

# Topographic corneal changes in patients with vernal keratoconjunctivitis

## *Alterações topográficas da córnea em pacientes com céra-to-conjuntivite vernal*

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### ABSTRACT

**Purpose:** To carry out a case-control clinical study in patients with vernal keratoconjunctivitis, aiming at information about the anterior corneal curvature and visual performance using a quantitative corneal descriptor analyzer (Holladay Diagnostic Summary). **Methods:** We examined 342 eyes of 171 patients divided into 2 groups. Group 1 with 142 eyes of 71 patients with a clinical diagnosis of vernal keratoconjunctivitis (cases) and Group 2 with 200 eyes of 100 patients (controls) from the Department of Ophthalmology/"Santa Casa" of São Paulo. Patients were submitted to a complete examination and corneal topography with a quantitative corneal surface contour descriptor (Holladay Diagnostic Summary). Clinical and topographic criteria were established to diagnose keratoconus in both groups. **Results:** The frequency of patients with a clinical diagnosis of keratoconus associated with vernal keratoconjunctivitis in Group 1 was 9.85% (7 patients). According to topographic criteria, the frequency in Group 1 was 22.53% (16 patients). In Group 2, no patient presented biomicroscopic, refractometric or topographic characteristics of keratoconus. All studied topographic variables, including corneal asphericity, presented statistical significance ( $p < 0.05$ ) between the two groups. **Conclusion:** Results of this study suggested high frequency of patients with keratoconus associated with vernal keratoconjunctivitis. Visual performance is compromised by aberrations and changes in corneal asphericity and other topographic variables.

**Keywords:** Conjunctivitis, allergic/diagnosis; Conjunctivitis, allergic/epidemiology; Keratoconjunctivitis; Keratoconus; Corneal topography; Cornea/pathology

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### INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a chronic allergic disease, with seasonal periods of exacerbation, predominantly observed in children and youngsters, inhabitants of hot and dry climates such as The Middle East, North Africa and parts of South America, being rare in North Europe and North America, where it seems to be of a milder clinical presentation<sup>(1)</sup>. Although it often presents as a relatively benign and self-limited condition, VKC has the potential to induce serious visual changes, not only as result of the disease itself, but also due to the complications associated with its evolution and management. Long standing disease and disabling lesion such as corneal ectasia have been reported descriptively as a complication of severe and prolonged VKC<sup>(2)</sup>. Chronic ocular trauma could be the environmental factor ("trigger") associated with keratoconus development in genetically predisposed individuals. Data from the literature suggest that the prolonged, slow

release of small amounts of degradative enzymes induced by chronic corneal epithelial trauma could cause tissue damage<sup>(3-5)</sup>.

Clinical and qualitative analyses have been done to study the frequency of the association between VKC and keratoconus<sup>(2,6-8)</sup>, indicating that a considerable number of patients with subclinical presentation of keratoconus could underestimate the statistics of this association. Quantitative analysis of the topographic characteristics of the anterior corneal surface by computerized corneal topography in patients with VKC may be a useful tool, either from the epidemiologic or the pathophysiologic point of view.

Recently, Totan et al., demonstrated that nearly 27% of VKC patients had abnormal VKG patterns but the authors did not compare them with the control group<sup>(9)</sup>. Lapid-Gortzak et al., found an abnormal pattern of corneal topography in nearly 71% of VKC patients, but only 15% (6 out of 40 patients) presented with topographically detected keratoconus<sup>(10)</sup>.

Taking into consideration the importance of accumulating data regarding the association of VKC with keratoconus from the epidemiologic, genetic and pathophysiologic view, we aimed to establish the frequency and correlation of keratoconus and VKC, analyzing the corneal contour pattern of patients with VKC by quantitative analysis of cornea curvature and to evaluate the repercussion upon the patient's visual performance, in order to answer the following questions:

1. What is the frequency of the association between VKC and keratoconus in the observed population?
2. When compared to controls, is there any change in the quantitative parameters of the corneal contour in patients with VKC? If altered, what are the more frequent forms of this change?
3. Is there any correlation between corneal asphericity and the visual performance in patients with VKC?
4. Is there any correlation between corneal asphericity and the parameters used in the Holladay Diagnostic Summary?
5. Is there any correlation between the presence of keratoconus and the VKC form of clinical presentation, disease duration and gender?

