

Risk Factors and Severity of Keratoconus on the East Coast of China

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Abstract

Purpose: This study aims to investigate the characteristics, potential risk factors and associated severity of keratoconus on the east coast of China.

Methods: In this prospective case-control study, patients diagnosed with keratoconus were invited to fill in the online electronic questionnaire designed with the help of the App named WenJuanXing. Several questions like, sex, age of diagnosis and eye care habits were administered to each subject through this e-questionnaire. Corneal topographies at diagnosis taken from Pentacam were also collected.

Results: 391 Chinese keratoconus outpatients were enrolled in this study, among which 159 patients were newly diagnosed. Only 3 patients (0.77%) had a positive family history of keratoconus. Atopy could be identified in 66.0% of our patients. A total of 357 patients (91.3%) mentioned the habit of eye rubbing, with 191 patients (48.8%) rubbing their eyes frequently. Patients with younger age at onset ($P=0.005$), male sex ($P=0.042$), frequent eye rubbing ($P=0.003$) and smoke ($P=0.002$) were found significantly associated with increased risk of acute hydrops. In newly diagnosed patients, 79.9% had the maximum keratometry (Kmax) more than 52D, with males and patients aged 21-30 being even more serious ($P=0.009$; $P=0.005$). Besides, in patients aged over 21, frequent eye rubbing was significantly associated with steeper Kmax and more severe astigmatism (all $P\leq 0.05$).

Conclusion: Our results suggest that frequent eye rubbing is closely related to the severity of keratoconus in Chinese patients. Chinese keratoconus patients always had much serious disease condition at the time of diagnosis. Thus, increasing the publicity of keratoconus and advocating appropriate eye care habits are needed urgently in China.

Introduction

Keratoconus (KC) is a functional and progressive corneal disorder which is characterized by progressive thinning and ectasia of central cornea¹. KC patients generally start with initial symptoms of blurred vision, nearsightedness, irregular astigmatism and eventually result in acute corneal hydrops and irreversible loss of vision^{2,3}. Although several exhilarating diagnostic and therapeutic methods have been enrolled in clinical application, aetiology and pathogenesis of KC still remain elusive⁴.

Previous studies have proposed that several genetic and environmental factors may have contribution to the development of KC⁵. Characteristics and risk factors of KC vary wildly in different regions and races. The estimated prevalence of KC ranges from 0.3 to 3300 per 100,000 in different populations⁶⁻⁸. The research of 2012 Beijing Eye Study showed a prevalence of $0.9\% \pm 0.2\%$ among Chinese population aged over 50 years⁹. Based on such a huge population, the number of potential KC patients might be enormous in China. Articles have unveiled the relationship between KC associated genetic loci (VSX1, IL1A, IL1B, COL4A3 and COL4A4) and Chinese Han ethnicity¹⁰⁻¹². However, epidemiological study of KC

among Chinese population is kind of a blank, except a research from Singapore in which only 60.3% of their subjects were made up of Chinese in 2011 and a research that simply illustrated several clinical features of Chinese KC patients in 2005^{13,14}. Consequently, confusions on the severity and epidemiological factors such as positive family history, eye rubbing and atopy among Chinese KC patients are still exist.

In this study, detailed epidemiological information of 391 KC patients and relevant corneal parameters of 159 newly diagnosed patients were enrolled to investigate the clinical characteristics, risk factors and severity of KC on the east coast of China.

Methods

Subjects

Patients mainly came from regions on the east coast of China. Patients including the first-visit and return-visit KC patients who met the KC diagnostic criterion were recruited from people who came directly to clinics. This prospective case-control study was conducted at the Eye Center of the Second Affiliated Hospital of Zhejiang University School of Medicine. The study followed the Declaration of Helsinki and was approved by Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine. A written informed consent was obtained from each participant.

