·Clinical Research·

Effects of vernal and allergic conjunctivitis on severity of keratoconus

Abdullah Kursat Cingu, Yasin Cinar, Fatih Mehmet Turkcu, Alparslan Sahin, Seyhmus Ari, Harun Yuksel, Muhammed Sahin, Ihsan Caca

Department of Ophthalmology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey

Correspondence to: Yasin Cinar. Dicle Üniversitesi Tip Fakultesi, Goz Hastaliklari A.D. 21280 Kampus,Diyarbakir, Turkey. dryasincinar@yahoo.com

Received: 2012-06-26 Accepted: 2013-04-20

Abstract

• AIM: To demonstrate the effects of two different types of allergic conjunctivitis on severity of keratoconus (KC).

• METHODS: We retrospectively reviewed the medical records of 171 KC patients referred between June 2010 and June 2011. The KC patients were divided into 3 groups as KC (group A), KC with vernal keratoconjunctivitis (VKC) (group B) and KC with allergic conjunctivitis (AC) (group C). Main outcome measures were demographic and ocular clinical features including age at presentation, gender, spherical equivalent (SE), best spectacle corrected visual acuity (BCVA), mean keratometric measurement (Km), central corneal thickness (CCT), and intraocular pressure (IOP). Groups were compared in term of study variables.

• RESULTS: The median age at presentation was significantly lower in group B (P<0.001). According to the median SE (P=0.003), BCVA(P=0.022), Km(P<0.001), CCT (P=0.015) and Amsler-Krumeich classification (P< 0.001), KC was more severe in group B. There was no significant difference in terms of IOP and corrected IOP among the groups (P=0.44), however there were 4 patients who had increased corrected IOP developed after topical corticosteroid use in group B. The differences among the groups persisted even after controlling for age and gender.

• CONCLUSION: Our findings demonstrated a more severe KC in VKC patients despite their younger age which suggests evaluation of VKC patients as a separate group in keratoconus disease.

• KEYWORDS: keratoconus; vernal keratoconjunctivitis; allergic conjunctivitis; intraocular pressure

DOI:10.3980/j.issn.2222-3959.2013.03.21

Cingu AK, Cinar Y, Turkcu FM, Sahin A, Ari S, Yuksel H, Sahin M, Caca I. Effects of vernal and allergic conjunctivitis on severity of keratoconus. *Int J Ophthalmol* 2013;6(3):370-374

INTRODUCTION

Allergic conjunctivitis (AC) which comprises a heterogeneous group of clinicopathologic conditions with a wide variety of signs and symptoms, ranging from simple intermittent tearing, itching, or hyperemia to severe sight-threatening corneal complications affects approximately 25% of the world population [1-3]. Vernal keratoconjunctivitis (VKC) which is seasonally exacerbated, allergic inflammation of the ocular surface involving tarsal and/or bulbar conjunctiva especially seen in children and young adults living in the regions with hot and dry climate such as Middle East, North Africa and some parts of South America and it is rare in North America and Europe [4].

Keratoconus (KC) is a bilateral, non-inflammatory, progressive condition associated with corneal ectasia, that thinning and protrusion of the cornea causing progressive myopia and irregular astigmatism especially after puberty. Previously its associations with VKC, atopy and eye rubbing were reported [5, 6]. Chronic ocular trauma could be one of the important environmental factors that lead to development of KC in genetically predisposed individuals. In atopic individuals, faster progression of KC, early need for surgery and more often surgical and immunologic complications were previously reported [7]. The tissue damage could be caused by chronic corneal epithelial trauma resulting in prolonged, slow release of small amounts of degradative enzymes called matrix metalloproteinases (MMP) [8-10].

The southeast part of Turkey, with hot-dry climate, poor socioeconomic conditions and widespread marriage between relatives, is different in many ways from developed regions of Turkey. We evaluated keratoconic patients living in southeast part of Turkey with or without ocular allergic disease (AC and VKC), where both the allergic ocular disease and KC were seen frequently, to demonstrate the effects of two different types of allergic conjunctivitis on the severity of KC.