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## METHODS

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### Study design

A case-control study was designed aiming to characterize aspects related to anterior corneal surface curvature changes in individuals with VKC, using a quantitative and descriptive method of corneal topography.

### Sample size and study power calculation

To calculate the size and power of the studied sample, we used two computer software: *Power and Sample Size Calculation* version 1.0.13™, from the Vanderbilt University, USA\*. We considered a statistical significance minimum level of 95%

\*available in: <http://www.mc.vanderbilt.edu/prevmed/>

( $p < 0.05\%$ ),  $\alpha$  error (risk of rejecting the null hypothesis  $H_0$ , when it is correct) of 0.05 and  $\beta$  error (risk of accepting the null hypothesis  $H_0$ , when it is false) of 0.01%. To preserve the statistical power of the study, we used a ratio of 1.5 controls/1 case. Using a statistical method described in the literature<sup>(11)</sup>, and the above mentioned variables, 70 cases and 100 controls would be necessary to obtain a statistical power of 95%.

### Patient selection

We examined 342 eyes from 171 patients, divided into two groups:

- Group 1: Included 142 eyes of 71 patients with clinical diagnosis of VKC from the Outpatient Clinic of Allergy, Corneal and External Disease Service, from March to December 2000. Patient mean age was  $10.61 \pm 3.96$  years (ranging from 4 to 22 years). There were 20 females (28%) and 51 males (72%).
- Group 2: Included 200 eyes of 100 patients from the Department of Ophthalmology, with non-corrected visual acuity of 20/20 and negative clinical history of corneal disease, ocular or systemic allergy and previous ocular surgery, during the same period of time (February to October 2000). Mean age of this group was  $9.77 \pm 3.15$  years (ranging from 5 to 20 years). There were 33 females (33%) and 67 males (67%).

All patients were submitted to full ophthalmologic examination and corneal topography. Videokeratography was done using a quantitative optical corneal contour descriptor (Holladay Diagnostic Summary), that provides standard maps, corneal asphericity values, the corneal refractive power, the corneal shape compared to the normal cornea in each analyzed point, the optical quality of the cornea in each analyzed point and 15 specific parameters, such as effective refractive power, simulated keratometry and corneal uniformity index, among others.

This study was approved without restrictions by the Ethics in Medical Research Committee of the "Santa Casa de São Paulo" Medical School, with subsequent revision and approval by the Ethics in Research Committee of the University of São Paulo. All patients, parents or responsible relatives were previously informed and signed an informed consent to participate in this study.

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## DIAGNOSTIC CRITERIA FOR KERATOCONUS

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### 1. Clinical

To characterize clinical keratoconus, we established that at least 4 of the following clinical findings should be present:

#### 1.1. Biomicroscopy

- Munson's signal;
- Central or paracentral stromal thinning, with or without scarring;
- Vogt's striae;
- Fleischer's ring.

## 1.2. Refractometry

- Detectable irregular astigmatism (“scissoring reflex” or “drop oil” retinoscopic signal).

## 2. Topographic

The combination of at least 4 of the following topographical finding, would confirm keratoconus as keratoconus:

- Localized area of corneal steepening greater than 47.00 D in the standard scale map (“true refractive corneal power”) and auto-scale;
- Differential profile map with steeper topographical pattern, with positive value ( $>0.50$ );
- Irregular astigmatism detected in the topographical map (*Steep RP and flat RP* not perpendicular);
- Average central simulated keratometry higher than 47.20 D;
- Optical quality (Corneal uniformity index - CUI) less than 90%.

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## STATISTICAL METHODS

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### 1. Descriptive statistics of the samples (demographics)

Groups with VKC and controls were described by arithmetic mean and standard deviation. To test evenness between the groups, we used the  $\chi^2$  (*chi-square*) test.

### 2. Analytic or comparative statistics of general data

Data related to the presentation of VKC (ordinal data) and extent of the disease (numerical data) received statistical treatment and were used for correlation analysis with keratographic data using Pearson’s correlation test for parametric data and Spearman’s and Kendall’s correlation for non-parametric data.

### 3. Analytic or comparative statistics of videokeratographic data

To facilitate the statistical study, we used the correlation test suggested by Ederer<sup>(12)</sup> and, given the positive correlation between data from right and left eye, we randomly choose the right eye and its variables for statistical treatment.

