Central corneal thickness and topographic indices in Malaysian children with vernal keratoconjunctivitis

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a chronic allergic disease characterised by intense ocular surface symptoms and corneal involvement. There is limited data about the corneal changes in children with VKC based on severity of the disease. We aimed to compare the central corneal thickness (CCT) and corneal topographic indices in Malaysian children with VKC, as well as among the varying grades of VKC severity.

Materials and Methods: This study is a comparative, cross-sectional and hospital-based study. We recruited 83 children with VKC and 83 healthy children as controls. All children underwent complete ocular examinations, CCT measurement using an ultrasound pachymeter and corneal topography using a Placido disc corneal analyser.

Results: There was a statistically significant difference of means CCT and topographic indices in children with VKC compared to controls (p<0.05). The probability keratoconus reached 18% in children with VKC. The mean CCT was observed to be thinnest in the severe-to-very severe groups of VKC compared to the mild-to-moderate (p<0.05). The means simulated-K1 and -K2, apical keratometry, apical gradient curvature, superior-inferior index and keratoconus prediction index were significantly different in severe-to-very severe VKC compared to mild-to-moderate VKC and controls (p<0.05). However, there was no significant difference in mean cylinder value and percent probability keratoconus when comparing different groups of severity of VKC (p=0.912 and 0.070 respectively).

Conclusion: Children with VKC have thinner CCT and topographic indices changes compared to healthy children. Similar pattern was observed between groups with VKC. Degree of astigmatism and probability of keratoconus were similar in mild-to-moderate and severe-to-very severe groups.

KEYWORDS:
Central corneal thickness, corneal topographic indices, children, vernal keratoconjunctivitis, severity

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic, bilateral, seasonal allergic inflammatory disease of the ocular surface. It is a chronic disease with episodes of acute exacerbation, primarily involving the tarsal and bulbar conjunctiva.[1,2] VKC has a wide geographical distribution. In the Asia-Pacific region, especially in Southeast Asian countries, no widely accessible studies have examined the prevalence of VKC. The closest available data that can be obtained is from the Allergies in Asia Pacific survey, which studied eight Asia Pacific countries and found that about 6-8% of the respondents from Malaysia had a physician diagnosis of acute rhinoconjunctivitis.[3]

VKC commonly occurs in school-age children aged six to 11 years old.[4,5] A male preponderance has been observed, especially in patients under 20 years of age,[4] who commonly present with symptoms of pruritus, hyperaemia, chemosis, photophobia and filamentous and sticky mucous discharge. VKC can be classified based on the site of predominant involvement, either tarsal, limbal or mixed type.[1] The late stage of the disease can present with severe and blinding complications involving the cornea, such as corneal scarring,[6] and amblyopia may be due to corneal opacity, irregular astigmatism and keratoconus.[7]

There are few studies highlighted corneal changes in VKC patients and control groups.[8-12] The chronic microtrauma caused by VKC can result in a chronic inflammatory process that damages the cornea, leading to a gradual loss of stromal mass. This can cause corneal thinning and steepening, resulting in acquired astigmatic refractive errors and, in severe cases, keratoconus which can be detected through pachymetry and corneal topography.[11]

Based on a PubMed search using corneal topography, VKC and severity as the keywords, we were unable to find published data comparing the severities of VKC in central corneal thickness (CCT) and corneal topography. It is essential for an early detection of subclinical keratoconus in patients with VKC. Early identification and prompt treatments should be instituted to prevent further complications leads to visual threatening conditions. This study aims to compare the mean CCT and corneal changes among these children with VKC, based on severity of the disease in two tertiary hospitals in the East Coast of Peninsular Malaysia.

MATERIALS AND METHODS

This research concerns a cross-sectional study conducted in the Ophthalmology Clinics of Hospital Universiti Sains

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Malaysia and Hospital Raja Perempuan Zainab II, Kelantan, Malaysia, from December 2020 to May 2022. Children who were diagnosed with VKC and healthy children aged between seven and 16 years old were recruited. The study was conducted in accordance with the Declaration of Helsinki for Human Research and approved by the Human Research Ethics Committee of Universiti Sains Malaysia, Malaysia (USM/JEPeM/20100531). Written consent and assent were obtained from the children and their parents.

Children who were diagnosed with VKC attended consultation visit at the ophthalmology clinics of both institutions were prospectively enrolled in the study. The healthy children were selected from the staffs' children in both institutions. The inclusion criteria for children with VKC were children diagnosed with VKC, aged seven to 16 years old. Healthy children were recruited from the same age group with no concurrent ocular diseases. Children who were known to have ocular pathology or who had undergone ocular surgery or trauma were excluded from the study. Additionally, healthy children to have a corneal scar, previous corneal diseases and refractive error exceeding ±3.00 spherical Dioptre (D) and -1.75 cylindrical D were also excluded from this study.