Diagnosis of KC

The diagnosis of the KC was made of using Pentacam (Pentacam; Oculus, Inc, Wetzlar, Germany) based on the Belin-Ambrósio enhanced ectasia display (BAD), which evaluated elevation data (anterior and posterior), pachymetry distribution and keratometry of the cornea. Typical symptoms (progressing vision loss and astigmatism) and signs evaluating by slit lamp microscope examinations (Fleischer' s ring and Vogt' stripes) were also supplementary information. Potential subjects with non-keratoconus ocular disease such as corneal ulcers and trauma, keratitis, cataracts, intraocular lens implants, macular disease and severe systematic diseases were not eligible for enrollment.

The online questionnaire

All identified KC patients were invited to scan a Q-R code that we posted on the wall of consulting room and fulfilled the online questionnaire. We designed this self-administered e-questionnaire with the help of the App named WenJuanXing, a professional online questionnaire platform. Questions of demographics such as the onset age, gender, ethnicity and potential risk factors such as eye-care status, contact lens wear, family history of KC, eye rubbing and atopy were included.

The analysis of cornea topography

For corneal topography examination assessing by Pentacam, flat (K1) and steep (K2) keratometric readings, maximum simulated keratometry (Kmax), corneal thickness of the thinnest point of the cornea (thinnest pachymetry) and astigmatism were recorded. The stage of keratoconus was classified as mild

when the greatest keratometric reading (Kmax) was less than 45 dpt, moderate when Kmax was between 45 and 52 dpt and severe when Kmax was more than 52 dpt. Kmax has been typically considered to be a reliable quantitative clinical variable to assess the severity of Keratoconus^{15,16}.

Data analysis

The epidemiology data obtained from e-questionnaire were described by number of patients while the data of cornea parameters and therapy were described by number of eyes. Statistical significance was set at $P < 0.05$ and data analysis were performed using SPSS (version 25, IBM, Armonk, NY, United States). Data were presented as means \pm SD. Mann-Whitney U test was used for the comparison of continuous variables and χ^2 -test was used for counting data.

Results

Demographic data

As shown in Table 1, a total of 391 Chinese KC patients with 582 eyes were included in this research, including 289 (73.9%) males and 102 (26.1%) females. Of these, 159 (40.7%) patients were newly diagnosed during the entire study process. The average age at the onset of symptoms was 20.22 ± 6.16 years (range from 6 to 49) and the average age of definite diagnosis was 22.24 ± 6.18 years (range from 7 to 50). 246 (62.9%) patients had bilateral KC and unilateral KC was found in 145 (37.1%) patients. The clinical symptoms and therapeutic managements of 582 eyes of 391 patients were shown in Table 2.

Table 1
Demographic characteristics of KC patients

	Patients with KC
Male	289 (73.9%)
Female	102 (26.1%)
Age at the onset (y)	20.22 ± 6.16 (6–49)
Age at the diagnosis (y)	22.24 ± 6.18 (7–50)
Bilateral KC	246 (62.9%)

Table 2
Clinical symptoms and therapeutic managements of KC patients

Eyes with KC (n = 582)	
Clinical symptoms	
Refractive error uncorrected by glasses	244
Poor visual acuity uncorrected by glasses	246
Image distortion	111
Eye pain, tearing, sore and swollen	42
Protrusion of cornea	37
Corneal rupture, swelling	12
Asymptomatic	26
Treatment	
Without Treatment	41
Glasses Only	44
Rigid gas permeable contact lens	242
Corneal collagen crosslinking	213
Keratoplasty	42

Risk factors of KC in China

Potential risk factors were demonstrated in Table 3. Only 3 (0.77%) patients revealed a positive family history of KC. For ocular-related risk factors, the most common disease among our patients was allergic conjunctivitis of 194 (49.62%) subjects, followed by high myopia of 47 (12.02%) subjects and dry eye of 32 (8.18%) subjects. For systematic diseases, 109 (27.88%) patients had allergic rhinitis and 26 (6.6%) patients had diabetes. Most of the KC patients (91.30%) had a habit of eye rubbing and only 69 (17.65%) patients had a habit of smoking.