SUBJECTS AND METHODS

Three-hundred-fifteen eyes of 171 consecutive patients with KC were included in this retrospective study. The KC patients were divided into 3 groups; 92 patients only with KC as group A including 166 eyes, 35 patients with KC plus VKC as group B including 68 eyes and 44 patients with KC plus AC as group C including 81 eyes. After history taking,

demographic characteristics of patients were noted, and detailed ophthalmological examination was performed containing best corrected visual acuity on a Snellen scale, slit lamp biomicroscopy, refraction, retinoscopy, intraocular pressure measurement with applanation tonometry, indirect ophthalmoscope, central corneal thickness (CCT) with ultrasonic pachymetry (US-4000, Echostar, Nidek, Japan), and placido disc based videokeratography (Magellan mapper; Nidek technologies, Vigonza, Italy). The patients' refractive errors were recorded and spherical equivalents were calculated. The patients with history of previous ocular surgery, ocular trauma, and recent use of contact lenses were excluded.

All patients were examined by the same two doctors (KC&YC). Diagnosis of AC and VKC were based on history and biomicroscopic signs. AC was diagnosed according to presence of itching at presentation or history of itching especially during spring and summer, and presence of serous conjunctival discharge, conjunctival hyperemia and mild papillae on the upper tarsal conjunctiva in biomicroscopic examination. Diagnosis of VKC was made according to presence of severe and intractable itching, giant papillae on the upper eyelid, Horner-Tranta's dots, ropy discharge and infiltration in the limbus. Presence of punctuate epithelial erosion, shield ulcer and pseudogerontoxon were also noted. According to Cameron classification VKC was typed as limbal, palpebral or mixed [11]. KC diagnosis was made by evaluation of scissor reflex on retinoscopy, central or paracentral steepening on corneal topography, and presence of central or paracenral thinning, protrusion of cornea, Fleischer's ring, Vogt's stria, Descements breaks, apical scars in biomicroscopic examination.

The keratoconus clinical stage was defined using the Amsler-Krumeich classification system [12]. In case of corneal scarring due to corneal hydrops with conic cornea in which corneal topography could not be applied; KC diagnosis was made by clinical examination and these corneas were assumed to have severe KC. When there was difficulty in performing videokeratography to the eyes with corneal scars due to hydrops sequelae central 3mm corneal readings were achieved by use of manual keratograph if possible.

We noted best spectacle corrected visual acuities (BSCVA) of all patients for comparison in the groups. Visual acuities were converted to a logarithm of the minimal angle resolution (logMAR) equivalents for statistical evaluation. Measured intraocular pressures (IOP) adjusted according to the reference CCT of 545μm and calculated with following formula:

Corrected IOP =Measured IOP-(CCT-545)/50×2.5mmHg [13].

Statistical Analysis SPSS statistical software, version 11.5 (SPSS Inc., Chicago, Illinois, USA), was used for the statistical analysis. Kolmogorov-Smirnov test was used to investigate distribution pattern of data. Since the data did not follow Gaussians' distribution the Kruskal-Wallis test was used to test differences in the continuous variables among the groups. Mann-Whitney U test was used to make a pairwise comparison, when a significant difference found among three groups. Categorical data were analyzed with the chi-square or the Fisher exact tests. To test the influence of age and sex on independent variables multivariate analysis of covariance (MANCOVA) was performed. SE, cylindrical value, VA, BCVA, Km, CCT, KC grading according to Amsler-Krumeich classification, IOP, and corrected IOP were used as independent variables and age and sex were selected as covariates in MANCOVA. *P* value less than 0.05 accepted as significant.

RESULTS

Of the 315 affected eyes, 166 were in group A, 68 were in group B, and 81 were in group C. Vernal keratoconjonctivitis patients complained about intractable itching and different degrees of eye rubbing all around the year. However, itching was described to be present especially during the spring and summer by the patients with AC.