All children were screened for inclusion and exclusion criteria during the interview sessions. Demographic data, including age, race, gender, family history and education level, were taken. Systemic history included a history of any co-morbidity, allergic history, duration of diagnosis and current treatment. The ocular history included ocular symptoms, past ocular history of ocular trauma, intraocular surgery and refractive surgery. Complete ophthalmic examinations were performed, including visual acuity, refraction, anterior segment, intraocular pressure measurement and fundus examination.

Children with VKC were then classified into mild-to-moderate and severe-to-very severe groups based on the symptoms and signs after careful examination by the paediatric ophthalmologist during the first presentation.[13] Parameters measured were CCT and topographic indices, i.e. anterior corneal surface and keratoconus screening. These measurements were performed on the same day.

Measurement of the CCT was performed using the Ultrasound Pachymeter Pocket II (Quantel Medical, France) machine, where the tip probe contacted the cornea at the visual centre. To ensure the repeatability of the positioning of the of the pachymeter in subsequent measurements, a fixation panel was placed in front of the children. An average of five consecutive readings were used for the data analysis.

Anterior corneal surface and keratoconus screening were measured using Corneal Analyzer CA 800 (Topcon, Europe). The device is a Placido disc based corneal topographer that generates a variety of quantitative measurements. The recorded measurements for anterior corneal surface were simulated keratometry (Sim-K1 and Sim-K2) and astigmatism. Parameters recorded for keratoconus screening included apical keratometry, apical gradient curvature, superior-inferior index, keratoconus prediction index and percent probability keratoconus. The average of three consecutive readings was documented for data analysis.

The Sim-K1 and Sim-2 calculates the average keratometry powers of the steepest and flattest meridians in the paracentral zone of the cornea. It is considered abnormal when the value is above 48 D. Cylinder is the difference between Sim-K1 and Sim-K2 of more than 1.5 D. Apical keratometry represents the value of instantaneous curvature in the corneal apex greater than 50 D. Apical gradient curvature is the average difference per length unit of the corneal power in relation to the apical power greater than 2D/mm. The superior-inferior index is the difference of average power between the superior area and inferior with a value of more than 2D. Keratoconus prediction index is considered more than 20%. Percent probability of keratoconus below 20% is considered normal, while value between 20-45% is rank suspicious for keratoconus and above 45% is considered keratoconus in this study.[14-16]

The IBM SPSS Statistics for Windows Version 27.0 programme was used for sample description calculation (mean, median, standard deviation and total index). The T-test was selected for comparison of the mean CCT and the mean corneal topography parameters between children with VKC and the control group as well as among different grades of VKC severity. The significance level was set at 5% ($p<0.05$).

RESULTS

As shown in Table I, this study consisted of 172 Malay participants. Among them, 101 were male and 71 were female. The ages of the participants ranged from 7 to 16 years old, with a mean age of 11.8 (2.5) for the children with VKC and 11.9 (2.8) for the controls. The mean duration of the illness was 2.5 (1.5) years.

The majority of children with VKC comprised the tarsal type, which was 41 (47.7%), followed by the mixed 25 (29.0%) and limbal type in 20 (23.3%) children. Twenty-four (27.9%) children were categorised as mild in disease severity, 19 (22.1%) as moderate, 38 (44.2%) as severe and five (5.8%) as very severe. About 74.4% of the children rubbed their eyes occasionally (<5 times per day), and 25.6% rubbed their eyes frequently (≥5 times per day). All children with VKC involved in this study were on treatment. Thirty-eight (44.2%) children were on topical anti-allergic only, 43 (50.0%) children were on steroids and five (5.8%) children required surgical procedures.

We did not find any statistically significant differences between the right and left eyes with regard to the variables studied; thus, only the results for the right eye were reported. Tables II shows comparisons between the VKC group and the control group. The mean CCT was 539.9 (13.40)µm in the VKC group and 546.59 (12.17)µm in the control group. A statistically significant difference ($p<0.05$) was found in the mean CCT among the two groups. Meanwhile, a comparison of the means of corneal topographic indices between the two groups showed a statistically significant difference ($p < 0.05$). Children with VKC reached 18% probability keratoconus based on corneal topographic measurements.

