Medical Hypothesis, Discovery & Innovation Ophthalmology Journal

Original Article

Consanguineous Marriage as a Risk Factor for Developing Keratoconus

Hossein JAMALI [1], Vahid BEIGI [1], Ali SADEGHI-SARVESTANI [1]

1. Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Heredity plays an important role in keratoconus (KC). Consanguineous marriage (CM) can affect the transmission of recessively inherited conditions. We aimed to investigate the role of consanguineous marriage in the development of KC. This study included two groups: the first group comprised 415 patients who underwent surgery for KC for the first time at Khalili University Hospital (Shiraz, Iran), between 2010 and 2014; the second group comprised 415 healthy individuals who served as age- and sex-matched controls for the patient group. All study subjects were from the Fars province in Iran. CM type was evaluated by a standard checklist in both groups. The mean inbreeding coefficient (α) was evaluated and compared between the two groups. The percentage of parental first-cousin marriages was 35.4% in the patient group and 18.3% in the control group. The mean inbreeding coefficient (α) was 0.0291 in the patient group and 0.0135 in the control group. Patients with KC had a significantly higher mean inbreeding coefficient (α) than controls ($T = 8$, $df = 828$, $P < 0.001$). Our study suggests that CM can play a role in the pathogenesis of KC. As this disease is among the most frequent ocular disorders in our country, CM should be considered by health care systems within their screening programs.

KEY WORDS

Consanguineous Marriage; Risk Factor; Keratoconus;

Correspondence to:

Vahid Beigi MD, Poostchi Ophthalmology Research Center, Department of Ophthalmology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: v.beigi66@gmail.com

INTRODUCTION

Keratoconus (KC) is a corneal ectasia that is bilateral, slowly progressive, and non-inflammatory. The reported prevalence and incidence of KC are largely variable because of differences in clinical definitions and diagnostic criteria. The estimated incidence of KC is one case per 2,000 people in the general population, and approximately 0.249% in Iran [1]. The prevalence of KC varies in relation to geographical differences and the source of the data. For example, in the USA, the prevalence of KC is approximately 600 cases per 100,000 individuals in the general population, but 54.5 cases per 100,000 individuals who were admitted to hospitals. The onset of KC typically occurs at puberty, but can appear as late as the fourth decade of life; however, its development varies across different populations. There is an inverse correlation between the severity of KC and

age, with new evidence suggesting that more severe clinical subtypes of KC are found in younger patients. The known histopathological features of KC include breaks in Bowman's layer and thinning of the corneal stroma; in the keratoconic cornea, all layers exhibit histopathological structural changes, with the exception of the endothelium [2-4]. Several risk factors have been identified, including contact lens wear, eye rubbing, atopic disease, connective tissue disorders, and inheritance [5-8]. Several reports have described associations between the presence of Down's syndrome, mitral valve prolapse, or Leber's congenital amaurosis with onset of KC. KC often occurs sporadically, but a significant minority of patients present with a positive family history. The etiology of KC is highly complex and multifactorial, with genetic and environmental factors [7-10]. The rate of family history is 6–23.5% among patients with KC [11, 12]. Consanguineous marriage (CM) is a widely accepted social custom among Asian families and a leading cause of birth defects [13, 14]. To the best of our knowledge, there has been no investigation of the role of consanguinity in the incidence of KC in Iran. The aim of this study was to determine the prevalence of CM in parents of patients with KC, compared with controls.

MATERILAS AND METHODS

We collected data from 415 patients who underwent surgery for KC for the first time at Khalili University Hospital (a referral center for ophthalmology in the Fars province) between 2010 and 2014. All patients were living in the Fars province in Iran. Surgery type included deep anterior lamellar keratoplasty (DALK), penetrating keratoplasty (PK), and corneal collagen cross-linking (CXL); the patients had been referred to this particular center because they required these operations. A total of 415 healthy individuals were randomly selected to enroll in the study and were age- and sex-matched to the participants in the patient group. The type of marriage of the parents of each individual in both groups was evaluated and recorded. Informed consent was provided by all participants. This study was approved by the ethical committee of our university.

