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DATE 1/13/2020
JOB NAME CORNEA

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MS NO: CORNEA-D-19-00964

A Case-Control Study of Keratoconus Risk Factors

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Purpose: To evaluate risk factors associated with keratoconus in a case-control setting.

Methods: This single center, prospective, case-control study was carried out from May 2014 to November 2017 at the Rothschild Foundation (Paris, France). Two hundred two patients with keratoconus and 355 control patients were investigated and followed by a single ophthalmologist. Data regarding multiple variables were gathered, including eye rubbing, pattern of eye rubbing, dominant hand, allergies, history of dry eye, screen time, sleep position, and night-time work.

Results: After multivariable analysis, the following variables showed significant results: eye rubbing with knuckles [odds ratio (OR) = 8.29; 95% confidence interval (CI): 3.92–18.26, $P < 0.001$] or fingertips (OR = 5.34; 95% CI: 2.44–12.21, $P < 0.001$), a history of dry eye (OR = 4.16; 95% CI: 2.3–7.7; $P < 0.001$), male sex (OR = 4.16; 95% CI: 1.47–11.89; $P < 0.001$), screen time (OR = 1.02; 95% CI: 1.01–1.04; $P < 0.001$), prone sleep position (OR = 11.63; 95% CI: 3.88–38.16), and side sleep position (OR = 10.17, 95% CI 3.84–33.73).

Conclusions: This study shows a strong correlation between eye rubbing and keratoconus, particularly when rubbing is performed with the knuckles. Additional associations were identified which may merit future investigation as risk factors, including sleep position, night-time work, and screen time.

Key Words: keratoconus, risk factors, eye rubbing, sleep position

(*Cornea* 2020;00:1–5)

Keratoconus is characterized by asymmetric progressive corneal thinning and steepening. It can lead to significant visual impairment, primarily because of progressive myopia and irregular astigmatism and secondarily because of corneal scarring.[1] Advanced cases may require corneal transplantation, making keratoconus the most common indication for penetrating keratoplasty in the developed world.[2] The reported prevalence of keratoconus continues to increase, partly because of earlier and more advanced detection techniques, and represents a significant public health issue.[3,4]

Received for publication September 11, 2019; revision received December 16, 2019; accepted December 20, 2019.

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The authors have no funding or conflicts of interest to disclose.

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The specific underlying cause of this condition is, however, not yet fully understood. Many different pathways have been investigated, including biochemical, genetic, and mechanical origins, and a multifactorial origin is often cited.[1,2] In 2015, the Global Delphi Panel of Keratoconus and Ectatic Diseases reported risk factors for developing keratoconus based on a postmeeting survey of the panelists, including ocular allergy, atopy, connective tissue disorders, and Down syndrome, as well as Asian and Arab ethnicity.[5]

Eye rubbing is implicated as a significant exogenous environmental factor inducing mechanical change in the cornea, often as the second hit in a 2-hit hypothesis.[6] Although asymmetry between eyes is common, keratoconus is usually bilateral. However, there are a number of reports of unilateral keratoconus developing in response to unilateral eye rubbing.[7–10] Certain reports suggest that keratoconus and atopy are associated because pruritus leads to eye rubbing, which causes mechanical wear of the cornea and progressive ectasia.[5,11–13] There is evidence to suggest that not only does eye rubbing induce mechanical warpage but is also linked to biochemical changes in the cornea which contribute to the keratoconus disease progression.[14,15] A recent study revealed that eyes with keratoconus respond differently to eye rubbing than normal eyes; eyes with keratoconus show significant increases after eye rubbing in posterior astigmatism, intraocular pressure, and anterior chamber volume compared with normal eyes.[16] The aim of this study was to further explore the factors associated with keratoconus in a case-control setting.

METHODS AND MATERIALS

Two hundred two patients with keratoconus, having attended either for initial consultation or follow-up consultation with one of the study authors (D.G.), in the Rothschild Foundation between May 2014 and November 2017 were included in this study. The study was carried out in accordance with the tenets of the Declaration of Helsinki. Institutional review board approval was obtained, and all patients consented to partake in the study. All patients underwent a complete ophthalmic examination. Patients in the keratoconus group underwent topography examination using Placido disc and slit-scanning technology (Orbscan II; Bausch & Lomb, Rochester, NY) as well as corneal tomography using Scheimpflug imagery (Pentacam HR; Oculus, Wetzlar, Germany). The diagnosis of keratoconus was confirmed based on the corneal topography analysis and clinical signs visible at the slit lamp. Inclusion criteria were patients with stage I to stage IV keratoconus according to the modified Amsler–Krumeich classification.[7,8]