Table I: Demographic and clinical data of children with VKC and controls

Variables	VKC (n = 86)	Control (n=86)	p-value
Age (years), mean (SD)	11.8 (2.5)	11.9 (2.8)	0.932[a]
Gender, n (%)			
Male	57 (66.3)	44 (51.2)	0.044b*
Female	29 (33.7)	42 (48.8)	
Types, n (%)		-	-
Tarsal	41 (47.7)		
Limbal	20 (23.3)		
Mixed	25 (29.0)		
Severity, n (%)		-	-
Mild	24 (27.9)		
Moderate	19 (22.1)		
Severe	38 (44.2)		
Very Severe	5 (5.8)		
Frequency of rubbing, n (%)		-	-
Less 5 times/day	64 (74.4)		
5 times or more/day	22 (25.6)		
Duration of illness (years)Mean (SD)	2.5 (1.5)	-	-
Treatment, n (%)		-	-
Topical anti-allergic	38 (44.2)		
Corticosteroid	43 (50.0)		
Surgical procedure	5 (5.8)		

VKC = Vernal keratoconjunctivitis; SD = Standard deviation
[a]Independent t-test; [b]Pearson chi-square test; *Statistically significant difference ($p < 0.05$).

Table II: Comparison of mean CCT and corneal topographic indices between children with VKC and controls

Variables	VKC (n = 86) Mean (SD)	Control (n = 86) Mean (SD)	Mean difference (95% CI)	t-statistic (df)	p-value
Pachymetry					
CCT (µm)	539.40 (13.40)	546.59 (12.17)	-6.651 (-10.5 to -2.8)	-3.407 (170)	0.01[a]*
Anterior corneal surface					
Simulated K1 (D)	45.77 (2.99)	43.97 (1.65)	1.80 (1.07 to 2.53)	4.88 (170)	<0.001[a]*
Simulated K2 (D)	47.07 (3.03)	44.71 (1.87)	2.36 (1.60 to 3.12)	6.14 (170)	<0.001[a]*
Cylinder (D)	1.32 (1.18)	0.72 (0.63)	0.60 (0.32 to 0.89)	4.19 (170)	<0.001[a]*
Keratoconus screening					
Apical keratometry (D)	48.57 (4.52)	45.72 (2.35)	2.84 (1.76 to 3.92)	5.17 (170)	<0.001[a]*
Apical gradient curvature (D/mm)	2.11 (3.30)	0.91 (0.85)	1.19 (0.47 to 1.92)	3.24 (170)	0.001[a]
Superior-inferior index (D)	1.24 (1.10)	0.77 (0.44)	0.47 (0.22 to 0.73)	3.71 (170)	<0.001[a]*
Keratoconus prediction index	13.67 (26.70)	2.41 (10.61)	11.27 (5.15 to 17.38)	3.64 (170)	<0.001[a]*
Percent probability keratoconus	21.90 (32.49)	3.62 (6.38)	0.18 (0.11 to 0.25)	5.12 (170)	<0.001[†]
Normal (less than 20%)*	66.0	93.0	NA	NA	NA
Suspicious (20-45%)*	16.0	7.0			
Keratoconus (more than 45%)*	18.0	0.0			

VKC = Vernal keratoconjunctivitis; SD = Standard deviation; CI = Confidence interval; D =Dioptre, *percentage, NA = Not applicable
[a]Independent t-test; *Statistically significant difference ($p < 0.05$).

Table III shows comparisons between mild-to-moderate VKC and severe-to-very severe VKC in the mean CCT and corneal topographic indices, respectively. The mean CCT in the mild-to-moderate VKC group was 546.79 (12.52)µm compared to 533.09 (10.52)µm in the severe-to-very severe VKC group. The difference between the two mean CCT values was found to be statistically significant ($p<0.05$). There was a statistically significant difference ($p<0.05$) between the two groups in almost all of the indices when comparing the means of corneal topographic indices between the two groups. Only the mean cylinder value ($p=0.912$) and percent probability keratoconus ($p=0.070$) was insignificantly different between the two groups. Probability keratoconus reached 9% in mild-to-moderate group and 26% in severe-to-very severe group.

DISCUSSION

VKC has been associated with CCT and corneal topographic changes in multiple studies.[8-10] We present new data on the means of CCT and corneal topography in children with VKC in this hospital-based study. Our study differs from others because we included a comparison of both the means of CCT and corneal topography between different severities of VKC. This information is important for an early detection of

Table III: Comparison of mean CCT and corneal topographic indices between mild to moderate VKC and severe to very severe VKC

