Keratoconus (KC) is a bilateral, asymmetric ectatic condition of the cornea that leads to inferior paracentral corneal steepening and irregular astigmatism. Typically, onset of KC is believed to occur at puberty, which tends to progress through adolescence, usually stabilizing at around the fourth decade of life. However, KC has also been reported to occur in younger children (<12 years of age), particularly among those from Middle Eastern and Asian ethnic groups. While KC in adults has been investigated extensively, the disease has not been well characterized in the pediatric population, especially the pre-teen age group.

Recent reports suggest that pediatric KC tends to be more severe and progresses more rapidly and aggressively than KC in adults. Ectasia in pediatric KC patients has also been noted to progress at a more rapid rate than in adults, and often coexists with vernal keratoconjunctivitis. On account of the advanced stage of the disease at presentation, pediatric KC bears a high risk of corneal scarring. In addition, since patients must contend with many more years of potential progression, there is often a greater need for corneal transplantation in these patients.

A detailed review of the literature indicates that information regarding the prevalence and incidence of KC in children is sketchy at best and altogether missing for very young children (2–12 years). We have, therefore, for the first time, undertaken this study to gather information on the clinical and presenting features of KC in a large cohort of young children from the pre-teen age group (2–12 years of age) in India.

Methods

The retrospective case series study protocol for this work was approved by the LV Prasad Eye Institute Human Research and Ethics Committee. The study protocol followed the tenets of the Declaration of Helsinki, and all privacy requirements for patients were met.

Setting

This study was conducted on patients examined at the cornea service at a tertiary eye care center in India.

Patients and study population

All medical records of patients seen between January 2006 and July 2015 were screened to obtain records of patients aged <12 years (at presentation) with a diagnosis of KC documented by topography or tomography. We chose this age range as per the United States Food and Drug Administration guidelines, wherein “children” are defined as the pediatric subpopulation of age 2–12 years. Patients with other active comorbid conditions of the eye were excluded from the study. Fig. 1 shows a flowchart of the numbers of pediatric patients suffering from KC included in the study, along with details of how the condition was managed.

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Keratoconus in pre-teen children: Demographics and clinical profile

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Purpose: To study the demographics and clinical profile of keratoconus (KC) presenting in pre-teen children in India. Methods: This was a retrospective case series conducted as a single-institutional study at a tertiary eye center in India. A total of 586 eyes from 294 KC patients (aged 12 years or less) without any active comorbid conditions of the eye were included in the study. Slit-lamp biomicroscopy was used to document the clinical signs of KC. Information on age; gender; reason for consultation; family history; history of allergy, atopy, and eye rubbing; manifest refraction; uncorrected and best-corrected distance visual acuity (UCVA and BCVA, respectively); clinical presentation; and contact lens usage were also analyzed, along with data on types of medical and surgical treatments for KC and their outcomes. Results: The mean age of this pediatric KC patient cohort was 9.3 ± 1.8 years, and there was a male (70%) preponderance. Baseline mean UCVA, BCVA, steep keratometry, and flat keratometry were 0.86 ± 0.58 logMAR, 0.44 ± 0.38 logMAR, 54.82 ± 8.4 D, and 48.21 ± 9.5 D, respectively. Progression, necessitating collagen crosslinking (CXL), was noted in 12.7% eyes. Post-CXL, visual and topographic parameters remained stable without any complications till 6 months posttreatment. However, in eyes that did not undergo CXL, significant progression over time (P < 0.001) was observed. A keratoplasty was required in 2.3% eyes. Conclusion: KC was present at an advanced stage in 25% of the pre-teens in our series, and therefore, it is an important diagnostic entity when a refractive error is diagnosed, even in very young children.

Key words: Crosslinking, early detection, keratoconus progression, pediatric keratoconus
Observational measures

The key variables recorded for each patient included details of age, gender, reason for consultation, family history, history of allergy and atopy, history of eye rubbing, manifest refraction, vision, contact lens usage, and any history of medical and surgical treatments. All patients included in the study underwent a detailed ophthalmic examination, including assessment of the uncorrected distant visual acuity (UCVA) and best-corrected distant visual acuity (BCVA), manifest refraction, slit-lamp biomicroscopy, and dilated fundus examination. Slit-lamp biomicroscopy included inspection of the ocular adnexa, conjunctiva, and cornea with documentation of corneal thinning and ectasia, Vogt’s striae, Fleischer ring, and the presence and severity of apical corneal scarring. The UCVA, BCVA (logarithm of the minimum angle of resolution [LogMAR]), sphere, cylinder, spherical equivalent (SE), and minimum (Kmin), average (Avg K), and maximum keratometry (Kmax) on corneal topography were noted during the first (baseline) and final visits. Orbscan topography was performed till 2008 and then replaced with advanced Pentacam imaging. As one can imagine, imaging in very young children was indeed challenging and needed repeated scanning till a reliable imaging was acquired.