Comparisons of the presenting demographic and ophthalmologic features of patients are shown in Tables 1 and 2. While there was no significant difference among the groups in gender and laterality; the median age at presentation was significantly lower in group B compared with other two groups(P<0.001). There was also a significant difference between the group A and C in age (P=0.014) (Table 1).

Although the median spherical equivalent was significantly higher in group B than that of the other two groups(P=0.003, P=0.002), no significant difference was found in cylindrical value among the groups. Median BSCVA value was significantly worse (P=0.013, P=0.013), mean K value was significantly greater (P<0.001, P=0.001), and median CCT reading was significantly thinner (P=0.008, P=0.013) in group B compared with group A and C. There was no significant difference in corrected IOP among the groups (P= 0.44, Table 2) but there were 4 patients (11.4%) having corrected IOP level more than 21mmHg in VKC group.

The percentage of eyes classified as grade 4 KC according to the Amsler-Krumeich classification in group A, B and C was 22%, 58.5%, and 28.4%, respectively (P<0.001) (Table 3). Twenty-one of 35 patients were palpebral type, 4 patients were limbal type, and 10 patients were mixed type in VKC group. All of the VKC and most of the AC patients had the history of topical corticosteroid eye drops use in different types and doses before referral.

The statistical differences observed between groups in terms of SE, cylindrical value, VA, BCVA, mean K value, CCT, IOP, corrected IOP and grade of KC have persisted even after controlling for age and gender by multivariate analysis of the data.

Table 1 Comparison of the presenting demographic features of the patients with KC in group A, B, and C *n* (%)

Features	Group A (*n*=92)	Group B (*n*=35)	Group C (*n*=44)	*P*	
	Mean (SD) Median (SEM) range			Kruskal-Wallis (3 groups)	Mann Whitney U (2 groups)
				Chi-squire	
Gender					
Male	48 (52.2)	19 (54.3)	15 (34.1)	0.10	
Female	44 (47.8)	16 (45.7)	29 (65.9)		
Laterality					
Unilateral	18 (19.6)	2 (5.7)	8 (18.2)	0.15	
Bilateral	74 (80.4)	33 (94.3)	36 (81.8)		
Age at presentation (a)	22.2 (7.6)	13.8 (3.8)	19.0 (5.4)		[1]<0.001
	20 (0.8)	13 (0.6)	18 (0.8)	<0.001	[2]<0.001
	11-56	9-23	8-36		[3]0.014

Group A: Patients with keratoconus, Group B: Patients with keratoconus plus vernal keratoconjunctivitis, Group C: Patients with keratoconus plus allergic conjunctivitis, SD: standard deviation, SEM: standard error of mean. [1]Group A *vs* group B; [2]Group B and group C; [3]Group A *vs* group C. Mann-Whitney U test.

Table 2 Comparison of the presenting features of the keratoconic eyes in group A, B, and C

Features	Group A *n*= 166 eyes	Group B *n*= 68 eyes	Group C *n*=81 eyes	*P*	
	Mean (SD) Median (SEM) range			Kruskal-Wallis (3 groups)	Mann Whitney U (2 groups)
Spherical equivalent (D)	-6.62 (4.61)	-10.5 (7.61)	-5.84 (3.95)	0.003	[1]0.003
	-5.62 (0.37)	-9.68 (0.99)	-5.00 (0.47)		[2]0.002
	-25.5/-0.88	-27.0/-0.25	-16.7/-0.38		[3]0.32
Cylindrical value (D)	-4.48 (2.23)	-4.63 (2.43)	-4.91 (2.59)		
	-4.25 (0.18)	-4.62 (0.31)	-5.00 (0.30)	0.34	
	-9.75-0.25	-10.5-0.80	-9.75-0.25		
Visual acuity (logMAR)	0.89 (0.39)	0.96 (0.43)	0.80 (0.45)		[1]0.1
	1.0 (0.03)	1.0 (0.05)	1.0 (0.05)	0.031	[2]0.012
	0-1.9	0-1.9	0-2.0		[3]0.12
Best spectacle corrected visual acuity (logMAR)	0.40 (0.33)	0.58 (0.44)	0.40 (0.41)		[1]0.013
	0.30 (0.02)	0.50 (0.06)	0.30 (0.04)	0.022	[2]0.013
	0-1.9	0-1.6	0-2.0		[3]0.57
Mean keratometry (D)	51.9 (6.57)	57.2 (8.40)	52.9 (7.34)		[1]<0.001
	50.5 (0.51)	57.9 (1.04)	51.1 (0.81)	<0.001	[2]0.001
	42.1-80.7	41.5-75.3	41.2-78.7		[3]0.33
Central corneal thickness (μm)	477.9 (49.4)	454.2 (64.4)	482.9 (60.6)		[1]0.008
	480.0 (3.86)	451.0 (7.93)	486.0 (6.82)	0.015	[2]0.013
	367-592	274-567	365-642		[3]0.56
Corrected IOP (mmHg)	15.1 (2.67)	15.4 (3.10)	14.6 (3.22)		
	14.7 (0.20)	15.3 (0.38)	14.8 (0.36)	0.44	
	9.5-23.3	9.3-24.3	6.15-25.0		

