SJIF IMPACT FACTOR: 5.79 CRDEEP Journals
International Journal of Life Sciences Reda et. al., Vol. 5. No. 4 ISSN: 2277-193x
International Journal of Life Sciences. Vol. 5 No. 4. 2016. Pp. 228-233

Full Length Research Paper

Allergens and Allergic Eye Manifestations Associated with Other Chronic Severe Atopic Disorders

[1,3,4]Ahmed M. Reda; [1]Reham Fawzy El Shinawy and [1,2,3]Enas Attia

[1]*Faculty of Medicine, Ain Shams University, Cairo, Egypt.*
[2]*Dar Al-Shifa Poly Clinic, Muscat, Oman.*
[3]*Queen Medical, Villaggio, Doha, Qatar.*
[4]*Dar El-Oyoun Eye Laser Center, Muscat, Oman.*

Article history
Received: 24-12-2016
Revised: 26-12-2016
Accepted: 29-12-2016

Corresponding Author:
Ahmed M. Reda
Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Abstract:
Atopy is the hereditary predisposition to allergy. Eye complications in atopy can be a source of substantial morbidity .To assess allergic eye manifestations in patients with other chronic severe atopy and to determine whether IgE-mediated sensitization could be a predisposing factor. Ninety consecutive patients with chronic severe atopy as assessed by Nottingham Eczema Severity Score (NESS), ARS (allergic rhinitis score) and/or ACT (asthma control test), were included. The enzyme-linked immunosorbent assay (ELISA) technique was used for total and specific serum IgE assays in 30 and 45 patients of them consequently. Sixty-two females (68.89%) versus 28 males (31.11%) were included, with no specific racial susceptibility (p=0.129). In 67 patients (74.44%), more than one allergic condition coexisted (atopic march), with asthma was the most common (30 patients), followed by allergic rhinitis (AR) and food allergy (each in 17 patients). In 49 patients (54.44%), eye symptoms were reported. On examination, all patients had ocular signs, with 22 (24.44%) patients showed blepharitis, 27 patients (30.0%) showed blepharo-conjunctivitis-dry eye, while 41 (45.56%) patients showed asymptomatic benign papillofollicular conjunctivitis. One patient (1.1%) had keratoconus. Allergic Skin and Eye manifestations were highly statistically significantly related to each other (p<0.001). There was no statistically significant relation between either of allergic skin or eye manifestations and the presence of family history of atopy, high total serum IgE, or specific serum IgE-aeroallergen panel (p<0.05). However, there was statistically significant relation between skin allergic manifestations and specific serum IgE-Food panel (p=0.012). This study demonstrates the potentially significant ocular involvement in chronic severe atopic patients, particularly those with skin allergic manifestations. It also highlights food allergy in a considerable ratio of severe atopic dermatitis (AD) patients. It, thus, identifies scope to enhance current international clinical guidelines for management of atopy, through the inclusion of ocular and food allergy screening, for possible co-morbidities.

Key Words: *Aeroallergen, Allergen, Atopy, Eye, Food Allergy, IgE*

Introduction

Atopy is the hereditary predisposition to allergy. Atopic diseases, including atopic dermatitis (AD), allergic rhinitis (AR) and asthma are increasing; affecting about 20% of the population worldwide[1]. AD is a chronic pruritic eczematous skin disease, while AR is chronic inflammation of nasal passage after exposure to allergen(s), and asthma is a life-long chronic inflammatory disorder of airways, strongly predisposed by atopy, and associated with variable structural changes[2]. Eye complications in atopy can be a source of substantial morbidity. Generally, patients report photophobia and pruritus, infraorbital darkening, eyelid dermatitis, and blepharitis. Atopic keratoconjunctivitis occurs in one quarter of patients, often presenting with bilateral itchy, watery eyes and copious mucoid discharge[3]. The aim of this study is to assess eye affection in patients with other severe atopic diseases and to determine whether total serum IgE and/or IgE-mediated sensitization to food and inhalant allergens could be a predisposing factor.

