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Original Article

Evaluating the Association of Keratoconus with Consanguinity

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ABSTRACT

Keratoconus (KC) is a chronic, non-inflammatory disturbance of cornea. **Objective:** To determine the relation between consanguinity and keratoconus (KC). **Methods:** Comparative cross-sectional study conducted at Ophthalmology department of The University of Lahore Teaching Hospital, Lahore from 12th February to 18th June, 2021. In this study, 30 KC diagnosed patients were included according to the sample size. A self-administered questionnaire was made to collect information about demographic data, various KC findings, clinical signs and nature of marriage between the parents of the participants. **Results:** Out of 30 recruited KC patients with age ranging between 10-30 years, 13 subjects were male and 17 were females, 56.7% of patients reported with first parental cousin marriage, 26.7% with second, 6.7% with third and 10% with out of family parental marriages. Relation between consanguinity and KC was obtained with $p< 0.05$, showing the results were significant. Results showed that the patients whose parents had consanguinity of first degree were more susceptible to the disease and had more severe keratoconus than rest of the population. **Conclusion:** This study supports the hypothesis that a significant direct association between KC and consanguinity persists. Results show, risk of KC development is much higher in parental consanguinity of first degree than other type of intermarriages. KC in such susceptible group was observed to be more progressive.

INTRODUCTION

Keratoconus (KC) is a disorder of cornea with unknown etiology. It is mainly characterized by stromal thinning of central/paracentral region of cornea, leading to a conical shape from apex. In early stage of KC, there are no specific symptoms, so KC go unnoticed. In later stages of KC, there is marked deterioration in vision with continually progressive astigmatism [1]. As the disease progresses, the patient notes blurring and distortion in vision due to induction of myopia and irregular astigmatism. However, near vision of KC patient is quite good than expected, in comparison to far vision. In advance cases, corneal scarring due to putrefaction and corneal edema leads to vision loss. Clinical manifestation of this ectatic disease differentiates depending on severity. Changes in cornea start developing during adolescence and the cascade slows down near 30-40 years of age, though at any age, the disease can depict itself [2]. KC is considered to be cause by multiple factors including environment and lifestyle. Eye rubbing, contact lens wear, allergy, genetics and inheritance are thought to be aggravating factors for this disease [3]. KC is present in all ethnicities and affects both genders. In general, occurrence of KC ranges from 4-600 cases per100,000 population (the statistics differ depending on the region and geographical area). Globally, it was reported as 0.0003% in Russia, 0.068% in Denmark, 0.249% in Iran,2.3% in central India [4]. High incidence and prevalence of KC is noted in Pakistan as compared to other western countries, with frequent patients showing genetic patterns over environmental. Comparative analysis has showed that areas comprising of cold climate like Russia, USA has less prevalence of KC, in comparison to Middle East and Asian countries [5]. Genetic relation of KC is

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demonstrated by twin study, genetic linkage analysis, family history [3].Marriage between close biological relatives or close kin marriages is termed as consanguinity. Intermarriages are widely practiced in many parts of the world, its prevalence differs from region to region depending on demographic characteristics, but this ritual is most commonly accepted in Asia especially among Hindu Muslim communities [6]. In Pakistan, 60% of all marriages are consanguineous, among which 80% are between first cousins. In rural areas of Pakistan, the percentage of consanguinity increases up to 70% due to lack of education, cast system and concept of cousin marriage as a religious obligation. As the result of this ancestry agitation, the inheritance chances of genetically linked diseases and expression of recessive abnormalities increases [7]. The gene contributing to KC development is transferred to next generation as autosomal dominant, loci on 73% of autosomal chromosomes are suggested to be involved. The mutant gene can also have recessive course depending on region and geographical area. More than 19 gene loci have been identified which contribute in the pathogenesis of KC and can be passed down to next generation e.g. a mutated VSX1 gene. These genes alter the normal pathological path and lead to changes in physiological process, thus leading to alteration in cornea. KC is also associated with more than 20 congenital disorders such as Leber congenital amaurosis, Marfan syndrome and Down syndrome [8]. Cousin marriage is a widely practiced tradition in South Asian families. Familial clustering among relatives through interbreeding is thought to be a source of many inherited disorders, including KC. First degree relatives with positive family history, have fourfold risk of developing KC than general population, and further inter marriages increases the chances of disease among offspring as close kin marriages provide more chances to the disease to express itself [9]. Due to increased acceptability of consanguinity in present region, the purpose of this study is to analyze the association of KC development with interbreeding.