KC was diagnosed by ophthalmologists at Khalili Hospital, according to abnormal topography (Figs 1, 2) and one or more signs on slit-lamp examination, including stromal thinning, Fleischer ring, Munson's sign, or Vogt striae. Because of PK in some advanced cases, only patients who had unilateral KC were enrolled in the study. The exclusion criterion was any other systemic disease that could be associated with KC [15]. A validated questionnaire was completed by both patients and controls to collect exposure information. The questionnaire was previously evaluated [16] and tested by Owens and Gamble [17]; it included demographic information (e.g., age, sex, religion, and potential risk factors). Parental consanguinity was categorized into unrelated, first cousins, and second cousins. Smoking, allergies, asthma, permanent use of sunglasses, eye rubbing, eczema, and family history of KC were assessed.

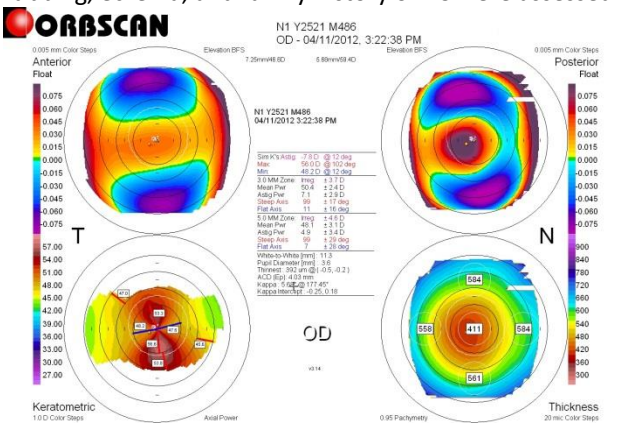

Figure 1. General Quad Map of a Patient with Keratoconus, showing Abnormalities in All Four Quarters

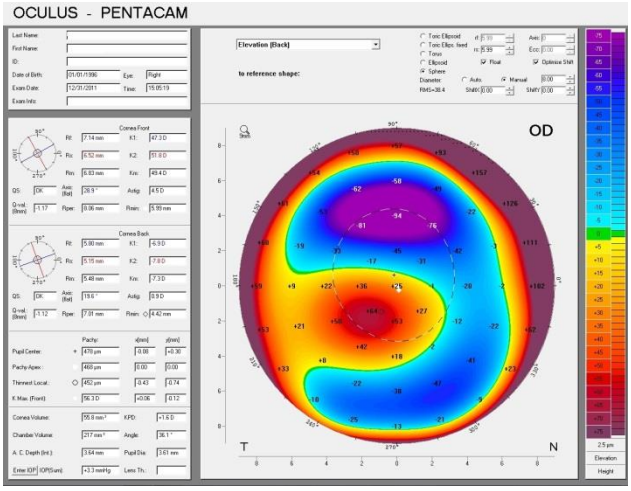

Figure 2. Pentacam Corneal Tomography of a Patient with Keratoconus, showing Abnormalities in elevation map.

The inbreeding coefficient (F) is defined as the probability that an individual has received both alleles of a pair from one of their parents or the proportion of loci for which the individual is homozygous. The inbreeding coefficient (F) was calculated by the degree of relationship between the couples: double first cousins (1/8), first cousins (1/16), first cousins once-removed (1/32), and second cousins (1/64). The mean inbreeding coefficient (α) was measured for each category in both groups [14].