Amsler–Krumeich’s classification was used to classify and assess the severity of KC.[14] Progression of KC was defined as an increase in the steepening of the central anterior corneal surface by more than 0.5 D (an increase of 0.5 D in Kmax) in consecutive examinations of corneal topography over a period of 3–6 months.[15,16]

Intervention procedure

Corneal collagen crosslinking (CXL) under general anesthesia was offered at the hospital as a treatment option for a limited subset of pediatric KC patients from 2010 onward due to lack of evidence of its safety and efficacy in this age group then.

Epithelium-off CXL following the standard Dresden protocol was performed in the early phase of the study, whereas in the later phase (since 2013), an accelerated protocol with 9 mW/cm² power for 10 min was followed.

Post-procedure, topical antibiotics were prescribed for a week and topical loteprednol 0.5% eye drops was tapered over a period of 4–6 weeks similar to the regimen followed in adult patients.

Statistical analyses

Statistical Package for the Social Sciences (SPSS) statistical software version 19 was used for all statistical analyses. Data normality was assessed using the Shapiro–Wilk test. The Wilcoxon signed rank test was used to compare vision and topography parameters at the first visit to those at the final visit. Comparisons in crosslinked and non-crosslinked eyes were performed at a minimum follow-up of 6 months or at the final visit [Table 1]. Results with a P value <0.05 were considered significant.

Results

Over a period of 10 years (2006–2015), a total of 5878 patients diagnosed with KC were examined at the hospital. Of these, 304 were children below 12 years of age (5.1%). Among these pre-teen children, 294 met the eligibility criteria and were included in the study. Ten children were excluded from the study due to incomplete data at diagnosis [Fig. 1]. The average duration of follow-up for the pediatric patients was 31.9 months (range: 6–84 months). The majority of subjects were boys (70%) with a mean age at diagnosis of 9.3 ± 1.8 years. The youngest age at presentation with KC in our cohort was 5 years. The demographic details of this pediatric cohort of KC patients are listed in Table 2. Unilateral KC with no topographic signs in the contralateral eye was seen in only two (0.68%) of the pediatric patients.

Clinical presentation

Details of the general characteristics and ocular symptoms of pediatric KC patients are presented in Table 2. Systemic atopic conditions like bronchial asthma were found to coexist in 3% of the subjects, and 17% of the subjects had history of ocular allergy. Frequent eye rubbing was reported in 36.73% subjects, which was either habitual or due to ocular itching induced by allergy.

A small proportion of the patients were also noted as having a positive family history of KC (6.5%), being the offspring of consanguineous marriages (4.08%), and suffering from Down’s syndrome (0.34%). The most commonly reported ocular symptoms at the time of presentation were blurred vision (38.4%) and eye redness with photophobia (31.9%). A small percentage (7.14%) of the patients were asymptomatic, and some of them presented (12%) as they had noticed a whitish appearance in their eyes.

The severity of KC, based on the Amsler–Krumeich’s classification was noted as grade 1 in 201 eyes (34.3%), grade 2 in 154 eyes (26.2%), grade 3 in 85 eyes (14.5%), and grade 4 in 146 eyes (24.9%) [Fig. 2].