Patients and Methods

Multicentric study including ninety consecutive patients with chronic severe atopy attending in the period from (March 2014) to (March 2015), were included in the study and institutes ethical committees approved the project and informed consent was taken from

the patients or their guardians. A short study questionnaire was used to collect demographic and clinical data from subjects, and clinical notes, including symptoms, disease duration, personal or family history of other atopic diseases, treatment history in the form of topical steroids, antihistamines, emollients, etc.

AD was diagnosed according to UK working party diagnostic criteria[4]. All patients must have an itchy skin condition in the last 12 months and have three or more of the following criteria. Criteria include history of involvement of skin creases such as antecubital, popliteal, dorsal ankles or neck, personal history of asthma or hay fever (or history in 1st degree relative), history of generally dry skin during last year, visible flexural dermatitis, and onset under age of 2 years. Severity of AD was determined by Nottingham Eczema Severity Score: NESS[5]. The body surface is divided into 45 different areas by a system of tick boxes. Each box on the surface area diagram is ticked, if more than 2 cm² (The size of a 10 pence coin) was involved in any given area. The number of involved areas is then calculated as a sum of the total of involved sites for assessment of extent of the disease. For assessment of disease intensity, parents or patients are asked to report average weekly sleep loss due to itching or scratching over the last 12 months. The response is then graded from 1 to 5, with higher scores representing a greater intensity of symptoms producing sleep loss. For assessment of clinical course, parents or patients are asked to comment on how long skin condition had been present during the previous 12 months. The response is graded from 1 to 5, with higher scores reflecting longer disease duration. A final score is achieved by adding each of the three modified parameters of intensity, clinical course and examined extent of disease score, to produce a possible range of scores from 3 to 15, with higher scores indicating more severe disease. Only patients with a total score 12-15 (severe AD) were included.
Severity of AR was evaluated with the total and component Allergic Rhinitis Score (ARS)[6]. Severe persistent AR sufferers are those patients whose symptoms are inadequately controlled despite adequate treatment. Evaluated manifestations included nasal symptoms, ear symptoms and sleep disturbance.

Severity of asthma was evaluated with the Asthma Control Test (ACT)[7]. Severe asthma is asthma requiring treatment with high dose inhaled corticosteroids and a second controller and/or systemic corticosteroids, or which remains "uncontrolled" despite this therapy. Diagnosis at presentation was made according to the following findings: Respiratory rate ≥25/min, Heart rate ≥110/min, and Inability to complete sentences in one breath. Patients not fulfilling any of the previous severity diagnostic criteria or who were under any kind of systemic treatment, likely to influence the study results, were excluded.

Recorded eye symptoms included itching, soreness, redness, swelling, and watery eyes. All the patients had complete ophthalmological examination including the lid, conjunctiva, and cornea. In addition, any evidence of cataract formation and retinal disorders was recorded through dilated fundus examination with indirect ophthalmoscopy. The enzyme-linked immunosorbent assay (ELISA) technique was used for total and specific serum IgE assays: Three milliliters of whole blood were withdrawn from 42 patients for assessment. Sera were separated out after blood coagulation for 30 minutes with centrifugation for 10 minutes. Sera were then stored in Eppendorf tubes at -20ºC until assay was done. Total serum IgE was evaluated in 30 patients with the use of Uni-CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Total serum IgE level greater than 100 kilo unit/Liter (kU/L) was regarded as elevated. EUROLINE Specific IgE Gulf Allergy test kit (EUROIMMUN, Medizinische Labordiagnostika, AG, Germany), was used to determine certain food and/or aeroallergens in 45 patients. The positive rates were analyzed using the cut off levels of class2 (0.7kU/L-3.5kU/L; low antibody titer with existing sensitization).

Statistical analysis was done using SPSS version 15. The relationship between the ocular findings and the clinical severity of atopy was determined. Chi Square test was used for the statistical analysis of the various parameters, A *P*-value of ≤ 0.05was considered statistically significant.

