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Abstract: Abstract
Purpose: To evaluate topographic corneal changes in relatives of patients with Keratoconus (KCN)

Methods: As a prospective study 300 eyes of 150 relatives of 45 KCN patients were evaluated. Complete slit lamp examination, refraction, and then Corneal Topography was performed for all the eyes. The topographic indices for diagnosis of Keratoconus were based on Rabinowitz criteria.

Results: The study included 84 (56%) female and 66 (44%) male subjects. Mean age was 32.4±15 years (range: 16-83). KCN was diagnosed in 14% of the subjects and other 7.3% as KCN suspect. The overall prevalence of astigmatism was 58% including 42.1% in the KCN group , 66.7% in the KCN suspect group, and 49.6% in the normal group. Thirty one eyes had high regular astigmatism (>1.5 diopters) including 17

(54.8%) in the KCN, and 14 (45.2%) in the normal groups. Oblique astigmatism was seen in 33 eyes(11%) including 34.2% in the KCN, 47.6% in the KCN suspect, and 4.6% in the normal groups.

Conclusion: Relatives of KCN patients have a high prevalence of undiagnosed KCN. Corneal topography is very important for the diagnosis of KCN and KCN suspects in family members of KCN patients. Therefore, keratorefractive surgery should be considered cautiously in these individuals.

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Topographic Evaluation of Relatives of Keratoconus Patients

Farid Karimian M.D.,Shiela Aramesh M.D. Hossein Mohammad Rabei M.D., Nasrin Rafati M.D.,Mohammad Ali Javadi M.D.,

Keratoconous (KCN) is a noninflammatory, usually progressive disease, characterized by gradual corneal thinning and ectasia. In advanced cases cornea will have a conical shape, and in almost all cases the disease is bilateral[1]. In 1992, in a prospective study Gonzalez reported unilateral KCN in 14.03% of cases, and KCN were more common in women[2]. However, in another study, Krachmer did not find any relation between sex and KCN[3]. Although KCN has a moderate prevalence in general (almost one in 2000)[4,5], its importance is highlighted because most of the keratoconus patients are between 20-40 years of age and in the active periods of their lives. As a result, reduced visual acuity will have a direct impact on decreased activity, disturbance in job selection and social performance. Of course, ocular examinations follow up and optical devices for correction of their visual acuity will be expensive. At the present time, any treatment either surgical or non-surgical is not able to prevent disease progression[1].

Many studies have been performed for determination of familial pattern of disease. KCN has familial prevalence of 6-8%[6,7]. It seems to have an autosomal dominant and/or recessive inheritance pattern. Of course in dominant form, it has a spectrum of manifestations; from mild to irregular astigmatism up to form fruste KCN[8-10]. Higher prevalence of astigmatism and topographic abnormalities may suggest KCN is not only a sporadic disorder[11], but also that familial presentations are more diverse than they have thought to exist.

With more prevalent keratorefractive procedures in recent years and especially their associated complications in KCN cases (even in mild and stable forms), it is very important to diagnose these patients among candidates for these surgeries[11,12]. Neither topography nor Orbscan alone, appear to be reliable devices for screening of these patients. Still in many centers

videokeratography or topography are the main and only device for screening and diagnosis of KCN[13,14].

Due to familial patterns of KCN, positive family history may be a risk factor for those who ask for refractive surgery. The initial presentation and course of KCN is not distinct. There may be no significant topographic or examination sign compatible with KCN before a successful refractive surgery operation, but the patients may develop signs of KCN consequently.[3,15]

In previous studies, still the exact familial patterns of KCN were not determined[r,2,3]. This study has been performed to evaluate the incidence of different topographic patterns in relatives of keratoconus patients.

Method and material:

This prospective study was performed on first, second and third degree relatives of previously proved KCN cases by topography and/or clinical examination who were followed by the authors (F.K, M.A.J). Considering the familial incidence (7%) and error value (4%) for KCN, 150 cases were enrolled in this study. Only up to 10 persons (≥15 year old) from each family were considered for evaluation. The procedure protocol was approved by ethics committee of ophthalmic research center.

