestations, which may be due to the disease nature or drug complications. This study aimed to determine the prevalence of ocular manifestations in patients with AD.

Materials and Methods: Eighty patients who fulfilled the UK Working Party's Diagnostic Criteria for Atopic Dermatitis were included in the cross-sectional study. A standardized case report form was formulated to collect the demographic data and disease profile of the participants. AD severity was evaluated using the EASI and SCORAD score. All patients underwent a complete ophthalmological evaluation.

Results: The prevalence of ocular manifestations among the patients with AD was 48.8%. Fifty-four (67.5%) patients had facial dermatitis and 37 (46.2%) showed periorbital signs. The mean AD disease duration was 10.99 ± 11.20 years. Majority of the patients had mild to moderate AD. The most frequent ocular manifestation was allergic conjunctivitis (18.75%) followed by cataract (8.75%) and ocular hypertension (8.75%). Among the patients with ocular manifestations, 27 (69.2%) patients regularly applied topical corticosteroids on the face. The use of systemic corticosteroids was seen in 19 (42.2%) patients. Prolonged AD duration was significantly associated with the development of ocular manifestations.

Conclusions: Nearly half of the patients with AD were complicated with ocular disease regardless of the AD severity, facial dermatitis and presence of periorbital signs. Long disease duration is associated with ocular manifestations, especially steroid related complications.

KEYWORDS:
Atopic eczema, ocular co-morbidities, ocular complications, ophthalmic disease, atopic conjunctivitis

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin disease that commonly occurs among children, but it also affects adults.[1] Patients with AD have higher prevalence of ocular co-morbidities compared to the normal population.[2] Various structures of the eyes may be affected, including the lids, ocular surface, conjunctiva, cornea, lens and retina. The frequency of these disorders ranges from 25-50%.[3]

The economic burden of atopic dermatitis to nations varies significantly across countries. The direct healthcare cost of a patient in less developed countries (Malaysia, Indonesia and Philippines) is estimated to range from USD199 to 743 which represents a substantial medical cost.[4] The development of ocular complications directly or indirectly secondary to atopic dermatitis may negatively impact the psychosocial wellbeing of the patients leading to higher incidence of depression and anxiety disorder.[5]

However, ophthalmological evaluation is not a routine standard procedure for patients with atopic dermatitis in Malaysia. Therefore, it can be important to detect ocular complications early and implement annual ocular screening for patients with atopic dermatitis. There is lack of data on ocular complications among patients in Malaysia with atopic dermatitis which necessitates clinical study on this topic.

The primary objective of this study is to determine the prevalence of ocular manifestations in patients with AD. The secondary objective of this study is to determine the association between the severity of AD and systemic corticosteroids use and the presence of ocular complications.

MATERIALS AND METHODS

This was a cross-sectional study done at Queen Elizabeth Hospital, a dermatology referral centre in Sabah, East Malaysia. All patients with AD attending the Dermatology Outpatient Clinic between 18th November 2019 and 31st December 2020 were invited to participate in the study.

The inclusion criteria were patients with atopic dermatitis aged 2 to 60 years. The diagnosis of AD was made based on the United Kingdom Working Party's Diagnostic Criteria for Atopic Dermatitis.[6] All patients were examined and evaluated by two investigators. The exclusion criteria were patients with underlying systemic disease requiring systemic

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Table I: Patient Demographics, Prevalence and Characteristics of Patients with Dysphagia