Results

The study included 90 consecutive patients; 62 females (68.89%) and 28 males (31.11%), with age range between 2 to 61 years, including 40 children (44.44%) (Age less than 18years) and 50 adults (55.56%). Fifty-three patients (58.89%) were Arabs, 17 patients (17.78%) were Caucasians, 16 (18.89%) were Asians, and 4 (4.44%) were Hispanics. Among the patients 67 (74.44%) reported family history of atopy. In 41 patients (45.65%), the severest condition and hence diagnosis was essentially AD, in 30 (33.33%) diagnosis was AR, and in 19 (21.11%), diagnosis was asthma. However, in 67 patients (74.44%), more than one allergic condition coexisted, with asthma is the most common (in 30 patients), followed by AR and food allergy (each was reported in 17 patients). In 49 patients (54.44%), eye symptoms were reported. However, on examination, all patients had ocular signs in form of either lid or conjunctival manifestations or both. Of those,22(24.44%) patients showed only lid manifestation in form of blepharitis, 27 patients (30.0%) showed both lid and conjunctival involvement in form of atopic conjunctivitis-dry eye, while 41(45.56%) patients showed conjunctival involvement in form of asymptomatic benign papillofollicular conjunctivitis. One patient (1.1%) reported keratoconus with previous surgery.

As regard the racial susceptibility for either skin or eye allergic manifestations, there was no statistically significant relation between the ethnicity and either of them (*p*-values: 0.082 and 0.275 respectively). In addition, there was no statistically significant relation between either of skin or eye manifestations and the presence of family history of atopy (*p*-values: 0.129 and 0.221 respectively).

Regarding the relation between the allergic skin and eye manifestations, there was a statistically highly significant relation between both of them (p-value :< 0.001) (Table 1).

Table 1: Relation between the skin manifestations and eye manifestations.

Skin Manifestations	Eye Manifestations								Chi-Square	
	Blepharitis		Asymptomatic papillofollicular conjunctivitis		Atopic conjunctivitis-dry eye		Total			
	N	%	N	%	N	%	N	%	X^2	P-value
No	0	0.00	15	36.59	8	29.63	23	25.56	39.450	<0.001*
AD	22	100.00	19	46.34	6	22.22	47	52.22		
Dry skin	0	0.00	3	7.32	8	29.63	11	12.22		
Urticaria	0	0.00	4	9.76	3	11.11	7	7.78		
Angioedema	0	0.00	0	0.00	2	7.41	2	2.22		
Total	22	100.00	41	100.00	27	100.00	90	100.00		

There was no statistically significant relation between either of skin or eye allergic manifestations and total serum IgE or specific serum IgE-aeroallergen panel (p<0.05). It is worth mentioning, however, that 22/44 assayed patients (50%) showed positive aeroallergens, with animal dander is the most frequently detected (13 patients), followed by house dust mites (12 patients), and pollens (11 patients). Nevertheless, there was statistically significant relation between skin allergic manifestations-but not eye manifestations- and specific serum IgE-Food panel (p=0.012) (Table 2).Among 41 patients, positive specific IgE-Food panel was reported in 20 (48.78%) with egg white and peanut as the most common (each in 8 patients), followed by nut mix and chocolate (each in 6 patients), then cow milk and soy (each in 4 patients).