METHODS

A comparative cross-sectional study was conducted at The University of Lahore Teaching Hospital, Lahore, to find the relation between consanguinity and KC. The data collection took place within period of 4 months by using non-probability convenience sampling technique. Patients of KC with age range of 10 to 30 were recruited from the hospital. Patients were excluded from the study if they had any systemic or ocular conditions positively or negatively associated with KC. Immunodeficient patient, anti-cancerous drugs users, patients with eye trauma, patients reported with ectasia or pellucid marginal degeneration were not involved in the study. 30 KC diagnosed patients, coming under inclusion criteria, were included in this study. These keratoconus patients were diagnosed by ophthalmologists after detail examination. An explanation of the research project was given to the KC diagnosed volunteers and a self-administered questionnaire was used to collect data. The questionnaire consisted of questions on demographics data, clinical signs and KC findings. Characteristics of right and left eye of KC patients were collected separately. The demographic information included age, sex, education and current residence. Subjects were asked about parent's consanguinity, which was categorized into first-cousin, second-cousin, third cousin and out of family. Best-spectacle corrected visual acuity (BCVA) of each eye using the log MAR chart was also obtained. KC was diagnosed based on abnormal topography and it's presenting signs. Munson sign, Fleischer ring and Vogt striae were observed by slit lamp, scissors reflex by using retinoscopy and oil droplet sign with the help of opthalmoscope. The results were further confirmed by corneal topography evaluation and KC was classified according to its severity levels, mild <48D, moderate 48-54 D and severe > 54D, in both eyes separately. In order to compare the ophthalmic parameters of the KC patients with and without a parental consanguinity of KC, topographic and keratometric measurements of KC patients were examined. The data was entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were expressed as frequency and percentages. Chi-square test was used to test the association of KC with consanguinity. $p< 0.05$ was considered statistically significant.

RESULTS

This study involved 30 KC patients, out of which 13 (43.3 %) were male and 17 (56.7%) were female. No sex predominance of KC was observed in present study. Participants had age ranging between 10-30 years. High frequency of patients with age between 19-22 years reported in this study, showing that KC is mostly diagnosed after the age of 18. 17 (56.7%) of the recruited patients had first parental consanguinity, 8 (26.7%) had second and 2 (6.7%) had third parental consanguinity. 3 (10%) of the subjects had parents who were married out of family. This showed that cousin marriage in present region is an accepted ritual and a common tradition. The analysis showed all of the patients had scissors and oil droplet reflex, thus these two signs were constant in this study. 26 (86.7%) Munson sign, 13 (43.3%) Fleischer ring, 16 (53.3%) Vogt's lines and 18 (60%) Rizzuti sign was observed within the participating patients. All the patients recruited in this

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study had visual acuity better than 0.50 Log Mar with glasses 15 (50%) of the right eyes and 16 (53.3%) of the left eyes. Vision ranging between 0.60-0.90 Log Mar with glasses was in 13 (43.3%) right and 11 (36.7%) left eyes. Only 2 (6.7%) right and 3 (10%) left eyes had vision 1 or less than 1 Log Mar with bifocals. This demonstrates that vision of KC patient improves with the use of spectacles. 12 (40%) right eyes and 13 (43.3%) left eyes of the patients had KC prediction index ranging between 60-79%. KPI ranging between 80-99% of right and left eyes of recruited subjects were reported as 16 (53.3%) and 15 (50%) respectively. KPI of 100% was observed in 2 (6.7%) of both eyes of patients separately. High number of consanguineous subjects having KPI between 80-99% showed that patients with parents having first degree of cousin marriage have greater KC prediction index. Table 1 and 2 shows the result of Chi square test, analyzing the relation between consanguinity and KC. Results demonstrate that subjects with parental 1st cousin marriage were greater in number and had higher KC severity than 2nd, 3rd and out of family marriages. 2nd degree of parental marriage comes second in line with KC severity greater than 3rd and out of family marriages. In patients with first degree of parental marriage, KC is observed to be more severe and progressive. Figure 1 and 2 shows the bar representation of the obtained relation between KC and consanguinity.

Parent's Consanguinity	Keratoconus in Right Eye			Total (n)	P-Value
	Mild < 48D	Moderate 48-54D	Severe >54D		
Out of Family	2	1	0	3	0.014
With 3rd Cousin	1	1	0	2	
With 2nd Cousin	4	3	1	8	
With 1st Cousin	3	10	4	17	
Total	10	15	5	30	

Table 1: Chi-Square test of Consanguinity * Keratoconus in right eye

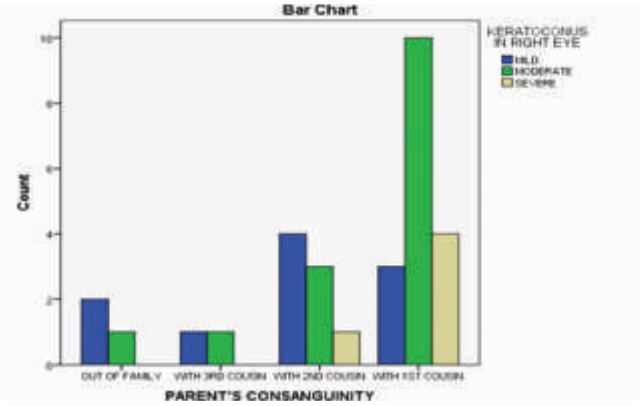

Figure 1: Bar Chart Representation of Consanguinity* KC in Right Eye

Parent's Consanguinity	Keratoconus in Right Eye			Total (n)	P-Value
	Mild < 48D	Moderate 48-54D	Severe >54D		
Out of Family	2	1	0	3	0.013
With 3rd Cousin	2	0	0	2	
With 2nd Cousin	3	4	1	8	
With 1st Cousin	4	9	4	17	
Total	11	14	5	30	