Videokeratographic data from the right eyes of both groups were submitted to the statistical asymmetry index, where:

$$A = \frac{X - M_o}{SD}$$

A= asymmetry index of a sample; X= sample mean; Mo= mode; SD= standard deviation of a sample

Asymmetric values lower than 1 were considered as parametric and statistically analyzed using Student’s *t* test for independent samples. Asymmetric values greater than 1 were considered non-parametric and statistically analyzed using the Mann-Whitney, Kolmogorov-Smirnov and Kruskal-Wallis tests.

We used a minimum statistical level of significance of 95% ( $p < 0.05$ ) in all applied tests.

To improve statistical data interpretation of visual acuity,

values related to the Snellen visual acuity scale were converted into logarithmic values, as suggested by Holladay<sup>(13)</sup>.

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## RESULTS

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### 1. Demographic analysis

Table 1 details demographic characteristics of each group and comparative statistics. There was no statistical significance between the two studied groups ( $p > 0.05$ ).

### 2. General and videokeratographic data

#### a. Frequency of the association between VKC and keratoconus

The frequency of patients with a clinical diagnosis of keratoconus associated with VKC in Group 1 was 7 patients (9.85%). In Group 2, none of the patients presented biomicroscopic and/or refractometric signs of keratoconus.

According to the established criteria for the topographic diagnosis of keratoconus, in Group 1, 16 patients were diagnosed with keratoconus (22.53%). None of the patients in Group 2 presented topographical characteristics compatible with the diagnosis of keratoconus.

The difference between clinical and topographic diagnosis was statistically significant ( $p < 0.05$ ).

#### b. Analysis of topographic parameters

All analyzed topographic variables presented statistical significance ( $p < 0.05$ ) between the groups (Table 2). Because its asymmetric index was  $>1$ , asphericity was studied by non-parametric methods.

#### c. Corneal asphericity and VKC

Only corneal asphericity (Q) presented asymmetric distribution ( $A > 1$ ), being analyzed by non-parametric tests (Kolmogorov-Smirnov, Mann-Whitney e Kruskal-Wallis). There was a statistically significant difference between the groups ( $p < 0.05$ ) (Table 3).

#### d. Statistical correlation of corneal asphericity and topographic parameters

There was a statistically significant correlation between these parameters in Group 1 ( $p < 0.05$ ).

**Table 1. Demographic characteristics of patients with (Group 1) and without VKC (Group 2)**

Group	Number of patients	Age Mean $\pm$ SD	Gender		p
			Male	Female	
1	71	10.61 $\pm$ 3.96	51 (72%)	20 (28%)	0.12
2	100	9.77 $\pm$ 3.15	67 (67%)	33 (33%)	0.13

Source: Department of Ophthalmology, “Santa Casa” of São Paulo, 2000

### e. Keratoconus, VKC and other variables (Table 4)

Of the patients with keratoconus diagnosed by topographic pattern (16 of 71 patients or 22.53%), 12 (75%) were males

	Groups	N	Mean	Standard deviation	p
VARE	1	71	0.3	0.4	0.001*
	2	100	0.0	0.0	
VALE	1	71	0.2	0.4	0.001*
	2	100	0.0	0.0	
AKRE	1	71	45.71	6.9	0.03*
	2	100	43.85	2	
AKLE	1	71	45.85	7.7	0.03*
	2	100	43.72	2	
PCARE	1	71	0.6	0.3	0.001*
	2	100	0.1	0.1	
PCALE	1	71	0.7	0.3	0.001*
	2	100	0.1	0.1	
CUIRE	1	71	82.67	25.63	0.001*
	2	100	98.80	3.83	
CUILE	1	71	83.57	27.02	0.001*
	2	100	99.00	4.14	
ERPRE	1	71	46.01	7.02	0.02*
	2	100	44.01	2.06	
ERPLE	1	71	46.31	7.59	0.01*
	2	100	43.86	2.00	

Source: Department of Ophthalmology, "Santa Casa" of São Paulo, Brazil, 2000. VARE= Visual acuity in the right eye (logMar); VALE= Visual acuity in the left eye (logMar); AKRE= Average keratometry in the right eye (in diopters); AKLE= Average keratometry in the left eye (in diopters); CUIRE= Corneal Uniformity Index in the right eye (in percentage); CUILE= Corneal Uniformity Index in the left eye (in percentage); ERPRE= Effective refractive power in the right eye (in diopters); ERPLE= Effective refractive power in the left eye (in diopters); \*= statistically significant. PS= Data from left eyes appears for informative reference.