Table 2: Relation between allergic skin and eye manifestations and specific serum IgE-Food panel

		Specific IgE-Food Panel						Chi-Square	
		Negative		Positive		Total			
		N	%	N	%	N	%	X^2	P-value
Skin Manifestations	No	7	33.33	0	0.00	7	17.07	10.997	0.012*
	AD	10	47.62	17	85.00	27	65.85		
	Dry skin	2	9.52	3	15.00	5	12.20		
	Urticaria	2	9.52	0	0.00	2	4.88		
Eye Manifestations	Blepharitis	5	23.81	9	45.00	14	34.15	5.608	0.061
	Asymptomatic papillofollicular conjunctivitis	14	66.67	6	30.00	20	48.78		
	Atopic conjunctivitis-dry eye	2	9.52	5	25.00	7	17.07		

Discussion

Atopic diseases are common and distressing disorders associated with chronicity and impaired quality of life. World Allergy Organization(WAO) (2013) estimated allergy prevalence of whole population by country ranges between 10 - 40%.AR affects between 10% and 30% of adults and as many as 40% of children (About 400 million people in the world).About 300 million people in the world suffers from asthma, with severe asthma constitutes ≈5-8% of total asthmatic population. Patients with AR frequently have symptoms of other allergic diseases, mainly AD, conjunctivitis and asthma. More than 40% of patients with AR have asthma, and more than 80% of asthmatic patients suffer concomitant AR[1].According to the theory of "Atopic March", young children with AD may develop airway allergy such as asthma or AR later in life[8]. Based on several longitudinal studies, approximately half of AD patients will develop asthma, particularly with severe AD, and two thirds will develop allergic rhinitis[8]. Epicutaneous sensitization has been thought to be responsible, with subsequent migration of sensitized T cells into the nose and airways, causing upper and lower airway disease. In this study, 74% of patients had more than one allergic condition coexisted, with asthma was the most common followed by AR and food allergy. In Hon et al. study, AR was present in nearly half of the AD patients and asthma reported in one-

fourth[9]. Early intervention is possible only when a physician caring for a child with AD maintains a heightened awareness for recognition and diagnosis of associated atopic diseases, given that the symptoms of other atopies are often confused with common viral illnesses.

In our study, about 74% of patients reported positive family history of atopy.Sattar et al. reported that 44% of asthmatic patients from Gulf region had a positive family history of asthma[10].Gelardi et al. showed that there was a high "global" familial incidence of allergy, asthma and nasal polyposis, not only between first and second degree relatives (44.9 and 31.9%), but also in third and fourth degree ones (23%) [11]. Our higher association with familial atopy could be attributed to the selection of patients with chronic severe atopic diseases. Thus, genetic background plays a crucial role in atopy, and should be taken into consideration, particularly in severe disease. Arab patients constituted the majority of our study population, followed by Caucasians and Asians, consistent with and proportionate to the population-estimated counts in the region. There is highest incidence of atopy in urban areas and in cooler temperature zones, although no clear racial predisposition appears to exist[12]. However, migration studies provide information on role of environmental factors on development of atopy. Migrants, especially from developing to more developed countries, are at increased risk to acquire atopy, particularly with early age and longer time[1].