Variables	n (%)
Gender	
Male	43 (53.8)
Female	37 (46.3)
Age of diagnosis (mean ± SD)	7.67±10.51 years
Age range	2-60 years
Age group	
2-18	47 (58.7)
>1833 (41.3)	
AD disease duration (mean ± SD)	10.99±11.20 years
< 1 year	4 (5)
1 - 5 years	28 (35)
5 – 10 years	19 (23.8)
> 10 years	29 (36.3)
Presence of family history of atopy	63 (78.8)
Past Medical History	
Atopy	40 (50)
- Bronchial asthma	15 (18.8)
- Allergic rhinitis	18 (22.5)
- Asthma & rhinitis	7 (8.8)
Hypertension	2 (2.5)
Others (IDA & fibromyalgia, ectodermal dysplasia, ADHD, hepatitis B)a	4 (5.0)
No past medical history	34 (42.5)
Presence of facial dermatitis	54 (67.5)
Periorbital signs	
- Dennie-Morgan fold	21 (26.3)
- Periorbital darkening	27 (33.8)
- Eyelid dermatitis	30 (37.5)
Severity of atopic dermatitis	
EASI score (mean ± SD)	11.61±10.18
SCORAD score (mean ± SD)	33.69±13.97
EASI	
Almost clear (0.1 – 1.0)	4 (5)
Mild (1.1 – 7.0)	28 (35)
Moderate (7.1 – 21.0)	35 (43.8)
Severe (21.1-50.0)	13 (16.3)
SCORAD	
Mild (<25)	29 (36.3)
Moderate (25-50)	40 (50)
Severe (>50)	11 (13.8)
Cumulative prednisolone dose/ year (mean)[b]	161.07±316.72mg
Range	50.0-9970.0mg
Treatment	
Topical corticosteroids	79 (98.8)
Topical calcineurin inhibitors	18 (22.5)
Systemic steroids	45 (56.3)
Systemic steroid sparing immunosuppressants *(e.g. Azathioprine, methotrexate)*	16 (20.0)

[a] IDA iron deficiency anaemia, ADHD attention deficient hyperactive disorders
[b] Cumulative amount of oral prednisolone used in mg per year

Table II: Types of ocular manifestations

Ocular manifestations	n (%)
Paediatric group (n=47)	22 (46.8)
Adult group (n=33)	17 (51.5)
Lid disorders	
- Blepharitis	2 (2.5)
Conjunctival disorders	
- Allergic conjunctivitis	15 (18.75)
- Keratoconjunctivitis	1 (1.25)
Cataract	
- Anterior subcapsular	3 (3.75)
- Posterior subcapsular	4 (5.0)
Ocular hypertension	7 (8.75)
Dry eye syndrome	1 (1.25)
Epiblepharon	6 (7.5)

Table III: Association between ocular manifestations and steroid use, disease severity & disease duration

Variables	Presence of ocular manifestation Frequency (%) n=39	No ocular manifestation Frequency (%) n=41	p-value
Topical steroid			
Face	27 (69.2)	24 (58.5)	0.319
Others	12 (30.8)	17 (41.5)	
Systemic corticosteroid			
Yes	19 (42.2)	26 (57.8)	0.185
Othersa (other treatment or none)	20 (57.1)	15 (42.9)	
Presence of facial dermatitis			
Yes	28 (71.8)	26 (63.4)	0.424
No	11 (28.2)	15 (36.6)	
Presence of periorbital signs			
Yes	18 (46.2)	19 (46.3)	0.987
No	21 (53.8)	22 (53.7)	
EASI severity index			
Almost clear to mild	14 (35.9)	18 (43.9)	0.465
Moderate to severe	25 (64.1)	23 (56.1)	
EASI severity index			
Mean (SD)	12.1 (10.78)	11.1(9.67)	0.630
SCORAD severity index			
Mild	13 (44.8)	16 (55.2)	0.477
Moderate	22 (55.0)	18 (45.0)	
Severe	4 (36.4)	7 (63.6)	
SCORAD severity index Mean (SD)	34.0 (13.3)	33.4 (14.7)	0.871
Disease duration Median (IQR)	10 (19.0)	5 (8.75)	0.031

[a]Others: Other systemic immunosuppressants such as azathioprine or methotrexate or none

Table IV: Association between steroid-related ocular complications and disease duration

	Steroid-related ocular complications (n=10) Frequency (%)	No ocular complications (n=70) Frequency (%)	p- value
Disease duration Median (IQR)	13.5 (27.0)	6.3 (9.0)	0.006

corticosteroids or immunosuppressants, presence of other skin diseases with ocular manifestations, patients with allergic rhinitis and or allergic conjunctivitis requiring topical immunomodulators and patients who were unable to undergo ocular assessment.