	Groups	N	Mean	Standard deviation	p
QRE	1	71	-0.36	0.77	0.021*
	2	100	-0.14	0.10	
QLE	1	71	-0.36	0.60	0.002*
	2	100	-0.13	0.11	

Source: Department of Ophthalmology, "Santa Casa" of São Paulo, Brazil, 2000. QRE= Right eye corneal asphericity; QLE= Left eye corneal asphericity; \*= statistically significant. PS= Data from left eyes appears for informative reference.

Patients with topographical keratoconus	Gender	Visual acuity (logMar)	Central keratometry (AK RE) in diopters	Presumed corneal acuity (PCA RE) (logMar)	Corneal uniformity index (%) (CUI RE)	Effective refractive power (ERP RE) in diopters	Corneal asphericity (Q RE)
N=16 (22.53%)	12 Males (75%) 4 Females (25%)	0.89±0.48	58.91±7.07	0.50±0.27	43.33±17.23	59.75±6.64	-1.01±1.49

Source: Department of Ophthalmology, "Santa Casa" of São Paulo, Brazil, 2000.

and 4 (25%) were female. Mean age was of 13.9±4.3 years. The patients in these groups presented VA of 0.89±0.48 LogMar in the right eye, average simulated keratometry (AK) of 58.91±7.07 diopters, presumed corneal acuity (PCA) of 0.50±0.27, corneal uniformity index (CUI) of 43.33±17.23, effective refractive power (ERP) of 59.75±6.64 diopters and corneal asphericity (Q) of -1.01±1.49.

Two patients (12.5%) with paracentral keratoconus presented a remarkable oblate cornea (Q=1.99), and 13 patients (81.25%) presented a remarkable prolate cornea (Q > -1.27). Only one patient with keratoconus presented normal corneal asphericity (Q=-0.14), with VA of 0.10 LogMar.

### f. Keratoconus and VKC clinical presentation

Sixty-nine out of 71 examined patients (97.18%) presented the palpebral form and two (2.81%), the limbal form. No patient presented the mixed form of the disease.

The palpebral form of presentation was associated with 100% of the keratoconus cases, diagnosed either by topography or clinically.

### g. Keratoconus and disease duration

In patients of Group 1, the mean age at early systemic symptoms of allergy (rhinitis, bronchitis) was 6.9±4.7 years. The interval between early symptoms of allergy and ocular symptoms (itchy and red eye) that led the patient to ophthalmologic evaluation was 3.8±4.2 years. In patients with keratoconus, the age at the beginning of allergic systemic symptoms was 10.4±5 years and the interval between the early systemic symptoms and the ocular symptoms that led the patient to ophthalmologic examination was 6.5±4.3 years.

## DISCUSSION

Data obtained by the topographic analysis of the corneal anterior surface of both groups clearly demonstrated that patients with VKC presented corneal contour changes when compared to patients with normal corneal asphericity. Of evident clinical interest, is the fact that the mean anterior corneal curvature of patients with VKC was more accentuated than in the control group (p<0.05). The parameters that verify anterior corneal contour such as AK and ERP, presented significantly higher values in patients with VKC (p<0.05). Previous studies on human ocular development demonstrated that mean kera-

tometric values of normal individuals, from the age of less than 3 years to adult life, are 43.00 to 44.00 D, with minimal, if any, changes during lifetime<sup>(14-15)</sup>.

It is important to emphasize that the observed statistically significant difference between patients with VKC and keratoconus diagnosed by clinical criteria (9.85%) and patients diagnosed exclusively by topographic criteria (22.53%) ( $p < 0.05$ ), demonstrated that approximately 1 of 4 patients with VKC presented topographic corneal change of the corneal anterior surface related to keratoconus, undetected by the clinical examination. The frequency of this association described in the literature, when exclusively clinical criteria are used, is lower than our findings, varying from 2%<sup>(16)</sup> to 12.5%<sup>(8)</sup>. The use of corneal videokeratography as an accessory tool in diagnosing keratoconus may allow quantitative and qualitative diagnosis of early or subclinical forms of keratoconus presentation, usually undetectable when only refractometric, biomicroscopic and keratometric data are considered<sup>(9-10,17)</sup>.