RESULTS

This study included a total of 244 (58.8%) women and 171 (41.2%) men. The mean age of all participants was 20.86 ± 5.76 years (range: 5–36 years). All individuals were Muslim. The mean spherical equivalent (SE) was -3.25 ± 2.35 in the patient group and -0.5 ± 0.75 in the control group. The mean uncorrected visual activity (UCVA) was 0.85 ± 0.53 logarithm of the minimum angle of resolution (logMAR) and the mean best-corrected visual activity (BCVA) was 0.45 ± 0.32 logMAR in the patient group. The mean UCVA was 0.1 ± 0.05 logMAR and the mean BCVA was 0.05 ± 0.25 logMAR in the control group. A positive family history of KC was reported in 54 (13%) of patients.

Table 1. Types of Consanguineous Marriage and the Mean Inbreeding Coefficient (α) of the Parents of the Participants in both Groups

Type of marriage	Patient group	Control group
Double first cousins	9	1
First cousins	147	76
Cousins once-removed	20	8
Second cousins	74	32
Unrelated marriages	165	298
Total	415	415
Mean inbreeding coefficient (α)	0.0291	0.0135

Table 2. Relationship between Eye Rubbing, Use of Sunglasses, Allergy, Asthma, Smoking, Eczema, and Keratoconus

Group	Number	Percentage	Odds ratio	P-value
Eye rubbing			6.800 (3.920–11.823)	0.000
Case	89	21.4%		
Control	16	3.9%		
Use of sunglasses			2.161 (1.430–3.267)	0.000
Case	76	18.3%		
Control	39	9.4%		
Allergies			1.318 (0.878–1.976)	0.109
Case	61	14.7%		
Control	48	11.6%		
Asthma			1.599 (0841–3.040)	0.100
Case	25	6.0%		
Control	16	3.9%		
Smoking			1.083 (0.763–1.539)	0.360
Case	79	19.0%		
Control	74	17.8%		
Eczema			1.150 (0.685–1.931)	0.346
Case	33	8.0%		
Control	29	7.0%		

Regarding the surgery type, CXL was performed in 316 (76.1%) patients, DALK in 81 (19.5%), and PK in 18 (4.3%). The types of CM and the mean inbreeding coefficient (α) of the parents of the participants in both groups are presented in Table 1.

The percentage of parental first-cousin marriage was 35.4% in the patient group and 18.3% in the control group. The incidence of first-cousin marriage was higher among parents of patients with KC than among parents of controls (χ^2 = 22.6, df = 1, P < 0.001). The patient group had a higher mean inbreeding coefficient (α) than the control group (T = 8, df = 828, P < 0.001). Eye rubbing was significantly more frequent in the patient group than in the control group (P = 0.000) (Table 2).

KC was a risk factor for the eye-rubbing symptom [odds ratio (OR) = 6.808, 95% confidence interval (CI) 3.92–11.823]. Sunglass wearing was significantly more frequent in the patient group than in the control group (Table 2) (P = 0.000). The frequency of sunglass wearing was 2.161 times more frequent among patients than among controls (OR = 2.161, 95% CI 1.43–3.267). There were no significant differences between groups for the other variables tested, including allergies (P = 0.182, OR = 1.318, 95% CI 0.878–1.976), asthma (P = 0.149, OR = 1.599, 95% CI 0.841–3.04), cigarette smoking (P = 0.654, OR = 1.083, 95% CI 0.763–1.539), and eczema (P = 0.597, OR = 1.15, 95% CI 0.685–1.931).