The mean age of children with grade 1 KC was 10.2 ± 1.4 years (6–12 years), grade 2 KC was 9.1 ± 2.0 years (5–12 years), grade 3 KC was 9.7 ± 1.5 years (7–11 years), and grade 4 KC was 10.1 ± 2.1 years (6–12 years).
Table 1: Comparison of changes in visual and topographic measures for eyes that received CXL (crosslinked eyes) before (pre-CXL) and after (post-CXL) the treatment, as well as for those eyes that did not receive the treatment (non-crosslinked eyes) at baseline and the final visit

|                         | Crosslinked eyes (n=75) | Non-crosslinked eyes (n=511) |
|-------------------------|-------------------------|-----------------------------|
|                         | Pre-CXL (mean±SD)       | Post-CXL (mean±SD)         | P    | Baseline (mean±SD) | Final visit (mean±SD) | P     |
| BCVA (logMAR)           | 0.4±0.2                 | 0.4±0.3                     | 0.76 | 0.4±0.3            | 0.3±0.3                  | 0.09  |
| Kmax                    | 53.5±6.7                | 56.7±6.5                    | 0.79 | 54.8±8.4           | 57.3±8.2                  | ≤0.001|
| Kmin                    | 49.4±6.9                | 49.1±6.5                    | 0.66 | 48.2±19.5          | 51.4±6.8                  | ≤0.001|
| Avg K                   | 52.0±7.1                | 52.9±6.3                    | 0.94 | 52.0±7.0           | 54.1±8.3                  | ≤0.001|
| Thinnest pachymetry     | 430.6±91.8              |                            |      | 397.9±85.6         |                           |       |
|                         |                         |                            |      | 397.9±85.6         |                           |       |

BCVA=best-corrected distant visual acuity, CXL=collagen crosslinking, K=keratometry, SD=standard deviation. Mean duration of follow-up post-CXL was 8.1±1.2 months (6-13 months).

Table 2: Demographics and clinical presentation of keratoconus in pediatric patients

| Characteristics                      | Number of patients (%)/mean±SD |
|--------------------------------------|--------------------------------|
| Mean age at diagnosis (years)        | 9.3±1.8                        |
| Gender, male                         | 206 (70)                       |
| Clinical presentation                |                                |
| Asthma                               | 9 (3)                          |
| Ocular allergy                       | 50 (17)                        |
| Down’s syndrome                      | 1 (0.34)                       |
| Parental consanguinity               | 12 (4.08)                      |
| Positive family history              | 19 (6.5)                       |
| Eye rubbing                          | 108 (36.73)                    |
| Ocular signs                         |                                |
| Asymptomatic                         | 21 (7.14)                      |
| Blurred vision                       | 113 (38.4)                     |
| Redness and photophobia              | 94 (31.9)                      |
| Whitish appearance of the eye        | 12 (4)                         |
| Corneal parameters                   |                                |
| Steep keratometry, K1                | 54.8±8.4 D                     |
| Flat keratometry, K2                 | 48.2±9.5 D                     |
| Avg K                                | 51.99±7.1 D                    |
| Corneal thickness                    | 431±93 μm                      |

SD=standard deviation

The mean UCVA and BCVA at diagnosis were 0.86±0.58 and 0.44±0.38, respectively, and only 19.9% of the subjects had a spectacle-corrected BCVA of 0.3 or better. Baseline mean spherical and cylindrical refractive power were –3.50±1.6 and –4.80±2.7 D, respectively, and the mean value of the SE was –6.03±6.01 D.

Fig. 3 shows the distribution of corneal signs of KC in the study cohort. The most frequently noted clinical sign on slit-lamp examination was corneal thinning (38.56%), followed by Vogt’s striae (32.76%) and Fleischer ring (25.76%). Advanced disease at the initial presentation was seen in the form of apical corneal scarring (15.1%) and acute hydrops (4.6%), and 18.3% of the patients had associated active vernal keratoconjunctivitis requiring medical management.

The topographic indices in children with KC, noted at the initial presentation, are presented in Table 2. The majority of eyes (50.3%) had moderate to severe KC at diagnosis with an Avg K value of 51.99±7.1 D, based on the keratometry criterion for assessing severity. The most common location of the cone on corneal topography (34.8% of eyes) was inferotemporal.

KC management
Contact lenses were prescribed for at least one eye in 92 children (31.2%), which improved their visual acuity. The most common varieties of contact lenses used were rigid gas-permeable contact lens (66%) and Rose K lens (14%). Of the children who were prescribed contact lenses, 25 were done so following resolution of acute hydrops.

Contact lenses were dispensed to older children above 8 years of age with a mean age of 10.4±1.5 years (range: 8–12 years). Proper counseling was given to both parents.
and children about handling of contact lens and appropriate hygienic measures that are to be followed. Older children tolerated CL well with good compliance. We did not observe any contact lens-related complication in our study.