A standardized case report form was formulated to collect the demographic data and disease profile of the participants. The usage of topical corticosteroids on periocular region as well as the cumulative dose of systemic corticosteroids were obtained. AD severity was evaluated using the EASI and SCORAD score.[7] A complete ophthalmological evaluation was performed by an ophthalmologist that included visual acuity, slit lamp examination, ocular tonometry and dilated fundus examination. Eyelid dermatitis, periorbital darkening and Dennie-Morgan fold were categorised as periorbital signs. Posterior subcapsular cataract and ocular hypertension were categorised as steroid-related complication. The ophthalmological evaluation was done once and subsequent review will be provided if any pathology is detected.

The data collected were analysed using Statistical Package for the Social Sciences version 24. Categorical data were analysed using Chi-square test and presented as numbers (percentages). Continuous data were analysed using t test and Mann Whitney test. The analysed data were presented as mean±standard deviation or median and interquartile range. The level of significance was set at $p<0.05$.

RESULTS

A total of 80 patients participated in the study with 43 (53.8%) males and 37 (46.3%) females. The mean age at presentation was 7.67±10.51 years. A total of 63 patients (78.8%) had family history of atopy. The mean disease duration was 10.99±11.20 years. Half of the patients had personal history of atopy which included bronchial asthma, allergic rhinitis, or both. The prevalence of ocular manifestations among the paediatric group (2-18 years) and the adult group were similar (46.8% and 51.5% respectively). Out of the 80 patients, 54 (67.5%) had facial dermatitis and 37 (46.2%) showed periorbital signs including eyelid dermatitis, periorbital darkening and Dennie-Morgan fold. The mean EASI and SCORAD scores were 11.61±10.18 and 33.69±13.97 respectively. The majority of the patients had mild to moderate AD. The mean cumulative dose of oral prednisolone was 161.07±316.72mg/ year. Thirty-nine (48.8%) patients had ocular manifestations and out of which, 15 (18.75%) had allergic conjunctivitis, seven (8.75%) had cataract, seven (8.75%) had ocular hypertension, two (2.5%) had blepharitis and one (1.25%) had keratoconjunctivitis. Table I shows demographic and clinical characteristics of AD

patients with ocular manifestations. Table II shows the types of ocular manifestations among AD patients.

Among the patients with ocular manifestations, 27 (69.2%) patients regularly applied topical corticosteroids on the face including the periorbital region. The use of systemic corticosteroids was seen in 19 (42.2%) patients. There was no significant correlation between presence of ocular manifestations and the use of topical corticosteroids (p=0.32) on the face as well as systemic corticosteroids use (p=0.19). The severity of AD, facial dermatitis and presence of periorbital signs did not affect the prevalence of ocular involvement. Table 3 shows the association between ocular manifestations and steroid use, disease severity and disease duration.

In our study, out of the seven patients with cataract, six (85.7%) had moderate to severe AD, five (71.4%) had history of topical application of class VI corticosteroids on the face or periorbital region; however, five of them also had history of systemic steroid usage with a mean cumulative prednisolone dose of 350-4135mg per year. A longer atopic dermatitis disease duration was significantly associated with ocular manifestations (p=0.002) and the development of steroid-related ocular complications (p=0.03). Table IV shows the association between steroid-related ocular complications and disease duration.

DISCUSSION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with various ocular manifestations. Patients with AD are at risk of developing ocular comorbidities, which includes allergic conjunctivitis, blepharitis, keratoconjunctivitis, keratoconus, glaucoma, cataract and retinal detachment.[2] These ocular diseases may be asymptomatic and therefore not identified during a routine dermatology review. The high prevalence of ocular manifestations among our AD patients were in line with the findings from previous studies.[8-10] It is important to be aware of these as some of these sight-threatening ocular comorbidities can progress to irreversible visual impairment if left untreated.

We found no association between the presence of ocular manifestations and the severity of dermatitis or presence of periorbital signs. Our findings concurred with the findings from previous studies among children with AD.[8,9] On the contrary, a registry based study found adult patients with AD were significantly at risk of developing conjunctivitis, keratitis and keratoconus and the risk was AD severity dependant; however no relationship was found between AD and glaucoma.[11] Factors possibly contributing to the development of ocular manifestations in adult patients with AD are longer disease duration of AD, habitual rubbing of the eyelids and side effects of topical and systemic therapy.