Exclusion criteria included: soft contact lens usage in recent one week, or RGP wearing within 4 weeks[16], any history of corneal or intraocular surgery, or those with unreliable corneal topography (e.g. corneal scar, history of previous keratitis or corneal inflammation),or poor cooperation for reliable examination.

After taking history, comprehensive ophthalmic examination was performed for all of them which included: uncorrected (UCVA), refraction, best corrected visual acuity (BCVA), retinoscopy (for evaluation of pupillary red reflex and detection of KCN), slit lamp biomicroscopy, direct ophthalmoscopy, were performed. Videokeratography (CSO topographer, Italy) was performed by one expert technician and at least 3 pictures with absolute scale and 0.25D interval have been taken for each eye and two with more similar patterns were selected for evaluation of each eye[17].

Finally KISA % formula was used for evaluation of KCN suspicious cases[18]:

$$\text{KISA\%}=\frac{K\times(I-S)\times AST\times SRAX}{3}$$ in which

K= central corneal keratometry power in diopter, I-S= Asymmetrical dioptric difference between superior and inferior parts of cornea (3mm apart), AST= difference between steep and flat on SimK meridians SRAX= smallest angle between two steep radius was subtracted from 180°.

For everyone whose K value was less than 42.2 diopters, in calculations K was considered equal to one . If I-S value was a negative number, its absolute value was entered into the formula. KISA percentage value was considered normal less than 60%, suspicious between 60-100%, and KCN over 100%. Definite diagnosis of KCN was based on McDonnell-Rabinowitz[18] criteria which included: central corneal keratometry (KC) over 47.2 diopter, I-S value over 1.4 diopters and SRAX over 21 degrees, difference between central keratometry (dk) of two eyes >1 diopter [19]. The results of examinations and topographic findings have been compared among different groups (Normal, KCN suspect and KCN) by chi-square and T-tests using the SPSS 10 software.

Results:

Between March till December 2006, as a cross-sectional case study 165 individuals of first, second and third degree relatives of KCN patients from 45 families were randomly selected and enrolled in this study. Final evaluation and analysis was done in 150 cases (300 eyes) including 84 women (56%) and 66 men (44%). Mean age was 32.4±15 (range 16-83) year old. One hundred thirteen (75.3%) were first degree, 14 cases (9.3%) second and 23 cases (15.4%) were third degree relatives. Of total 300 eyes, only in 23 eyes (7.7%) clinical KCN was detectable as corneal thinning, Fleischer's ring and Vogt's Striae. Finally KCN was diagnosed in 37 eyes (12.3%) of 21 persons and another 20 eyes (6.7%) were KCN suspect. (Table .1)

Table 1: Comparison of KCN and KCN suspect in different sexes.

Diagnosis	Number of Eyes (Percentage)		Total
	Men	Women	
KCN	16 (12.4)	21(12.3)	37 (12.3)
KCN suspect	6 (4.7)	14 (8.2)	20 (6.7)

From 45 studied families 4 families had 3 KCN cases, 4 families had 2, and 12 families had only one case of KCN or KCN suspect. KCN was unilateral in 13.6% (3 persons) and bilateral in 81.7% of cases (17 persons). KCN suspect was unilateral in 36.4% (4 persons) and bilateral in 63.6% (7 cases). Refractive errors of study cases were: myopia 90 eyes (30%), hyperopia 114 eyes (38%), and 96 eyes (32%) were within ±0.5D of emmetropia. Astigmatic refractive error was present in 174 eyes (58%). 143 eyes (47.7%) had low regular astigmatism (under 1.5 diopters) and 31 eyes (10.3%) had high regular astigmatism (equal or more than 1.5 diopters). The incidence of high astigmatism (≥1.5 diopters) was 44.7% in KCN patients, but in non-KCN cases it was only 7.1% (P<0.0001). In KCN suspect group, no one had high astigmatism. (Table 2)