CXL was performed in 59 patients (75 eyes) to halt or slow the progression of KC. Of these, 16 patients underwent CXL in both eyes and 43 patients underwent the procedure in one eye only. Minimal haze was noticed in a few children, but none of them developed visually significant haze in our study. No major complications were reported in these patients following CXL.

In the patients who underwent CXL, the BCVA values remained stable and there were no statistically significant changes in the corneal topographic parameters pre- and post-CXL at 6 months follow-up (P > 0.05) [Table 1].

The mean duration of follow-up post-CXL was 8.1 ± 1.2 months (6–13 months). We did not observe any progression or treatment failure in crosslinked eyes during the study period.

The remaining 511 eyes which did not undergo CXL showed significant progression in KC as noted by corneal curvature and thickness measurements (P < 0.001) [Table 1]. The duration of follow-up in non-crosslinked eyes ranged from 6 to 48 months.

Corneal transplantation was performed in 14 eyes of 14 patients, with eight of them undergoing deep anterior lamellar keratoplasty (DALK) and six undergoing a penetrating keratoplasty. Out of the eight eyes that underwent DALK, three developed a graft infiltrate at the 1-month post-surgery visit. Microbiology cultures from corneal scrapings of these three eyes grew Streptococcus pneumoniae, Moraxella, and Staphylococcus aureus. The graft infiltrate resolved in two of these eyes with topical antibiotic therapy, with complete visual recovery. However, the graft with Moraxella keratitis failed over a period of 6 months. All the eyes that underwent penetrating keratoplasty did well until 1 year of follow-up, except for one eye, which eventually failed after an episode of rejection. Additionally, one graft required resuturing at 1-month post-surgery due to loose sutures.

Discussion

In this study, we present data on the characteristics, range of clinical features, and management of KC in a large cohort of pre-teen children aged 2–12 years in India. As of now, the available literature on KC includes very few reports on this condition in the pediatric population.[14,17] Experience in the clinic and the numbers of young children with KC examined at our institute led us to believe that this condition is not rare in young children in India. Over a span of 10 years (2006–2015), a total of 5878 patients were diagnosed with KC at our tertiary center. Of these, 51% were pre-teen children aged 12 years or younger, with the average age of presentation being 9.3 ± 1.8 years. Though this proportion appears to be relatively small, clinicians must be especially vigilant for KC cases in this age group as pediatric KC has been reported to be more severe at presentation, progress rapidly, and potentially impacts the patients for a longer period than KC in adults. It has also been reported that in pediatric KC, the interval between onset of functional symptoms and progression to a severe form of KC is shorter than for this condition in adults.[12]

In keeping with the generally observed trend that KC is more prevalent in males than in females,[14,18] our data also indicates that the condition was more common in male children, with about 70% of pediatric KC patients in our study cohort being boys. However, with regard to the prevalence of true unilateral KC in Asian populations, our data differs from previously reported values (4.3%); we find that in our cohort, the prevalence of true unilateral KC is only 0.6%, which is much lower than that cited by other studies.[18‑20] Almost all pediatric patients in our study exhibited bilateral KC; this fact, coupled with our observations of the rapidly progressive nature of the condition in this age group of patients, leads to suggest timely management of both eyes to maintain a better quality of life for pediatric KC patients.

KC is a multifactorial disease, and its manifestation is dependent on complex interactions between genetic and environmental factors. According to our observations, only 6.5% of pediatric patients had a positive family history of KC, with either a sibling or a parent being affected with the condition. The existing literature, however, indicates that the proportion of patients having a family history of KC varies from 6% to 23.5%.[14,21] Conversely, it is possible that our data may not represent a truly accurate measure of positive family history, since this information was based on what the patients’ parents have reported. Due to a lack of knowledge about the disease on the parents’ part, it is likely that this phenomenon may be underreported. Another factor in the development of KC is consanguinity. Gordon-Shaag et al.[22] reported that the chances of KC developing in children born of consanguineous marriages are four times higher than in children born of non-consanguineous marriages; this correlates with the findings of our study. In the light of these two points, we recommend that children presenting with a positive family history or parental consanguinity be screened regularly to monitor for early signs of KC. As an extension of this hypothesis, siblings of children with KC need to be screened for the disease as well.