Steeper corneal curvature (AK and ERP) and higher negative asphericity (Q), associated with low corneal uniformity index (CUI) and consequently with poor visual performance (PCA), were evident in the group of patients with VKC when compared to the control group ( $p < 0.05$ ). In patients with VKC and keratoconus (22.53%), the same above mentioned parameters above were more expressive and evident even when compared to patients with VKC without keratoconus ( $p < 0.05$ ).

In the group of patients with VKC and keratoconus diagnosed by corneal topography, the initial allergic symptoms presented later ( $10.4 \pm 5$  years) and remained for a long time, until the first changes in visual performance ( $6.5 \pm 4.3$  years), when compared to patients with VKC without keratoconus ( $6.9 \pm 4.7$  years and  $3.8 \pm 4.2$  years, respectively), suggesting that disease chronicity could be related to the severity of corneal ectasia. The same reasoning could be applied to the form of clinical presentation, once the palpebral form of the disease was found in 100% of the cases with keratoconus associated with VKC.

The above mentioned findings suggest that, in susceptible individuals, long-term disease with a chronic traumatic factor on the corneal epithelium could be related to keratoconus, because, as Kim et al., pointed out, persistent and chronic corneal trauma on the corneal epithelium (in this particular situation, itching or chronic trauma provoked by giant papillae), induces a "silent" and chronic inflammatory process, leading to progressive loss of stromal mass and consequently to less biomechanical resistance, and thus to anterior corneal steepening, decreasing the optical competence of the anterior corneal surface<sup>(3)</sup>.

In patients with VKC, corneal uniformity (CUI) and optical quality (PCA) were more affected ( $p < 0.05$ ). This could be responsible, at least in part, for the low mean visual acuity found in these patients ( $0.29 \pm 0.45$  LogMar). Contributing to the low visual acuity, we found statistically significant correlation between VA, indexes that monitor the anterior corneal curvature (AK and ERP), corneal uniformity (CUI) and optical quality of this surface (PCA), showing that a steeper cornea

with CUI less than 80%, could lead to either low VA or PCA ( $p < 0.05$ ). It is important to emphasize that the cornea is the predominant refractive component, when the eye is considered *in totum* in the evaluation of visual performance, contributing with more than 80% to the non-accommodative refractive power of the eye. Disturbances in visual performance, such as below normal best-corrected visual acuity, low contrast sensibility, and subjective visual symptoms are strongly related to anterior corneal surface topographical aberration<sup>(18)</sup> and their relationship has been described in eyes with keratoconus<sup>(19)</sup>.

Regarding corneal asphericity, there was a significant statistical difference between Group 1 (patients with VKC) and the control group ( $p < 0.05$ ). In the majority of the cases, patients with VKC presented more prolate corneas (more negative Q) than the controls ( $p < 0.05$ ), meaning discrepancy between steeper central cornea and flatter periphery. In patients with VKC and keratoconus ( $n = 16$ ), this difference became pathologic, meaning steeper central cornea, due to the cone in 13 patients (81.25%) with  $Q > -1.27$ . Two patients (12.5%) with paracentral keratoconus presented more oblate corneas ( $Q = 1.99$ ). Only one patient with VKC and keratoconus presented normal cornea asphericity ( $Q = -0.14$ ), with VA of 0.10 LogMar and 60% CUI. There was a positive correlation between Q, CUI, ERP, PCA and AK ( $p < 0.05$ ), influencing the low visual performance in these patients. A cornea with abnormal asphericity could generate excessive corneal optical aberration, resulting in monocular diplopia, low VA, low contrast sensibility and glare in low mesopic and scotopic conditions<sup>(19)</sup>.