Table 3
Potential risk factors of KC patients

Exposure Factor	N (%)
Family history of KC	3 (0.77%)
High myopia	47 (12.02%)
Allergic conjunctivitis	194 (49.62%)
Dry eye	32 (8.18%)
Keratitis	18 (4.60%)
Trichiasis	10 (2.56%)
Diabetes	26 (6.65%)
Allergic rhinitis	109 (27.88%)
Eczema	33 (8.44%)
Urticaria	30 (7.67%)
Asthma	22 (5.63%)
Smoking	69 (17.65%)
Eye rubbing	357 (91.30%)

The severity of KC related to age and gender

159 corneal topographies of newly diagnosed eyes taken from Pentacam were collected. In bilateral patients, more severe eyes were chosen for further analysis. Mean flat (K1) and steep (K2) keratometry were to be 48.76 ± 8.62 and 52.65 ± 9.45 dioptres (D) respectively. Average maximum simulated keratometry (Kmax) was 60.57 ± 12.79 D and average astigmatism was 3.83 ± 2.16 . Mean thinnest pachymetry was 447.55 ± 48.19 μm . When divided by ages, patients under 20 years old and aged 21–30 had significantly steeper Kmax compared with patients aged over 31. Besides, compared with patients younger than 21, patients aged 21–30 had much thinner thinnest pachymetry (Table 4). When divided by gender, Kmax in male patients was significantly higher than that in female patients, while there were no differences in K1, K2, thinnest pachymetry and astigmatism between males and females (Table 5).

Table 4
Comparison of cornea topography variables in different age groups

	Age < 20	Age 21–30	Age > 31	P ₁	P ₂	P ₃
K1	48.81 ± 6.74	49.53 ± 10.68	46.01 ± 4.26	0.695	0.245	0.347
K2	52.92 ± 7.15	53.33 ± 11.83	49.61 ± 4.84	0.279	0.108	0.384
Kmax	60.77 ± 10.23	61.95 ± 15.47	55.00 ± 6.07	0.841	0.02*	0.005*
Thinnest pachymetry	457.10 ± 52.04	437.50 ± 47.70	455.71 ± 29.46	0.011*	0.507	0.149
Astigmatism	4.16 ± 2.18	3.72 ± 2.19	3.26 ± 1.90	0.176	0.117	0.576
* $p < 0.05$ for significant difference. P ₁ : differences between age < 20 and age 21–30. P ₂ : differences between age < 20 and age > 31. P ₃ : differences between age 21–30 and age > 31.						

Table 5
Comparison of cornea topography variables in different gender groups

	Male	Female	P
K1	48.83 ± 7.83	48.57 ± 10.61	0.394
K2	52.82 ± 8.31	52.19 ± 12.16	0.101
Kmax	61.32 ± 10.85	58.73 ± 16.64	0.009*
Thinnest pachymetry	444.38 ± 48.85	455.31 ± 46.14	0.242
Astigmatism	3.95 ± 2.06	3.52 ± 2.37	0.163
* $p < 0.05$ for significant difference			

KC severity related to eye rubbing

In 391 KC patients, 91.3% mentioned the habit of eye rubbing while only 8.7% KC patients never rubbed their eyes. The analysis of the association between eye rubbing and Kmax or astigmatism in 159 newly diagnosed patients was shown in Table 6. Patients who frequently rubbed their eyes were found to have a significantly steeper Kmax and more severe astigmatism while no difference was found in patients aged under 20 (Table 6). No significant relationships were found between eye rubbing and K1, K2 and thinnest pachymetry (data not shown).