About 69% of our study populations were females, similar to previous studies that showed female predominence[13, 14]. Eye complications in atopic dermatitis can be a source of substantial morbidity; however, allergic keratoconjunctivitis typically affects young individuals with male preponderance[15-17]. Leonardi and co-workers in two separate observation including a multicentric study from Italy found male to female ratio between 3.3 and 3.5[18, 19]**.** All other series have reported male to female ratio between 4:1 and 2:1[20, 21]**.** Ukponmwan reported a female preponderance from Nigeria[22]; however, another report from that region suggested male predominance[21]. It seems that before puberty more boys than girls are affected but beyond puberty there is no gender bias[23]. Greater prevalence is seen in the regions with hot, humid climate, and higher load of airborne allergens. Thus, it is more among Afro-Caribbean, Arabs and Asians and less among the white population. It is a common ocular surface disorder in the Mediterranean region, central Africa, India, and South America[15-21]. To our knowledge, this is the first report from subtropical Middle East regions. Further larger studies are warranted to find out real gender and racial distribution of different atopic disorders. Ocular complications in atopic patients have been known for several years. These complications include blepharitis, keratoconjunctivitis, keratoconus, uveitis, subcapsular cataract and retinal detachment[21]. The frequency of these complications varies between 25% and 50%[23, 24]. In the current study, about 54% of patients had symptomatic eye problems, while all patients had ocular signs in form of either lid or conjunctival manifestations or both. Our higher figures could be related to the selection of patients with chronic severe atopic disorders. In earlier studies, eyelid changes have been reported to occur in 16-62.2% of the AD patients[14]. In addition, Carmi et al. reported external ocular signs in 15 (25.4%) studied children, benign papillofollicular conjunctivitis in 11, and chronic atopic blepharitis in one patient[25]. Moreover, Kaujalgi et al. reported that 43% AD patients showed ocular abnormalities in the form of lid and conjunctival changes. Of these, 18 (41.9%) patients showed only lid involvement, 16 (37.2%) only conjunctival involvement and both conjunctival and lid changes were seen in nine (20.9%) patients[26]. Similar to our study, their eye findings were limited to only the lid and conjunctiva and no other structure of the eye was affected in any of the patients. However, one of our patients (1.1%) reported keratoconus. Keratoconus is bilateral non-inflammatory ectasia of the cornea, mostly occurs at puberty, impairing the vision. It is regarded as a complication of long standing atopic disorders affecting the eye[14]. Keratoconus in AD patients has been observed in 0.5-39.0%[27, 28]. Other series have reported a very low incidence of this complication from 0.5 to 2.1%[17]. Physicians, patients and their families should appreciate the significance of eye co-morbidities of atopy, particularly in severe atopic diseases.

Allergic conjunctivitis (AC) is a complex disease occurs in association with a history of other allergies, with its characteristic symptoms of itching, redness, pains, watery/mucoid discharge, puffy eyes and photophobia, which interfere with the normal individual activities [23].

In the current study, there was a statistically highly significant relation between the presence of skin and eye allergic manifestations. Long-standing, severe AD with repeated scratching and rubbing of the face predisposes the patient to various ocular complications, including dermatitis of the eyelids, blepharitis, keratoconjunctivitis and keratoconus[26]. Tuft et al., noted differences between the clinical features of allergic keratoconjunctivitis in tropical and temperate countries and showed that tropical countries exhibit lesser association with atopy[29]. Higher association with atopy, particularly AD, seems to characterize allergic eye manifestations in the subtropical Middle East regions, for further larger studies.

Atopy is primarily caused by cellular immune deficiency and elevated IgE. The pathogenesis can be traced to a genetically inherited, bone marrow–derived cell associated with chromosome 11q. Abnormal reactivity also plays a major role in the development of the disease. Irritants are believed to predispose an individual to develop the disease more often than simply exposure to an allergenic trigger. Nonetheless, patients frequently have a history of food or inhalant allergies or eventually develop them[30]. In the current study, there was no statistically significant relation between either of skin or eye allergic manifestations and total serum IgE. **Bonini et al**. reported that serum IgE may be raised or normal and radio-allegro-sorbent test (RAST) skin prick testing may be negative or nonspecific[31].About 50% of our assayed patients showed positive specific IgE test for aeroallergens, with animal dander was the most frequently detected, followed by house dust mites (HDMs), and pollens. Pollens were reported to be responsible for seasonal

conjunctivitis associated with hay fever and tend to recur at the same time each year in those with atopy, while perennial conjunctivitis occurs as a result of several allergens such as HDMs and animal dander[23, 32].In a previous regional review, a wide range of "global" and "local" aeroallergens (pollens, fungal spores, insect allergens, dander and HDMs) has been observed in the region[33].
We found statistically significant relation between skin allergic manifestations-but not eye manifestations-and specific serum IgE-Food panel. About 49% of assayed patients showed positive specific IgE test for Foods, with egg white and peanut as the most common, followed by nut mix and chocolate, then cow milk and soy. Approximately 40% of infants and young children with moderate to severe AD were reported to have food allergy[34]. However; recent studies have shown that patients with eye involvement may have an increased likelihood of food sensitivity as well[12], for further investigations. Therefore, screening for food allergy is recommended in atopic patients, particularly those with allergic skin manifestations.