Group A: Eyes with keratoconus, Group B: Eyes with keratoconus plus vernal keratoconjunctivitis, Group C: Eyes with keratoconus plus allergic conjunctivitis, SD: standard deviation, SEM: standard error of mean, IOP: intraocular pressure. [1] Group A versus group B; [2] Group B and group C; [3] Group A versus group C. Mann-Whitney U test.

Table 3 Grading of the keratoconic eyes according to Amsler-Krumeich classification in the group A, B and C *n* (%)

Grading	Group A (*n*=166)	Group B (*n*=68)	Group C (*n*=81)	[1]*P*
Grade 1	46 (27.7)	10 (14.7)	25 (30.9)	0.0001
Grade 2	66 (39.7)	15 (22)	25 (30.9)	
Grade 3	18 (10.8)	4 (5.8)	8 (9.9)	
Grade 4	36 (21.6)	39 (57.3)	23 (28.4)	

Group A: Eyes with keratoconus, Group B: Eyes with keratoconus plus vernal keratoconjunctivitis, Group C: Eyes with keratoconus plus allergic conjunctivitis. [1]*P* value of Fisher exact test between group A, B, and C.

Table 4 Biomicroscopic findings of the keratoconic eyes *n* (%)

Biomicroscopic findings	Group A *n*=166	Group B *n*=68	Group C *n*=81	[1]*P*
Vogt's striae	99 (59.6)	56 (82.4)	49 (62)	0.003
Punctuate epithelial erosion	8 (4.8)	21 (30.9)	12 (14.8)	<0.001
Corneal hydrops/sequela	7 (4.2)	8 (11.8)	4 (4.9)	0.07

Group A: Eyes with keratoconus, Group B: Eyes with keratoconus plus vernal keratoconjunctivitis, Group C: Eyes with keratoconus plus allergic conjunctivitis. [1]*P* value of chi-square test between group A, B, and C.

The important signs noted in slit-lamp biomicroscopy and indirect ophthalmoscopy was shown in Table 4. The rates of Vogt's striae (P=0.003) and punctuate epithelial erosion (P< 0.001) were significantly higher in group B than those of

group A and C. Corneal hydrops or central corneal scarring that indicate hydrops sequela were not different among three groups (P=0.07).

DISCUSSION

Keratoconus is known as noninflammatory, progressive and usually bilateral corneal ectasia with the incidence of approximately 1/2 000 in the general population. Allergic ocular disease and abnormal videokeratographic patterns and KC association with VKC has previously been reported[14-16]. In our study all subjects were KC patients and 35 had accompanying VKC and 44 had accompanying AC. We compared three groups of KC patients with each other to demonstrate whether severity of KC affected by presence of these two different allergic conditions or not.