Several studies report that environmental factors such as eye rubbing, atopy, and allergy may play a role in the progression of KC.[12,24] In accordance with these reports, we also find that many of the pediatric patients in our study exhibited these atopic conditions—18.3% had associated vernal keratoconjunctivitis and 36.73% had a history of eye rubbing. These numbers are in agreement with the results of a study by El-Khoury et al.[27] in which 43.8% of pediatric KC patients had a history of eye rubbing and 18.75% of these patients had allergies.[17] Although allergies are well-known causes for eye rubbing, it is possible that the allergies themselves may not be the precipitating factors for KC; this is because the percentage of patients who rubbed their eyes was far higher than the percentage of patients known to have allergies.[18,25] On the other hand, epithelial microtrauma, which is common in Down’s syndrome and is also caused by eye rubbing, vernal and atopic disease, as well as contact lens wear, could be a very important factor in the development and progression of KC.[25]

The most common presenting signs of KC observed in our data were corneal thinning (37.8%), followed by the presence of Vogt’s striae (32.76%) and Fleischer ring (25.76%) [Fig. 4]. In this, our data differed from those of Rabinowitz et al.,[21] who reported that the presence of Fleischer ring was the most common presenting sign of KC in an adult population.[13] Furthermore, we found that even at the time of diagnosis, 24.9% of the pre-teen population of KC in our study already exhibited grade 4 disease; this is very similar to the results
published by Léoni-Mesplié et al.,[^14] who reported that grade 4 disease occurred in 27.8% of French pediatric KC patients at the time of diagnosis, whereas only 7.8% of the adults in the same population presented such severity at the time of diagnosis.[^14]

Besides this, Gordon et al.[^26] reported that penetrating keratoplasty was required in 12% of pediatric KC patients over the course of 8 years of follow-up;[^26] however, in our study, only 1.02% of pediatric KC patients underwent keratoplasty. This difference could be attributed to our reluctance to perform keratoplasty in young children. Since keratoplasty can lead to potential complications like suture-related infiltrates[^27] and there is a need for more frequent administration of general anesthesia, this procedure is usually only recommended when all other options have been exhausted.

As of now, the most common methods of vision correction in KC include the use of spectacles, rigid gas-permeable contact lenses, and other specialized lenses.[^26] In our study, 66% of pediatric KC patients who used rigid gas-permeable contact lenses were comfortable using these lenses and had satisfactory vision. However, to halt the progression of pediatric KC, numerous studies have validated the safety and efficacy of CXL.[^29-31] Despite this, our data shows low usage of this intervention technique, as the procedure was offered as a treatment option only during the later part of the study (from 2010 onward). In addition, we were reluctant to offer CXL to very young KC patients initially due to lack of data about its effects for this age cohort in the existing literature. In the subset of pediatric KC patients in our study who did undergo CXL (12.7%), we observed a halt in the progression of KC and found no complications for up to 6 months of follow-up after the treatment. Chatzis and Hafezi,[^29] however, reported that the stabilizing effect of pediatric CXL might not last very long, as keratometric progression was observed in pediatric patients during a 3-year follow-up after the procedure.[^29] Conversely, due to the aggressive nature of the disease in pediatric patients and the coexisting risk factors such as eye rubbing, allergies, and a positive family history that could contribute to KC progression, the use of CXL (even for short-term stabilization) may be beneficial. Even we observed significant progression in the non-crosslinked eyes during the follow-up period, which emphasizes the importance of CXL at presentation, especially in young children with advanced KC. In fact, Chatzis and Hafezi[^29] propose that in pediatric and adolescent patients, CXL should be performed soon after diagnosis.[^29] As of now, however, there is no consensus about this proposed treatment pathway.

In conclusion, our data suggests that bilateral KC seems to be the predominant presentation in pre-teen patients. This, combined with advanced disease characteristics at presentation, may have profound impact on the long-term quality of life of these children, especially since KC is a progressive condition. All these findings suggest that we, as clinicians, must be aware of KC presenting in the pre-teens as a likely diagnosis and must be sought out, especially in children with a history of eye

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[^14]: Gordon et al.,[^26] Chatzis and Hafezi.[^29]
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rubbing or atopy. It may also be necessary to further explore the underlying etiology in pre-teen KC patients and develop a specific therapeutic algorithm to address associated conditions as well and consider stabilization of the disease with early CXL.

**Conclusion**

This manuscript presents the clinical characteristics of keratoconus in very young children aged less than 12 years and provides essential information about this entity, earlier believed to manifest later on in life.

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**Conflicts of interest**

There are no conflicts of interest.

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