Blepharitis, or inflammation of the eyelid margin is characterized by pruritus and irritation of the eyelids, dry eyes, burning sensation and photophobia.[12] It is estimated to affect >6% of AD patients compared to the general population which is less than 1%.[2] The pathophysiology of blepharitis is multifactorial, including immune-mediated damage, abnormal lid-margin secretions, bacterial colonisation of the eyelids and Meibomian gland dysfunction.[13] The eyelid tissues in blepharitis showed increased levels of Th2 cytokines such as IL-4, IL-5 and IL-13. Patients with chronic blepharitis often exhibit corneal complications and additional ocular pathologies resulting from prolonged allergic inflammation.14 Patients with AD were more likely to develop blepharitis with an odd ratios of 10.99 compared to the general population.[2] A previous study reported 16 out of 18 patients with eyelid involvement had blepharitis.[8] Another cross sectional study on patients with AD found 41.1% had blepharitis and the affected patients had higher mean periocular skin symptoms score (erythema, infiltration and lichenification).[15] The low prevalence of blepharitis in our cohort might be due to the low prevalence of eyelid dermatitis among our patients.

Allergic conjunctivitis is a non-infectious inflammation of the conjunctiva often caused by an immediate type 1 hypersensitivity reaction to airborne allergens. The estimated prevalence based on previous studies ranged from 15% to 40%.[16] In our study, the prevalence of allergic conjunctivitis was 18.75%. The symptoms of allergic conjunctivitis include hyperaemia of the eye, ocular pruritus, burning discomfort, continuous watery or serous discharge, photophobia and blurring of vision.[17] The risk of conjunctivitis is significantly higher among patients with AD compared to those without AD, especially allergic conjunctivitis, with an eight-fold higher risk.[18] AD and conjunctivitis share the common pathogenesis as the impairment of physical barrier function is present in both disorders. The dysfunctional ocular surface epithelium serves as an entry portal for both pathogens and environmental allergens to enter the eye.[19] Therefore, AD patients are more susceptible to develop allergic conjunctivitis due to ocular barrier dysfunction. Dry eye syndrome has been suggested to be associated with allergic conjunctivitis caused by tear film instability, Meibomian gland dysfunction and excessive evaporation from ocular surface.[20] A study done by Dogru et al., showed the presence of tear film instability was higher in allergic conjunctivitis. The conjunctival squamous metaplasia and loss of goblet cells may lead to reduced conjunctival mucin production which eventually results in tear film instability. The frequent use of antihistamine in patients with AD may be one of the contributing factors for tear film abnormalities due to the anticholinergic properties of antihistamine.[21]

Keratoconjunctivitis is a chronic form of allergic conjunctivitis with the involvement of cornea which is characterised by the presence of cobblestone papillae at the tarsus.[22] Atopic keratoconjunctivitis is characterized by the presence of bilateral eyelid dermatitis which affects patients with AD at any point during their disease, regardless of cutaneous disease severity. The prevalence of keratoconjunctivitis is 1.25% in our study but it is substantially higher in the United States.[23] The difference in prevalence could be due to climate, socioeconomic status and genetic diversity. In addition, patients with keratoconjunctivitis were more likely to have higher periocular skin symptoms score and the habit of slapping around the eyes.[15] Superficial corneal involvement due to

inflamed tarsal conjunctiva and irregular lid margins may progress to frank erosion and ulceration. Persistent inflammation causes corneal scarring and neovascularization which may eventually lead to irreversible vision loss.[24]

We found a statistically significant correlation between prolonged AD disease duration and steroid-related ocular complications. The estimated prevalence of cataract in adults with AD varies between 8% and 11.59%, which is similar with our study.[20,25] The incidence of cataract caused by oral steroid use increases with higher dosage and prolonged duration of treatment, usually at least 1 year or dosage equivalent to oral prednisolone 10mg per day.[26] The association between peri-ocular usage of topical steroid usage and cataract needs further study. Association between application of class III topical steroid and posterior subcapsular cataract has been reported.[27,28] On the other hand, a retrospective study found prolonged use of moderate to potent topical corticosteroid for an average of 6 months a year for almost 5 years was associated with cataract; however those patients with steroid-related cataract had also received oral steroid.[25] The pathogenesis of cataracts in AD is multifactorial, including repetitive trauma secondary to eye rubbing, long-term steroid therapy and oxidative stress. The increased serum lipid peroxide together with decreased superoxide dismutase activity led to high level of free radicals which contribute to the formation of cataracts.[5,19] The cataracts in patients with AD are usually bilateral with anterior or posterior subcapsular opacities. Anterior subcapsular cataract (ASC) is more specific to AD, but steroid-induced posterior subcapsular cataract (PSC) appears to be more frequently described in AD patients.[29] In our study, ASCs and PSCs were seen in three patients and four patients respectively.