Considering the results of videokeratography 42.1% of KCN group, 66.7% of KCN suspect and 46.9% of non KCN group had low corneal astigmatism. In 89 eyes (29.7%), with-the-rule astigmatism was observed: 18.4% in KCN, %38.1 in KCN suspect and 30.7% in non-KCN group. This difference among three groups was not statistically significant (P=0.2). (Table -2)

Against-the rule astigmatism was seen in 39.5% of KCN and 18.7% of non KCN group. No one in KCN suspect group had against- the- rule astigmatism. This difference among groups was not statistically significant (P=0.001) (table 2). Oblique astigmatism was seen in 34 eyes (11.3%) and in three groups as follows: in KCN group 34.2%, KCN suspect group 47.6% and non KCN group 4.6%, the difference among three groups was statistically significant (P=0.0001). Irregular astigmatism was detected only in the KCN group.

Table 2: Distribution of refractive errors in 300 studied eyes with respect to different groups.

Refractive error	(Percentage) number				P1-value	P2-vlaue
	KCN	KCN suspect	Normal	Total		
Myopia	8(50)	16(59.3)	66(41)	90(30)	0.41	0.25
Hyperopia	8(50)	11(59.3)	95(59)	114(38)	0.54	0.48
Low regular astigmatism	17(5.9)	13(65)	114(47.3)	144(48)	0.912	0.12
High regular astigmatism	15(40.5	**0**	17(7)	32(10.7)	<0.0001	0.22
With the rule astigmatism	5(13.5)	8(40)	75(30.9)	88(28.3)	0.03	0.39
Against the rule Astigmatism	15(40.5	0	45(18.5)	60(20)	0.002	0.03
Oblique astigmatism	13(35.1)	9(45)	11(4.5)	33(11)	<0.0001	<0.0001
Irregular astigmatism	**2** (5.4)	0	0	2(0.7)	<0.000 **1**	-

P1: comparison between KCN and normal group.
P2: comparison between KCN suspect and normal group

Different parameters of refractive errors have been shown in table 3. Mean myopia in KCN patients was more than KCN suspect and also in these 2 groups' more than normal cases. General topographic patterns of cases were geographic in 26 eyes (8.6%), oval in 58 eyes (19.3%) and round in 106 eyes (35.4%). In 69 eyes (71.9%) astigmatic pattern was symmetrical bow-tie and in the other 27 eyes (28.1%) it was asymmetrical pattern. Other topographic findings in 3 groups have been shown in table 4.

Table 3: General parameters and distribution of spherical refraction (diopter) in different groups.

Groups / Parameters	KCN	KCN suspect	Normal	P1-value	P2-vlaue
M± SD	-1.25±2.83	-0.39±0.96	-0.1±1	0.001	0.23
Range	+1.75 to -8.5	+0.5 to -2.75	+3.5 to -8.5	-	-

M: Mean spherical refraction
SD: Standard Deviation
P_1: comparison between KCN and normal group
P_2: comparison between KCN suspect and normal group

Table 4: Corneal topographic parameters in normal eyes, KCN suspect and KCN patient groups.

Parameters \ Groups		Normal	KCN suspect	KCN
KC	M±SD	44.28±1.46	45.55±1.96	46.98±3.63
	Range	40.75-47.53	41.29-48.68	41.67-54.70
I-S	M±SD	-0.13±0.54	1.46±1.21	3.67±3
	Range	-1.75-2.46	-1.58-3.22	-1.8-9.5
AST	M±SD	0.98±1.2	1.26±0.52	2.7±1.8
	Range	0-12.69	0.37-2.17	0.31-6.7
SRAX	M±SD	45.37±48.43	53.84±49.45	62.79±42.89
	Range	0-177	0-146	0-164
dK	M±SD	0.88±0.73	1.34±0.63	2.69±1.85
	Range	0-4.3	0.37-2.99	0.31-6.67

KC: central keratometry, I-S: inferior-superior dioptric asymmetry difference, AST: Steepest minus Flattest Sim K reading, SRAX: 180 minus the smaller of the 2 angles between 2 steepest radii, dK: central keratometry difference between 2 eyes.