Atopy could seriously affect the patient's quality of life especially during the acute episodes. It could lead to children missing school for some days because of acute inflammation with attendant discomfort. The most commonly used treatments include stress control, avoidance of allergens and irritants, and prolonged treatment regimens due to the chronic nature of the disease.
This study demonstrates the potentially significant ocular involvement in chronic severe atopic patients, particularly those with skin allergic manifestations. It also highlights food allergy in a considerable ratio of severe AD patients. It, thus, identifies scope to enhance current international clinical guidelines for management of atopy, through the inclusion of ocular and food allergy screening, for possible co-morbidities. The knowledge of the frequency and significance of these co-morbidities may allow their early diagnosis and treatment.

References

1. Pawankar R, Canonica GW, ST Holgate ST, Lockey RF, Blaiss M. The WAO White Book on Allergy (Update. 2013).
2. Izquierdo-Domínguez A, Valero AL, Mullol J. Comparative analysis of allergic rhinitis in children and adults. Curr Allergy Asthma Rep. 2013 Apr; 13(2):142-51.
3. Casey R, Abelson MB. Atopic keratoconjunctivitis. Int Ophthalmol Clin 1997; 37(2):111-7).
4. Fleming S, Bodner C, Devereux G, Russell G, Campbell D, Godden D, Seaton A. infants Invest Dermatol. 2001 Dec; 117(6):1526-30.
5. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: preliminary refinement of the Rajka and Langeland grading. British J Dermatol 2000; 142(2):288-97.
6. Prenner BM, Chervinsky P, Hampel FC, Howland WC, Lawrence M, Meltzer EO, Munk ZM, Ratner PH, Seltzer JM, Settipane GA, Lorber RR, Harrison JE. Double-strength beclomethasone dipropionate (84 micrograms/spray) aqueous nasal spray in the treatment of seasonal allergic rhinitis. Journal of Allergy Clin Immunol 1996; 98(2):302-8.
7. Liu AH, Gilsenan AW, Stanford RH, Lincourt W, Ziemiecki R, Ortega H. Status of asthma control in pediatric primary care: results from the pediatric Asthma Control Characteristics and Prevalence Survey Study (ACCESS). J Pediatr 2010; 157(2):276-81.
8. Spergel JM. From atopic dermatitis to asthma: the atopic march. Ann Allergy, Asthma, Immunol 2010; 105(2):99-106.
9. Hon KL, Wang SS, Leung TF.airways. Iran J Allergy Asthma Immunol. 2012 Mar; 11(1):73-7.
10. Sattar HA, Mobayed H, al-Mohammed AA, Ibrahim AS, Jufairi AA, Balamurugan P, Mary VP, Bener A.The pattern of indoor and outdoor respiratory allergens in asthmatic adult patients in a humid and desert newly developed country. Eur Ann Allergy Clin Immunol. 2003 Oct; 35(8):300-5.
11. Gelardi M, Iannuzzi L, Tafuri S, Passalacqua G, QuarantaN.Allergic and non-allergic rhinitis: relationship with nasal polyposis, asthma and family history. Acta Otorhinolaryngol Ital. 2014 Feb; 34(1):36-41.
12. Lowery RS. Ophthalmologic Manifestations of Atopic Dermatitishttp://emedicine.medscape.com/article/1197636-overview (Updated: Sep 07, 2016).
13. Sehgal VN, Jain S. Atopic dermatitis: Ocular changes. Int J Dermatol 1994; 33:11-5.
14. Garrity JA, Liesegang TJ. Ocular complications of atopic dermatitis. Can J Ophthalmol 1984; 19: 21–24.
15. Leonardi A, Secchi AG. Vernal keratoconjunctivitis. Int Ophthalmol Clin 2003; 43:41-58.
16. Bonini S, Coassin M, Aronni S, Lambiase A. Vernal keratoconjunctivitis. Eye (Lond) 2004; 18:345-51.
17. Saboo US1, Jain M, Reddy JC, Sangwan VS. Demographic and clinical profile of vernal keratoconjunctivitis at a tertiary eye care center in India. Indian J Ophthalmol. 2013 Sep; 61(9):486-9.
18. Leonardi A, Busca F, Motterle L, Cavarzeran F, Fregona IA, Plebani M, Secchi AG. Case series of 406 vernal keratoconjunctivitis patients: A demographic and epidemiological study. Acta Ophthalmol Scand 2006; 84:406-10.
19. Lambiase A, Minchiotti S, Leonardi A, Secchi AG, Rolando M, Calabria G, Orsoni J, Zola E, Ferreri G, Aragona P, Reibaldi A, Chisari G, Bonini S. Prospective, multicenter demographic and epidemiological study on vernal keratoconjunctivitis: A glimpse of ocular surface in Italian population. Ophthalmic Epidemiol 2009; 16:38-41.
20. Tabarra KF. Ocular complications of vernal keratoconjunctivitis. Can J Ophthalmol 1999; 34:88-92.
21. Akinsola FB, Sonuga AT, Aribaba OT, Onakoya AO, Adefule-Ositelu AO. Vernal keratoconjunctivitis at Guinness Eye Centre, Luth (a five year study). Nig Q J Hosp Med 2008; 18:1-4.
22. Ukponmwan CU. Vernal conjunctivitis in Nigerians: 109 consecutive cases. Trop Doct 2003; 33:242-5.
23. Malu KN. Allergic conjunctivitis in Jos-Nigeria. Niger Med J. 2014 Mar; 55(2):166-70.
24. Rich LF, Hanifin JM. Ocular complications of atopic dermatitis and other eczemas. Int Ophthalmol Clin 1985; 25: 61–76.