Table 6
Effects of frequent eye rubbing on Kmax and astigmatism in different age groups

	Kmax			Astigmatism		
	Eye rubbing	Without eye rubbing	<i>p</i>	Eye rubbing	Without eye rubbing	<i>p</i>
Age < 20	61.25 ± 10.93	60.38 ± 9.75	0.91	3.96 ± 2.27	4.39 ± 2.08	0.377
Age 21–30	64.01 ± 13.86	60.19 ± 16.69	0.043*	4.25 ± 2.12	3.25 ± 2.17	0.032*
Age > 31	57.38 ± 6.25	51.13 ± 3.26	0.01*	3.76 ± 1.56	2.50 ± 1.56	0.005*

* *p* < 0.05 for significant difference

Risk factors for corneal hydrops

Among 391 enrolled patients, 12 patients had corneal acute hydrops, one of the most severe complications of KC. By comparing patients who had hydrops with those did not, Patients with younger age at onset (*P* = 0.005), eye rubbing (*P* = 0.003), and habit of smoking (*P* = 0.002) were found to have an increased risk for developing corneal hydrops. Besides, male keratoconus patients were much easier to develop into corneal hydrops than female ones (*P* = 0.042). However, allergic diseases and alcoholic were found having no relationship with the occurrence of corneal hydrops (Table 7).

Table 7
Risk factors for developing corneal hydrops in patients with KC

Variables	No Hydrops	Hydrops	P
Male sex, n (%)	277 (70.84%)	12(100.00%)	0.042*
Bilateral, n (%)	238(62.80%)	8(66.67%)	0.785*
Age at onset of symptoms	20.55 ± 6.28	16.25 ± 1.76	0.005Φ
Family history of keratoconus	3(0.79%)	0(0%)	1*
History of allergic diseases	250(66.0%)	8(66.67%)	0.960*
Alcoholic	54(14.35%)	4(33.33%)	0.156*
Smoke	44(11.61%)	5(41.67%)	0.002*
Contact lens use	43(11.35%)	0(0%)	0.377*
Excessive use of eye	265(70.0%)	10(83.33%)	0.317*
Frequent eye rubbing	184(48.55%)	11(91.7%)	0.003*
Conjunctivitis	188(49.61%)	6(50.00%)	0.978*
* Using χ^2 -test			
* Using Fisher exact test			
Φ Using Mann-Whitney test			

Discussion

Although KC has been well documented in Western populations and some Asian countries, seldom was the epidemiology study on KC done in Chinese populations. This study aimed to demonstrate the basic clinical profiles of KC in Chinese patients.

The mean age of diagnosis was 22.24 ± 6.18 years in our study, which is similar with most other Asian or Western studies (ranged from 20.00 ± 6.4 to 24.05 ± 8.97)^{17, 18}. Published male and female ratios of KC varied from 1:1.1 to 2.5:1 in other Asian countries and 1:2 to 3:2 in Western countries¹³. Our research showed a gender ratio of 2.83:1, which is slightly larger than other Asian researches. The skewed sex ratios with high male majority in China may account for this.

Three (0.77%) patients revealed a positive family history of KC in our study, which is much lesser than the published rates in other countries that vary from 5–23.5%^{19, 20}. The prospective research in Singapore showed 26.3% of their KC patients had asthma, while only 0.9% of patients had vasomotor rhinitis¹³.

Instead of asthma, allergic conjunctivitis and allergic rhinitis were the most common diseases accompanying with Chinese KC patients we studied. And the incidence of atopy diseases among Chinese KC patients was 66.0%, which is much higher than that cited by other studies^{17, 21}. Different populations, unknown hereditary and especially the environmental factors could be reasons for this. As the urbanization and industrialization in China is accompanied by bad air quality, and the prevalence of asthma in China has been increasing in recent years²², the impact of deteriorating environment on KC should not be underestimated.