In addition to above, in 12 eyes (4%) other corneal findings were detected: fleck corneal dystrophy in 6 eyes (2%), granular dystrophy in 2 eyes (0.7%), pellucid marginal degeneration (PMD) in 2 eyes (0.7%) and posterior polymorphous corneal dystrophy (PPMD) in 2 eyes (0.7%).

Discussion:

In this study, KCN was diagnosed in 21 persons (14%) among 150 persons in 45 families of relatives of KCN patients. Most of the KCN suspect and KCN patients were detected by topographic evaluation[19]. This prevalence is similar to the previous studies[6,7]. This finding illustrates that many of the relatives of KCN patients can be in subclinical state of disease (i.e. with no clinical sign). Topographic evaluation can play a useful role in detecting many of them. The relationship between clinical and topographic findings has not been clarified in other studies, so comparison between this study and the others from this point of view is not possible.

The sampling of this study was not completely randomized, and known cases of KCN were diagnosed before study, which is a weak point. The same problem also exists in other published reports[2,5,7]. Evaluation and examination of these 150 participants (considering familial prevalence 7% and error coefficient 4%) increases the validity of the study. In Rabinowitz study[4], only 5

families (including 24 persons) and in Gonzalez[2] study only 12 families (included 28 persons) were evaluated. These small sample size groups can not precisely determine the detailed changes in relatives of KCN patients. Evaluation of 45 families in present study can be more useful for detection of those changes in family members of KCN patients.

Most of the cases in this study were under 40 years of age (71.8%), due to the higher prevalence of KCN in the younger age group.[1] Therefore case selection seems to be appropriate in this study and the results will also be reliable. In this study, women participated more than men probably because of social situations that accounted for a higher referral rate. In those who were randomly selected and diagnosed as KCN, there has been no sexual difference, but prevalence of KCN suspect was higher in women. In previous reports[1,2,4] there has been no sexual difference in KCN patients, but there is no report regarding this difference in KCN suspect cases. In this study 75.3% of participants were first degree relatives of KCN patients. Previous studies have not reported any degree for relative involvement in studied KCN family members. Rabinowitz[1] attempted to show a relation between presences of high astigmatism in relatives of KCN patients as a clinical presentation, but the number of samples in his study was low and he was not able to show this relationship. In the present study, almost 50% of KCN family members had astigmatism under 1.5 diopters and 11.3% of them had over 1.5 diopter of regular astigmatism. Generally, this finding cannot be a predictor for direct relation between astigmatism prevalence in family members of KCN patients. Based on topography, KCN may be detected in relatives of KCN cases with any type of refractive error (even if they may be hypermetrope). Therefore type of refractive error does not exclude the diagnosis of KCN.

In this study, the difference between spherical equivalent (SE) in normal and KCN patients was statistically significant but in KCN suspect cases, the difference was not significant. In other similar studies, refractive parameters and SE have not been evaluated. Therefore, we can not compare our findings to others.

The most common corneal topographic patterns found in relatives of KCN patients were as follows: round, oval and geographic and in most cases a

symmetrical pattern. This finding is similar to those reports of general population[4,5]. Because there was no control group, the importance of this prevalence pattern remains till becomes clear. Comparison of topographic parameters like central keratometry (KC), showed there was no significant difference between normal and KCN suspect cases but it was different from KCN group which was statistically significant. Unfortunately, in other studies topographic parameters were not reported. Kertometric difference (dk) values between the 2 eyes in KCN suspect cases were between normal and KCN groups. It seems to be an important factor in the differentiation of normal, KCN suspect and KCN patients[19].