Variables	Mild to moderate (n = 43) Mean (SD)	Severe to very severe (n = 43) Mean (SD)	Mean difference (95% CI)	t-statistic (df)	p-value
Pachymetry					
CCT (µm)	546.79 (12.52)	533.09 (10.52)	13.70 (8.74 to 18.66)	5.49 (84)	<0.001[a]*
Anterior corneal surface					
Simulated keratometry1 (D)	44.51 (2.23)	47.04 (3.15)	-2.53 (-3.70 to -1.36)	-4.30 (84)	<0.001[a]*
Simulated keratometry2 (D)	45.80 (1.82)	48.35 (3.46)	-2.55 (-3.73 to -1.36)	-4.27 (84)	<0.001[a]*
Cylinder (D)	1.33 (1.42)	1.31 (0.90)	0.28 (-0.48 to 0.54)	0.11 (84)	0.912 [a]
Keratoconus screening					
Apical keratometry (D)	46.33 (1.94)	50.80 (5.23)	-4.47 (-6.16 to -2.78)	-5.26 (84)	<0.001[a]*
Apical gradient curvature (D/mm)	1.06 (1.00)	3.15 (4.34)	0.68 (-3.43 to -7.35)	-3.07 (84)	0.003[a]*
Superior-inferior index (D)	0.77 (0.44)	1.71 (1.34)	-0.94 (-1.37 to -0.51)	-4.35 (84)	<0.001[a]*
Keratoconus prediction index	1.26 (3.20)	26.09 (33.42)	-24.84 (-35.02 to -14.66)	-4.85 (84)	<0.001[a]*
Percent probability keratoconus	0.12 (0.27)	0.31 (0.35)	-0.19 (-0.32 to -0.05)	-2.80 (84)	0.070[a]*
Normal (less than 20%)*	80.0	51.0	NA	NA	NA
Suspicious (20 45%)*	9.0	23.0			
Keratoconus (more than 45%)*	9.0	26.0			

VKC = Vernal keratoconjunctivitis; SD = Standard deviation; CI = Confidence interval; D = Dioptre, *Percentage, NA = Not applicable
[a] Independent t-test; *Statistically significant difference (p< 0.05).

subclinical keratoconus prior to reduced visual acuity, changes in cylinder values and keratometric changes.

In our demographic result, there was a statistically significant difference in gender between children with VKC and controls (p<0.05). VKC was found to be two times more common in males than in females, with a total of 57 (63%) male subjects and 29 (33.7%) female subjects. This male-biased pattern is aligned with previous studies that have reported male-to-female ratios ranging from 4:1 to 2:1.[11,12,17]

Our study shows that the mean CCT is thinner in the children with VKC when compared to the control group (p<0.05). This result is consistent with several published studies on the same topic.[18-20] Meanwhile, Kavitha et al. reported no significant difference in the mean CCT between the VKC group and the controls.[21] We found a similar trend of finding when comparing the mild-to-moderate group with the severe-to-very severe group (p<0.05).

Several factors have been hypothesised to contribute to a thinner CCT in the VKC. In susceptible individuals, the act of rubbing the eyes can cause microtrauma, injuring the epithelium and triggering the release of cytokines, differentiation of myofibroblasts, a shift in biomechanical forces and thinning of corneal tissue.[22,23] Research has demonstrated that rubbing the eyes increases the level of matrix metalloproteinase-13 (MMP) in tears, which plays a crucial role in the apoptotic activity of keratocytes. This leads to a loss of stromal volume as the extracellular matrix is degraded, leading to thinning and ectasia of the cornea.[10,24,25] The tears of patients with VKC were found to contain higher levels of the active forms of MMP-2 and MMP-9 compared to healthy individuals, suggesting that these two MMPs may contribute to the corneal thinning frequently observed in VKC patients.[10,26]

In our study, children with severe-to-very severe VKC had significantly higher values in almost all corneal topographic indices (i.e. Sim-K1, sim-K2, apical keratometry, apical gradient curvature, superior-inferior index and keratoconus prediction index) compared to the mild-to-moderate VKC group (p<0.05). The mild-moderate group showed 9% probability of keratoconus, while severe-severe group reached 26% based on more than 45% probability keratoconus. This group needs a close monitoring as they may reach clinical detection of keratoconus if the disease progresses. The other previous studies reported that keratoconus-like topography ranged from 14-27% in patients with VKC.[18,27-31]

Among the recorded indices, the level of astigmatism extracted from the cylinder value was significantly higher in the VKC group compared to the controls (p<0.05). This finding is in agreement with reports published by Gupta et al. and Thiagarajan et al.[29,30] However, when comparing VKC groups based on severity, mild-to-moderate VKC and severe-to-very severe VKC, the difference in astigmatism was statistically insignificant (p=0.912). Thus, we hypothesise that these outcomes may reflect that even at a lower frequency, eye-rubbing in mild-to-moderate VKC patients causes mechanical and biochemical trauma to the cornea, which leads to mild astigmatic changes.

CONCLUSION

Children with VKC showed significantly thinner CCT and topographic indices changes compared to healthy children. The similar observations were displayed by the severe-very severe group compared mild-moderate group except for astigmatism and percent probability keratoconus remains insignificant between the two groups.

Thus, it is crucial to diagnose and treat even the mildest forms of corneal involvement in VKC, as delays in the management of corneal complications could lead to poor visual outcomes. Routine corneal thickness and topography assessment is recommended for children with VKC.

CONFLICT OF INTEREST

None

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