Steroid-induced ocular hypertension was first reported in 1950 as intraocular pressure (IOP) was found to be elevated after chronic administration of systemic steroids.[30] Persistent IOP elevation of significant level without treatment may progress to glaucomatous optic neuropathy which is called steroid-induced glaucoma.[31] Aggarwal et al reported a series of patients who developed marked elevations in IOP following topical facial application of steroids.[32] In our study, four out of seven (57.1%) patients with ocular hypertension had history of topical application of low to medium-potency corticosteroids on periorbital region and systemic steroid usage with mean prednisolone dose of range from 50 to 1850mg per year. The elevation of IOP usually develops within the first few weeks of corticosteroids administration. It has been reported that raised IOP secondary to chronic administration of steroids may not return to normal despite discontinuation and refractory to medical therapy.[32] A new clinical entity, atopic glaucoma, has been proposed by Takakuwa et al., in 2015. The diagnostic criteria include the presence of severe atopic dermatitis with face involvement, cup-disc ratio >0.7 and/ or notching, visual field loss, IOP >21mmHg and no association between IOP and glucocorticoid use.[33] Patients with raised IOP are often asymptomatic until advanced stages.[34] Therefore, periodic glaucoma screening would be ideal for patients at risk and those with prolonged history of topical and systemic steroid use. All the six patients in our study were asymptomatic and they were given regular follow-up.

None of the patients had keratoconus or retinal detachment in our study. Keratoconus is a non-inflammatory ocular disease characterized by progressive thinning and cone-shaped bulging of the cornea. Patients often experience reduced visual acuity, irregular astigmatism and light sensitivity due to changes in corneal topography.[3] Rahi et al., reported that a definite history of atopy in 35% of keratoconus compared with 12% in the control group.[35] The most significant factor that causes keratoconus is habitual eye rubbing due to itch of atopy.[36] Retinal detachment is one of the serious ocular complications of AD affecting visual prognosis. It often affects the younger population at a frequency of 8%.[37] Most of the patients with retinal detachment were reported to have facial involvement, especially periorbital regions. The possible theories of pathogenesis of retinal detachment in AD include retinal oedema, retinal breaks secondary to diseased vitreous or retinal vascular changes, and self-inflicted ocular contusion by vigorous rubbing or tapping.[38]

We incidentally found 6 cases of epiblepharon which is not known to be associated with AD. Epiblepharon is a congenital eyelid condition in which a redundant horizontal skin fold results in misdirected lashes towards the cornea. It often involves bilateral lower eyelids and frequently seen in East Asian children with the mean age of 9 years. The majority of the children had no or mild symptoms and are outgrown with the growth of the eyelids and facial bones. However, it is usually associated with potential complications of conjunctival irritation and keratopathy when symptomatic.[39]

Routine ophthalmological evaluation is not a part of the management of patients with AD. Early recognition of these ocular manifestations facilitates appropriate treatment which will prevent potential vision loss. Increased awareness among patients and identification of risk factors such as habitual eye rubbing, and prolonged corticosteroids use can decrease the development of steroid-related ocular complications We recommend incorporating periodic ophthalmological assessment into the management of AD patients with prolonged disease duration regardless of the severity of AD.

This study was limited by its cross-sectional design. A prospective study involving eye assessment upon diagnosis and changes over time with the AD disease progression would provide more valuable information. The sample size was small because the data collection was severely affected due to the constraints during the coronavirus pandemic. There was a lack of information on the lifetime topical and systemic corticosteroids use as the amount of over-the-counter topical corticosteroids and the total dose of systemic corticosteroids given by the referring general practitioners were not available.

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CONFLICT OF INTEREST

There is no conflict of interest.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia.

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