DISCUSSION

Our study showed that the percentage of parental first-cousin marriage was 35.4% among patients with KC and 18.3% among controls. The mean inbreeding coefficient (α) was greater in the patient group (0.0291) than in the control group (0.0135). Approximately 6–8% of patients with KC have a positive family history or present evidence of familial transmission [8]. The US Collaborative Longitudinal Evaluation of Keratoconus study reported a rate of family history of 13.5%, and a study from Israel—where the prevalence of KC is high—reported a rate of family history of 21.74%, which was higher than the 13% that we reported previously [18]. Recently, several candidate genes have been suggested to play a role in the pathogenesis of KC, including *VSX1*, *SOD1*, *COL4A3*, and *COL4A4* [9]. Few studies have evaluated the effect of consanguineous marriage on the development of KC. Gordon-Shaag et al. demonstrated a strong link between KC and parental first-cousin consanguinity via univariate analysis and genetic studies; they confirmed the hypothesis that consanguinity and genetics may play an important role in the development and progress of KC [15]. The findings of their study are consistent with our findings. CM can increase the risk of recessive forms of genetic diseases, such as ocular diseases, because of the increased possibility of the presence of variable mutations in a homoallelic condition [19]. CM is more common in Asia and Africa [20]; interestingly, Akrami et al. reported an increasing trend for CM in Tehran, Iran [21]. Many new consanguineous couples want to understand the consequences of consanguinity for their offspring. General practice physicians should be aware of potential pathological mechanisms associated with consanguinity. Therefore, the screening guidelines should be adapted to properly evaluate consanguineous couples and their offspring.

To investigate the relationship between CM and KC in Iran, we studied the prevalence of CM in parents of patients with KC and compared these data with a control group. The mean inbreeding coefficient (α) was higher in patients with KC than in controls. This finding highlights the importance of raising awareness for the need to monitor consanguineous couples. Such a strategy may prevent the progression of KC to advanced stages and enable adequate management of KC. A national research project in the Shiraz province in Iran showed that the inbreeding coefficient of the general population was 0.0152 [22], which was similar to that of our control group. In a case-control study, Gordon-Shaag and colleagues found a significant association of eye rubbing, allergy, family history, and education >12 years with KC [15]. The OR of wearing sunglasses in the KC cohort was 75% lower than that in the control group. Eczema, asthma, and smoking were not significantly different between the two groups. Similar to their study, we found (in the present study) that eye rubbing was significantly more frequent among subjects with KC. However, we found that wearing sunglasses was more frequent in the patient group than in the control group; the difference between the two studies could be related to geographical and cultural issues. Our study had an important limitation in that the population of eligible patients only included those patients who were referred to a single Eye Hospital for surgical management; outpatients with KC were not included. In conclusion, CM may play a role in the pathogenesis of KC. As this disease is among the most frequent ocular disorders in our country, CM should be considered within health care screening programs.

DISCLOSURE

No funding or sponsorship was received for this study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

REFERENCES

1. Ziaei H, Jafarinasab MR, Javadi MA, Karimian F, Poorsalman H, Mahdavi M, et al. Epidemiology of keratoconus in an Iranian population. Cornea. 2012;31(9):1044-7. doi: 10.1097/ICO.0b013e31823f8d3c pmid: 22710491
2. Khaled ML, Helwa I, Drewry M, Seremwe M, Estes A, Liu Y. Molecular and Histopathological Changes Associated with Keratoconus. Biomed Res Int. 2017;2017:7803029. doi: 10.1155/2017/7803029 pmid: 28251158
3. Gatzioufas Z, Panos GD, Hamada S. Keratoconus: is it a Non-inflammatory Disease? Med Hypothesis Discov Innov Ophthalmol. 2017;6(1):1-2. pmid: 28428967
4. Jadidi K, Nejat F, Mosavi SA, Naderi M, Katiraee A, Janani L, et al. Full-ring Intrastromal Corneal Implantation for

Correcting High Myopia in Patients with Severe Keratoconus. Med Hypothesis Discov Innov Ophthalmol. 2016;5(3):89-95. pmid: 28293654