In the current study there was a slight female predominance (F/M=1.07/1) in the whole cohort in agreement with some previous studies [17,18]. However in VKC patients there was male predominance of KC parallel to the results of some other previous reports [11,14,19]. Totan *et al* [14] reported that the mean age was 15.78 years in VKC subjects with KC. In the present study the median presenting age of KC in our VKC patients was 2 years earlier than that of Totans' group. Furthermore our VKC associated KC patients have 7 years and 5 years younger median presentation ages than that of the patients only with KC and the KC patients with accompanying AC respectively.

Barreto *et al* [20] reported that VKC patients had higher elevation values, thinner corneas, and increased frequency of KC patterns detected by keratometric maps compared to normal subjects. In the present study the patients with VKC had more severe KC than that of the patients in other groups according to their median SE, keratometric values, BCVA and CCT. Grade 4 KC were found to be significantly higher in patients with VKC than that of the other two groups.

Although itching was usually seasonal in AC, it may affect the severity and progression of KC. Hargrave *et al*[7] reported that, patients with atopy showed rapid progression of KC and they need keratoplasty earlier. They also reported that refractive and immunological complications were more frequently seen in KC patients with atopy. Corneal hydrops may be the presenting sign of KC as a very common complication in VKC [21]. Khan *et al* [19] reported 12.5% and Cameron *et al* [11] reported 30% of acute hydrops in VKC patients in their studies. They also reported eye rubbing as a risk factor for the development of acute hydrops. In the present study severe itching and eye rubbing were also common in VKC patients. Additionally patients presented with acute hydrops or central corneal scarring that mimic previous hydrops history were significantly higher in group B patients (11.8%) than that of group A (4.2%) and C patients (4.9%) in our study. Not only itching and eye rubbing, complex interactions between hereditary and environmental factors against the cornea in vulnerable individuals may result in acute hydrops [14]. The environmental factors may be dry, hot and dusty climate. These complex factors may cause rapid progression of KC disease in VKC patients.

MMP-2 and MMP-9 are known as gelatinases and they are normally present in tear fluid [22]. Since they function in normal epithelial turnover in physiologic amounts, overexpression of them results in excessive extracellular matrix degradation and tissue destruction. MMP-2 is mainly originated from activated fibroblasts in the course of wound healing and MMP-9 is expressed mainly by regenerating epithelial cells and recruits inflammatory cells to the wound area[23]. Kumagai *et al* [24] showed active forms of MMP-2 and MMP-9 in tear fluids of nearly all of their patients with VKC but minority of the patients with AC in their study. On the other hand they did not found activated form of these enzymes in the tear fluids of healthy voluntaries. These proteinases may play role in the severity of KC in VKC patients. T cells also express or regulates MMPs[25,26]. In active disease infiltration of T lymphocytes was shown in the conjunctiva of the VKC patients [27]. Besides, the efficacy of topical cyclosporine which is a selective T cell inhibitor, has been shown in VKC [28]. In the current study, percentage of severe KC was very high in group B whereas percentage of moderate KC was higher in group A and group C. Most of the KC patients particularly with VKC have dry eye symptoms, significant punctuate epithelial erosion, as well as chronic eye rubbing which was previously described in pathogenesis of KC [5, 6, 29, 30]. These may cause increase in the rate of epithelial turnover and expression of MMP-9 which may bear a part in the progression of the disease.

In the current study, the median IOP of all groups found to be within normal ranges. However patients without VKC showed greater measured IOP with Goldman applanation tonometry and there were 4 patients (11.4%) having corrected IOP level more than 21mmHg in VKC group. Ultrasonic pachymetry technique is most widely accepted method to measure corneal thickness. Kaya *et al* [31] reported that keratoconic eyes with atopy had lower CCT and steeper cone than that of eyes without atopy. Consistent with their results VKC patients in our study had thinner and steeper corneas. In KC patients increment in IOP and chronic glaucoma were reported[33] and also topical corticosteroid use was previously reported to be associated with glaucoma[33,34]. Totan *et al* [14] suggested that none of their patients presented with increased IOP even all of them received strong steroids for long periods of time. In the present study, measured IOP levels were within normal limits whereas there were some eyes with corrected IOP more than 21mmHg in VKC group. This may be related with use of strong steroids at different times during their disease course before referral. Thus, even incidental measurement of IOP could be normal in patients

with VKC, they should be carefully examined for glaucoma. Scheimpflug imaging system is superior to placido disc based corneal topographic systems to detect the posterior elevation and to determine early KC. Accurate measurement of the thinnest corneal pachymetry is not possible by use of ultrasonic method but ultrasonic pachymetry is gold standard for CCT. In the current study we used ultrasonic pachymetry in the measurement of CCT.