In Brazil, VKC seems to be the most common presentation of ocular allergy, being responsible for 53.2% of all the patients seen in the Outpatient Clinic of Ocular Allergy at the Department of Ophthalmology of the "Santa Casa" of São Paulo, according to statistics of the last 3 years, conflicting with the available literature, generally from Europe and the United States of America, where seasonal or perennial allergic conjunctivitis are predominant (60% of all cases). In Europe, specifically in Italy, VKC represents only 8% of all cases of allergic conjunctivitis<sup>(20)</sup>. Additionally, we found keratoconus associated with VKC at an earlier mean age ( $13.9 \pm 4.3$  years) than that described in the literature. Statistical data available show a frequency of only 2.1% of patients in the age range of 8 to 16 years in the normal population<sup>(21)</sup>. Such numbers are alarming, if we consider that VKC characteristically affects school-age children and has the potential to induce severe visual disability, right at the initial phase of intellectual formation. Moreover, a child diagnosed with keratoconus represents a real challenge to the ophthalmologist. Eyeglasses are frequently unable to correct the refractive error induced by corneal aberration and contact lenses are difficult to fit in these patients. Surgical treatment of keratoconus at this age is difficult and involves increased risk of rejection. We believe that using methods to early detect abnormal anterior corneal surface curvature associated with a rigid therapeutic control of those patients, avoiding chronic trauma on the corneal epithelial cells could be of great value in the prevention and control of

corneal ectasia in patients with VKC. Long-term prospective clinical studies are necessary to confirm this hypothesis.

The inferences related to the clinical findings in this study are applicable, from a statistical point of view, to the population that supplied the samples, however extrapolation to the general population could be made.

In the proposed conditions of this study, we conclude that:

There was higher frequency of keratoconus in patients with VKC (22.53%) than in the control group when computerized videokeratoscopy was used as instrument of detection. This number is significantly higher than that detected by clinical criteria (9.85%).

Patients with VKC presented corneal asphericity changes when compared to the control group, with a tendency of a steeper mean keratometric curvature. In those with VKC and keratoconus, corneal change is expressed by prolate cornea (negative asphericity higher than -0.85), found in 81.25% of them.

Corneal asphericity alone demonstrated to affect visual acuity of patients with VKC and keratoconus. There was a positive statistical correlation between corneal asphericity, visual acuity and PCA.

Changes in corneal asphericity associated with other parameters used by the Holladay Diagnostic Summary have a significant effect on the low visual performance in patients with VKC and keratoconus.

There was correlation between the diagnosis of keratoconus and the clinical presentation of VKC (100% palpebral), disease during (the longer the duration of the disease, the higher the corneal distortion) and gender (predominant in males).

## RESUMO

**Objetivo:** Propôs-se estudo clínico caso-controle de pacientes com cérateo-conjuntivite vernal, com finalidade de obter-se, por meio de descritor quantitativo da superfície anterior da córnea (Sumário diagnóstico de Holladay), informações sobre as alterações topográficas, que pudessem determinar a frequência da associação entre cérateo-conjuntivite vernal e ceratocone, além de seus efeitos sobre o desempenho da visão destes pacientes.

**Métodos:** Foram examinados 342 olhos de 171 pacientes divididos em 2 grupos. Grupo 1 com 142 olhos de 71 pacientes com diagnóstico clínico de cérateo-conjuntivite vernal (casos) e Grupo 2 com 200 olhos de 100 pacientes do Departamento de Oftalmologia da Santa Casa de São Paulo (controles). Todos os pacientes foram submetidos a exame oftalmológico completo, além de topografia de córnea com o uso de descritor quantitativo do contorno óptico da superfície anterior da córnea (Sumário diagnóstico de Holladay). Critérios clínicos e topográficos foram estabelecidos para o diagnóstico de ceratocone nos grupos estudados. **Resultados:** Diagnóstico clínico de ceratocone associado a cérateo-

conjuntivite vernal correspondeu a 9,85% (7 pacientes), ao passo que 22,53% (16 pacientes), de acordo com critérios estabelecidos para diagnóstico topográfico, apresentavam ceratocone no Grupo 1 ( $p < 0,05$ ). **Conclusões:** Os resultados obtidos neste estudo mostram alta frequência de ceratocone em pacientes com cérateo-conjuntivite vernal. A performance visual destes pacientes é influenciada pelas aberrações provocadas por alterações da asfericidade corneal e de outras variáveis topográficas.

**Descritores:** Conjuntivite alérgica/diagnóstico; Conjuntivite alérgica/epidemiologia; Ceratocone; Topografia de córnea; Córnea/patologia

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