5. T AI, Elmor O. Intracorneal Rings (INTACS SK) Might be Beneficial in Keratoconus; A Prospective Nonrandomized Study. Med Hypothesis Discov Innov Ophthalmol. 2013;2(2):35-40. pmid: 24600640
6. Norouzpour A, Mehdizadeh A. A novel insight into keratoconus: mechanical fatigue of the cornea. Med Hypothesis Discov Innov Ophthalmol. 2012;1(1):14-7. pmid: 24600612
7. Akkaya S. Rate of Parental Consanguineous Marriage among Patients with Visual Impairments in Turkey. Med Hypothesis Discov Innov Ophthalmol. 2016;5(4):115-20. pmid: 28293658
8. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol. 1984;28(4):293-322. pmid: 6230745
9. Stabuc-Silih M, Strazisar M, Ravnik-Glavac M, Hawlina M, Glavac D. Genetics and clinical characteristics of keratoconus. Acta Dermatovenerol Alp Pannonica Adriat. 2010;19(2):3-10. pmid: 20664914
10. Fournie P, Touboul D, Arne JL, Colin J, Malecaze F. [Keratoconus]. J Fr Ophtalmol. 2013;36(7):618-26. doi: 10.1016/j.jfo.2013.05.004 pmid: 23911067
11. Hughes AE, Dash DP, Jackson AJ, Frazer DG, Silvestri G. Familial keratoconus with cataract: linkage to the long arm of chromosome 15 and exclusion of candidate genes. Invest Ophthalmol Vis Sci. 2003;44(12):5063-6. pmid: 14638698
12. Rabinowitz YS. The genetics of keratoconus. Ophthalmol Clin North Am. 2003;16(4):607-20, vii. doi: 10.1016/s0896-1549(03)00099-3 pmid: 14741001
13. Kumaramanickavel G, Joseph B, Vidhya A, Arokiasamy T, Shridhara Shetty N. Consanguinity and ocular genetic diseases in South India: analysis of a five-year study. Community Genet. 2002;5(3):182-5. doi: 10.1159/000066334 pmid: 14960889
14. Bagheri M, Farvardin M, Saadat M. A study of consanguineous marriage as a risk factor for developing comitant strabismus. J Community Genet. 2015;6(2):177-80. doi: 10.1007/s12687-015-0213-9 pmid: 25644872
15. Gordon-Shaag A, Millodot M, Essa M, Garth J, Ghara M, Shneor E. Is consanguinity a risk factor for keratoconus? Optom Vis Sci. 2013;90(5):448-54. doi: 10.1097/OPX.0b013e31828da95c pmid: 23584486
16. Millodot M, Shneor E, Albou S, Atlani E, Gordon-Shaag A. Prevalence and associated factors of keratoconus in Jerusalem: a cross-sectional study. Ophthalmic Epidemiol. 2011;18(2):91-7. doi: 10.3109/09286586.2011.560747 pmid: 21401417
17. Owens H, Gamble G. A profile of keratoconus in New Zealand. Cornea. 2003;22(2):122-5. pmid: 12605045
18. Zadnik K, Barr JT, Edrington TB, Everett DF, Jameson M, McMahon TT, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci. 1998;39(13):2537-46. pmid: 9856763
19. Khan AO, Shinwari J, Abu Dhaim N, Khalil D, Al Sharif L, Al Tassan N. Potential linkage of different phenotypic forms of childhood strabismus to a recessive susceptibility locus (16p13.12-p12.3). Mol Vis. 2011;17:971-6. pmid: 21541264
20. Hamamy H. Consanguineous marriages : Preconception consultation in primary health care settings. J Community Genet. 2012;3(3):185-92. doi: 10.1007/s12687-011-0072-y pmid: 22109912
21. Akrami SM, Montazeri V, Shomali SR, Heshmat R, Larijani B. Is there a significant trend in prevalence of consanguineous marriage in Tehran? A review of three generations. J Genet Couns. 2009;18(1):82-6. doi: 10.1007/s10897-008-9191-y pmid: 18843527
22. Saadat M, Ansari-Lari M, Farhud DD. Consanguineous marriage in Iran. Ann Hum Biol. 2004;31(2):263-9. doi: 10.1080/03014460310001652211 pmid: 15204368