The present study has some limitations. A prospective design would enable us to form a more clear cause and effect relationship between the variables noted in the study. However, by using multivariate statistical tests the impact of confounding factors has been controlled in the present study.

In conclusion, KC patients with accompanying vernal conjunctivitis were younger at age, had more severe KC and higher frequency of increased IOP that suggest evaluation of VKC patients as a separate group in keratoconus disease for a better clinical care.

REFERENCES

1 Tuft SJ, Ramakrishnan M, Seal DV, Kemeny DM, Buckley RJ. Role of Staphylococcus aureus in chronic allergic conjunctivitis. *Ophthalmology* 1992;99(2):180-184

2 Cvenkel B, Globocnik M. Conjunctival scrapings and impression cytology in chronic conjunctivitis.Correlation with microbiology. *Eur J Ophthalmol* 1997;7(1):19-23

3 Abelson MB, George MA, Garofalo C. Differential diagnosis of ocular allergic disorders. *Ann Allergy* 1993;70(2):95-109

4 Colby K, Dohlman C. Vernal keratoconjunctivitis. *Int Ophthalmol Clin* 1996;36(1):15-20

5 Karseras AG, Ruben M. Aetiology of keratoconus. *Br J Ophthalmol* 1976; 60(7):522-525

6 Yeniad B, Alparslan N, Akarcay K. Eye rubbing as an apparent cause of recurrent keratoconus. *Cornea* 2009;28(4):477-479

7 Hargrave S, Chu Y, Mendelblatt D, Mayhew E, Niederkorn J. Preliminary findings in corneal allograft rejection in patients with keratoconus. *Am J Ophthalmol* 2003;135(4):452-460

8 Kim WJ, Rabinowitz YS, Meisler DM, Wilson SE. Keratocyte apoptosis associated with keratoconus. *Exp Eye Res* 1999;69(5):475-481

9 Kao WW, Vergnes JP, Ebert J, Sundar-Raj CV, Brown SI. Increased collagenase and gelatinase activities in keratoconus. *Biochem Biophys Res Commun* 1982;107(3):929-936

10 Sawaguchi S, Yue BY, Sugar J, Gilboy JE. Lysosomal enzyme abnormalities in keratoconus. *Arch Ophthalmol* 1989;107(10):1507-1510

11 Cameron JA, Al-Rajhi AA, Badr IA. Cornealectasia in vernal keratoconjunctivitis. *Ophthalmology* 1989;96(11):1615-1623

12 Krumeich JH, Daniel J, Knulle A. Live-epikeratophakia for keratoconus. *J Cataract Refract Surg* 1998;24(4):456-463

13 Shih CY, Graff Zivin JS, Trokel SL, Tsai JC. Clinical significance of central corneal thickness in the management of glaucoma. *Arch Ophthalmol* 2004;122(9):1270-1275

14 Totan Y, Hepsen IF, Cekic O, Gunduz A, Aydin E. Incidence of keratoconus in subjects with vernal keratoconjunctivitis: a videokeratographic study. *Ophthalmology* 2001;108(4):824-827

15 Jacq PL, Sale Y, Cochener B, Lozach P, Colin J. Keratoconus, changes in corneal topography and allergy. Study of 3 groups of patients. *J Fr Ophtalmol* 1997;20(2):97-102

16 Lapid-Gortzak R, Rosen S, Weitzman S, Lifshitz T. Videokeratography findings in children with vernal keratoconjunctivitis versus those of healthy children. *Ophthalmology* 2002;109(11):2018-2023