25. Foster CS, Calonge M. Atopic keratoconjunctivitis. Ophthalmology 1990; 97:992-1000.
26. Carmi E1, Defossez-Tribout C, Ganry O, Cene S, Tramier B, Milazzo S, Lok C.Ocular complications of atopic dermatitis in children. Acta Derm Venereol. 2006; 86(6):515-7.
27. Kaujalgi R, Handa S, Jain A, Kanwar AJ. Ocular abnormalities in atopic dermatitis in Indian patients. Indian J Dermatol Venereol Leprol. 2009 Mar-Apr; 75(2):148-51.
28. Harrison RJ, Klouda PT, Easty DL, Manku M, Charles J, Stewart CM. Association between keratoconus and atopy. Br J Ophthalmol 1989; 73:816-22.
29. Tuft SJ, Cree IA, Woods M, Yorston D. Limbal vernal keratoconjunctivitis in the tropics. Ophthalmology 1998; 105:1489-93.
30. Jung T, Stingl G. Atopic dermatitis: therapeutic concepts evolving from new pathophysiologic insights. J Allergy Clin Immunol. 2008 Dec. 122(6):1074-81.
31. Bonini S, Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O,Rama P, Magrini L, Juhas T, Bucci MG. Vernal keratoconjunctivitis revisited: A case series of 195 patients with long-term followup. Ophthalmology 2000; 107:1157-63.
32. CampuzanoArgüello M, JuárezEchenique JC, López Pérez G, PenagosPaniagua MJ, OrdazFavila JC. Allergens and risk factors in pediatric patients with allergic seasonal conjunctivitis. Rev Alerg Mex. 2002 Jul-Aug; 49(4):105-11.
33. Goronfolah L. Aeroallergens, atopy and allergic rhinitis in the Middle East. Eur Ann Allergy Clin Immunol. 2016 Jan; 48(1):5-21.
34. Ellman LK, Chatchatee P, Sicherer SH, Sampson HA.Food hypersensitivity in two groups of children and young adults with atopic dermatitis evaluated a decade apart.Pediatr Allergy Immunol. 2002 Aug; 13(4):[29]5-8.