Table 2: Chi-Square test of Consanguinity * Keratoconus in left eye

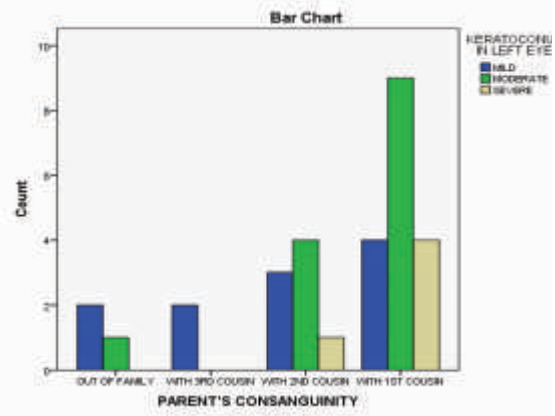

Figure 2: Bar Chart Representation of Consanguinity* KC in Left Eye

DISCUSSION

The results of present study demonstrated that prevalence of KC higher in first cousin married parent's offspring as compare to second and third cousin and very low among the children with parents that are married out of family. This relation of consanguinity proves the involvement of genetics, which can be passed down to the next generation [10]. Various previous studies also depicted a direct role and association between KC and consanguinity, their outcomes showed that the effect of cousin marriages is proportional to the closeness of blood relationships of the concerned parents. The results of study conducted by Gorden-Shaag A et al., showed significant relation, as in present study, between keratoconus and consanguinity [3]. Contribution of genetics were also discussed in his study with strong evidence.

Hossein Jamali et al., study also supports the hypothesis that consanguinity plays prominent role in development of KC [9]. It was demonstrated in Awwad ST et al., cross sectional study that first degree relatives of KC patients are at greater risk of developing KC [11]. If the recessive gene of KC persists within the family, intermarriages can cause gene dominance in off spring. In most recent studies of authors like Crawford AZ et al., it was reviewed that development of KC is the combined effect of genetics and environmental contributors and same mechanism applies

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on manifestation of other ocular diseases [12]. Thomas, [13] Jochen Graw, [14] Duke Elder and Leigh, [15] studies were work of early literature which presented several cases in which patients were the children of cousin parents.

High frequency of parental first degree consanguinity was observed in this study, which can be due to accepted ritual of intermarriages in present territory. Gordan-Shaag A et al., in his article discussed that many regions of the developing world, most specifically in West and South Asian countries, marriages between close biological kin still remains common [4]. Ullah MA et al., in his study also discusses that Hindu and Muslims prefer consanguinity due to its consideration as religious practice and Pakistan has high reported consanguinity especially among first degree relatives [7]. Studies discussing the prevalence of KC found that India, [16] Lebanon, [17] Saudi Arabia [18] and Israel [19], have high persistence of KC as compared to others, they explained that tradition of consanguinity and environmental factors are behind this peak. A comparative study conducted in Yorkshire, England found that the Pakistani who came from a consanguineous family have KC susceptibility of 1 in 400 as compare to 1 in 30,000 whites [4]. Many studies are conducted to determine the involvement of other factors in KC formation as it is considered to be multi factorial, genetic relation of KC was demonstrated by twin study [20], genetic linkage analysis [21], consanguinity [3,9] and family history [22]. Consanguinity as a risk factor is also proved in present study.The results of this study show that KC due to parental consanguineous marriage and KC severity are related, depicting that consanguinity has a direct relation with progression of disease. Naderan M et al., in his study discovered that severity of KC was linked to a positive family history of KC and patients with more KC family members had more severe disease [23]. It was further elaborated that due to genetic piling, the mutated gene gets more chances to depict itself. Genetic crowding due to inter marriages can also be seen in present study, which may be the possible cause of KC severity and increased KPI among such patients. Naderan's and other previous studies have reported male preponderance in development of KC [24, 25] in contrast, studies such as Fink BA et al., reported high frequency of KC within females [26]. In present study, we did not find a significant effect of gander distribution associated with the development of KC. Most of the cases reported in present study were ranging between 19-22 years, depicting high frequency (43.3%) of reported cases in young age. Ertan A et al., study also demonstrated that the distribution ratio of reported KC eyes was low as 7.5% in older age, 17.2% in mid age and higher in younger age group (75.3%), as KC is mostly diagnosed after 18 years of span [27], which provides strong supports to present study.

CONCLUSION

This study provides evidence and supports the hypothesis that a significant direct association between keratoconus and consanguinity persists. Results show, severity and risk of Keratoconus development is much higher in parental consanguinity of first degree than other type of intermarriages.

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