17 Sorsby A. ed. Modern Ophthalmology, 2nd ed. London: Butterworths 1972; v.3, chap 1, 244

18 Franschetti A. Keratoconus. In: King JH Jr, McTigue JW, eds. The Cornea World Congress: Papers. Washington: Butterworths 1965:157

19 Khan MD, Kundi N, Saeed N, Gulab A, Nazeer AF. Incidence of keratoconus in spring catarrh. *Br J Ophthalmol* 1988;72(1):41-43

20 Barreto J Jr, Netto MV, Santo RM, Jos é NK, Bechara SJ. Slit-scanning topography in vernal keratoconjunctivitis. *Am J Ophthalmol* 2007;143(2): 250-254

21 Rehany U, Rumelt S. Corneal hydrops associated with vernal conjunctivitis as a presenting sign of keratoconus in children. *Ophthalmology* 1995;102(2):2046-2049

22 de Souza GA, Godoy LM, Mann M. Identification of 491 proteins in the tear fluid proteome reveals a large number of proteases and protease inhibitors. *Genome Biol* 2006;7(8):R72

23 Gabison EE, Mourah S, Steinfels E, Yan L, Hoang-Xuan T, Watsky MA, De Wever B, Calvo F, Mauviel A, Menashi S. Differential expression of extracellular matrix metalloproteinase inducer (CD147) in normal and ulcerated corneas: role in epithelio-stromal interactions and matrix metalloproteinase induction. *Am J Pathol* 2005;166(1):209-219

24 Kumagai N, Yamamoto K, Fukuda K, Nakamura Y, Fujitsu Y, Nuno Y, Nishida T. Active matrix metalloproteinases in the tear fluid of individuals with vernal keratoconjunctivitis. *J Allergy Clin Immunol* 2002;110 (3): 489-491

25 Johnatty RN, Taub DD, Reeder SP, Turcovski-Corrales SM, Cottam DW, Stephenson TJ, Rees RC. Cytokine and chemokine regulation of proMMP-9 and TIMP-1 production by human peripheral blood lymphocytes. *J Immunol* 1997;158(5):2327-2333

26 Weeks BS, Schnaper HW, Handy M, Holloway E, Kleinman HK. Human T lymphocytes synthesize the 92 kDa type IV collagenase (gelatinase B). *J Cell Physiol* 1993;157(3):644-649

27 Abu El-Asrar AM, Struyf S, Al-Mosallam AA, Missotten L, Van Damme J, Geboes K. Expression of chemokine receptors in vernal keratoconjunctivitis. *Br J Ophthalmol* 2001;85(11):1357-1361

28 Akpek EK, Dart JK, Watson S, Christen W, Dursun D, Yoo S, O'Brien TP, Schein OD, Gottsch JD. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004;111(3):476-482

29 Shapiro MB, France TD. The ocular features of Down's syndrome. *Am J Ophthalmol* 1985;99(6):659-663

30 Boger WP, 3rd, Petersen RA, Robb RM. Keratoconus and acute hydrops in mentally retarded patients with congenital rubella syndrome. *Am J Ophthalmol* 1981;91(2):231-233

31 Kaya V, Karakaya M, Utine CA, Albayrak S, Oge OF, Yilmaz OF. Evaluation of the corneal topographic characteristics of keratoconus with orbscan II in patients with and without atopy. *Cornea* 2007;26(8):945-948

32 Duke-Elder S. ed. System of Ophthalmology. London: Kimpton, 1965;8, pt.2,chapt7:964-976

33 Razeghinejad MR, Katz LJ. Steroid-Induced Iatrogenic Glaucoma. *Ophthalmic Res* 2012;47(2):66-80

34 Oner V, Türkcü FM, Tas M, Alakus MF, Iscan Y. Topical loteprednol etabonate 0.5% for treatment of vernal keratoconjunctivitis: efficacy and safety. *Jpn J Ophthalmol* 2012;56(4):312-318