In present study, a few number of relatives also had clinical signs of fleck , granular and posterior polymorphous dystrophy of cornea. Although this findings seems to be incidental, although in some studies other dystrophies have been reported to be associated with KCN[1]. In current study one patient (2 eyes) was diagnosed as pellucid marginal degeneration (PMD), but it is also in the spectrum of corneal ecstatic disorders (like KCN).[5,20]

To avoid any corneal warpage induced by contact lens wearing any patient with a recent history of contact lens use was excluded from this study. It was not possible to invite them again after discontinuation of contact lens. It is possible that some undetected KCN cases may have been in that gorup.[16]

Considering higher prevalence of KCN and KCN suspects in the relatives of KCN patients every positive familial history especially in keratorefractive surgery candidates, must be considered as an important alarming factor and their Corneal topographic evaluation must be considered more carefully. If there is any suspicious point, more precise methods like Orbscan or pentacam must be employed to confirm the presence or absence of KCN.

We believe more extensive studies are needed to evaluate and compare orbscan with topographic findings in these patients.

Conclusion:

Both types of KCN (definite and suspect) are more prevalent in relatives of KCN patients. Videokeratography, a widely available device in many ophthalmology centers, is a valuable and reliable method for detecting these cases. Any KCN suspect patient among the relatives of KCN patients must be approached cautiously, because it can be a preliminary sign for evolution of definite KCN in the future. It is still not clear which percentage of KCN suspect cases will progress to the definite form of KCN.

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Table

Table 1: Comparison of KCN and KCN suspect in different sexes.

Diagnosis	**Number (Percentage)**		**Total**
	Men	Women	
KCN	16 (12.4)	21(12.3)	37 (12.3)
KCN suspect	6 (4.7)	14 (8.2)	20 (6.7)

Table 2: Distribution of refractive errors in 300 studied eyes with respect to different groups.

Refractive error	(Percentage) number				P1-value	P2-vlaue
	KCN	KCN suspect	Normal	Total		
Myopia	8(50)	16(59.3)	66(41)	90(30)	0.41	0.25
Hyperopia	8(50)	11(59.3)	95(59)	114(38)	0.54	0.48
Low regular astigmatism	17(5.9)	13(65)	114(47.3)	144(48)	0.912	0.12
High regular astigmatism	15(40.5	**0**	17(7)	32(10.7)	<0.0001	0.22
With the rule astigmatism	5(13.5)	8(40)	75(30.9)	88(28.3)	0.03	0.39
Against the rule astigmatism	15(40.5	0	45(18.5)	60(20)	0.002	0.03
Oblique astigmatism	13(35.1)	9(45)	11(4.5)	33(11)	<0.0001	<0.0001
Irregular astigmatism	**2** (5.4)	0	0	2(0.7)	<0.000 **1**	-

P1: comparison between KCN and normal group.
P2: comparison between KCN suspect and normal group

Table

Table 3: General parameters and distribution of spherical refraction (diopter) in different groups.

Groups / Parameters	KCN	KCN suspect	Normal	P1-value	P2-vlaue
M± SD	-1.25±2.83	-0.39±0.96	-0.1±1	0.001	0.23
Range	+1.75 to -8.5	+0.5 to -2.75	+3.5 to -8.5	-	-

M: Mean spherical refraction
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P_1: comparison between KCN and normal group
P_2: comparison between KCN suspect and normal group

Table

Table 4: Corneal topographic parameters in normal eyes, KCN suspect and KCN patient groups.

Parameters \ Groups		Normal	KCN suspect	KCN
KC	M±SD	44.28±1.46	45.55±1.96	46.98±3.63
	Range	40.75-47.53	41.29-48.68	41.67-54.70
I-S	M±SD	-0.13±0.54	1.46±1.21	3.67±3
	Range	-1.75-2.46	-1.58-3.22	-1.8-9.5
AST	M±SD	0.98±1.2	1.26±0.52	2.7±1.8
	Range	0-12.69	0.37-2.17	0.31-6.7
SRAX	M±SD	45.37±48.43	53.84±49.45	62.79±42.89
	Range	0-177	0-146	0-164
dK	M±SD	0.88±0.73	1.34±0.63	2.69±1.85
	Range	0-4.3	0.37-2.99	0.31-6.67

KC: central keratometry, I-S: inferior-superior dioptric asymmetry difference, AST: Steepest-F1attest sim K reading, SRAX: 180 minus the smaller of the 2 angles between 2 steepest radii, dK: central keratometry difference between 2 eyes.