The association between eye rubbing and KC has been validated for many years. In 2000, Bawazeer et al found that eye rubbing was the most significant risk factor for KC in their multivariate analysis²³. In-depth studies have illuminated the underlying mechanisms between eye rubbing and KC, as the microtrauma of epithelium caused by eye rubbing may cause abnormal improved inflammatory factors, such as IL-6 and TNF- α , which may in turn contribute to apoptosis of keratocytes²⁴. Thus, gradual corneal thinning is inevitable. In our research, more than 90% of Chinese patients rubbed their eyes. And 48.5% of patients mentioned the habit of frequent eye rubbing, similar to the 48.2% in the case series by CLEK study²⁵. Naderan M. et al found that in their Iranian patients, the higher frequency of eye rubbing and positive family history were associated with a more severe clinical stage of KC²⁶. Similarly, we found in Chinese patients aged over 21, frequent eye rubbing significantly aggravate the disease condition, with these patients having more serious Kmax and more terrible astigmatism at diagnosis than those who did not. However, no relationship was found between positive family history, allergic diseases and the severity of KC in our study. But the correlation analysis showed patients with atopy were more likely to rub their eyes frequently ($P = 0.045$). This is consistent with the conclusion of Bawazeer et al that atopy may contribute to KC most probably via eye rubbing provoked by itching. As allergic diseases and eye rubbing were quite common among our patients, while their KC family history was sparsely positive. We speculate that differences may exist in the pathogenesis of KC between China and foreign countries, with environmental factors contributing more among Chinese patients than genetic ones.

KC was typically considered as a progressive disease that usually stabilizes by the third or fourth decade of life²⁷, our data suggested that Chinese patients aged 21–30 have steeper Kmax and thinner thinnest pachymetry compared with other age group also accord with this. And similar with studies performed by other races²⁸, the severity of Chinese KC was more serious in male patients than females. According to the value of Kmax, the majority of our patients (79.9%) being diagnosed were in severe stage ($\geq 52D$). The proportion of patients with severe KC in our study was significantly larger than that published by other countries^{4, 25}. We suppose the weak awareness of KC may lead to the serious condition of disease, as the majority of our patients never heard of KC and realized eye rubbing was an important risk factor for KC before diagnosis.

Similar with the research of Reena¹⁷, our study found patients with earlier age at onset and eye rubbing had an increased risk for corneal acute hydrops. Besides, we also found male patients with smoking habit were more likely to get hydrops. This may partly contradict with the study of Spoerl, which indicated

that fewer were smokers in KC patients received CXL and postulated that by-products of cigarette may lead to cross-linking of collagen, thus prevent the progression of KC²⁹. Since the methodologies of these two studies were very different and no research had unveiled the inherent mechanism between smoke and KC, the interpretation should be with caution. Since all patients with history of smoking revealed the habit of frequent eye rubbing, we assume the behaviour of smoking may be related to terrible emotion that would cause vigorous eye rubbing and further lead to the happen of corneal hydrops.

Despite positive outcomes, there are still some limitations of our study: First, this study was conducted in a 3A (Class Three/Grade A) hospitals in China, Hangzhou. Thus, compared with general population, the patients reported in our study may have more serious disease. Second, as the majority of our patients reside in ZheJiang province, our results may have geographical limitations and may not reflect the accurate profile of all Chinese KC patients. Overall, further research awaits a more detailed study with evaluation of a larger number of Chinese cases.

Conclusions

Chinese KC patients that we investigated were always with serious disease at the time of first-visit, had a high prevalence of eye rubbing and atopy, but with little positive family history. And we found Chinese KC patients with younger age at onset, male sex, history of frequent eye rubbing and smoke habit were more easily to develop into acute hydrops, the deep understanding of such risk factors may help clinicians make more informed management strategies to delay or prevent the progression of this disease among Chinese patients. Besides, our data also showed frequent eye rubbing can significantly aggravate the disease in Chinese patients aged over 21, indicating the essential role of eye rubbing in the late pathogenesis of KC among Chinese patients. Thus, strengthening public health outreach of KC and indoctrinating appropriate eye care habits among Chinese populations are urgent affairs.

Declarations

Registration: The research was retrospectively registered and the trial registration number is ChiCTR1900021273 and the registration date is 2019/02/09.

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Conflict of interests: The authors declare they have no financial conflict of interest related to the study.

Data availability: The raw data used to support the findings of this study are available from the corresponding author upon request.

Author contributions: YM and QQ were responsible for experimental design, HX and QQ were responsible for data collection and analysis, YM and XH were responsible for article drafting and revising.

Ethic approval: The study followed the Declaration of Helsinki and was approved by Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine.

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