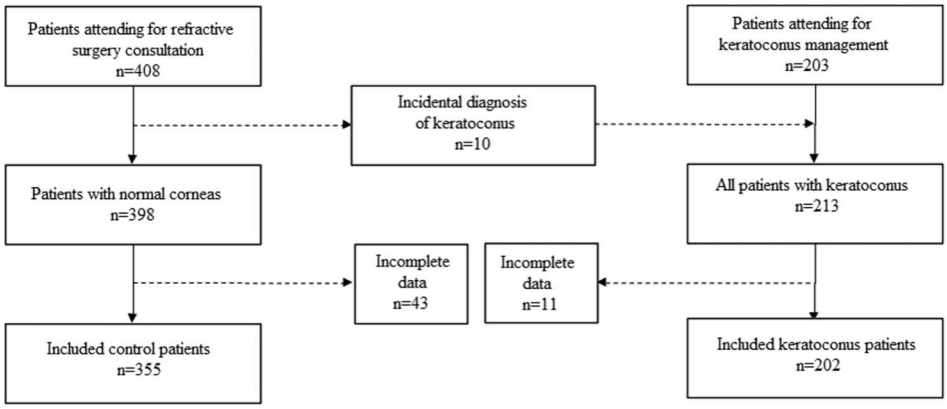

FIGURE 1. Study population.

All patients who attended for refractive surgery consultation between November 2016 and November 2017, excluding those incidentally diagnosed with keratoconus, were included in the control group comprising 408 patients. Control patients underwent topography examination using Placido disc and slit-scanning technology (Orbscan II; Bausch & Lomb). Any patient found incidentally to have keratoconus during their refractive surgery consultation was transferred to the keratoconus study group.

Each patient in the study and control groups was questioned regarding their ophthalmic and medical history and surveyed on the following variables: sex, age, dominant hand, presence of family history of keratoconus or corneal graft, presence of dry eye syndrome, history of allergies, estimated daily screen time, night shift work, make-up application, history of eye rubbing of at least 2 years duration, dominant side of rubbing, type of eye rubbing (beneath the eyes, with the knuckles or base of thumbs, with fingertips, or inside the eye), sleep position (supine, prone, or on the side), and head position while sleeping. Patients who admitted to eye rubbing were asked to describe or demonstrate their usual rubbing technique, which were then assigned to the following patterns: rubbing with knuckles, rubbing with base of thumbs, rubbing with fingertips, beneath the eyes, or inside the eye.

Statistical analysis was performed by a statistician using the R software system (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). Baseline continuous variables were compared between cases and controls using the Mann–Whitney U test, and baseline categorical variables were compared between cases and controls using the χ^2 or Fisher exact tests as appropriate. Odds ratios were calculated using univariate and multivariate logistic regression. The results were adjusted for make-up use, age, allergies, and eye rubbing. The final model was adjusted for age. Generalized variance inflation factor was used to check for multicollinearity. A P value <0.05 was considered significant. All statistical analyses were performed using R version 3.6.1.

RESULTS

In total, 601 patients (203 patients with keratoconus and 408 control patients) were included in this study (Fig. 1). Of the control group, 10 of the included patients were incidentally diagnosed with keratoconus during a refractive surgery consultation and transferred to the keratoconus group. Eleven patients with keratoconus and 43 control patients were excluded because of incomplete data. F1

In total, 202 patients were included in the keratoconus group, of whom 149 were men and 53 were women, with an average age of 32.5 ± 10 years (range 15–62 yrs).

The control group (n = 355), comprised 149 men and 206 women with an average age of 30.7 ± 6.2 years (range 17–57 yrs) (Tables 1 and 2). Adjustment for gender was made, given the large number of women in the control group (Tables 3–6). T1 – T2 AQ:2 T3 – T6

DISCUSSION

Our study confirms a significant association between eye rubbing and keratoconus, a risk factor which has been reported in numerous studies to date.[11,17–19] An important study by Bawazeer et al[11] found eye rubbing to be the most significant predictor of keratoconus in multivariate analysis, with a reported odds-ratio of 5.38. They concluded that atopy

AQ:6 **TABLE 1.** Description of Quantitative Data

Variables	n	Min	q1	Median	Average	q3	Max	s	IQR	#NA
Age	557	15	26	30	31.3	36	62	7.8	10	0
% screen-time	557	5	40	70	58.6	80	100	25.1	40	0

IQR, interquartile range; Min, minimum; q1, first quartile; q3, third quartile.

AQ:1

AQ:7 **TABLE 2.** Description of Qualitative Data

Variables	Study (n)	Study (%)	Control (n)	Control (%)
Total	**202**		**355**	
Gender				
Women	53	26%	207	58%
Men	149	74%	149	42%
Eye rubbing				
Yes	201	99.5%	181	51%
No	1	0.5%	175	49%
Rubbing beneath eyes				
Yes	5	3%	48	14%
Knuckle rubbing				
Yes	116	57%	36	10%
Fingertips				
Yes	58	29%	35	10%
Inside eyes				
Yes	22	11%	62	18%
Dominant hand				
Left	17	8%	22	6%
Right	185	92%	322	
Preferred rubbing side				
Right	44	22%	13	4%
Left	43	21%	13	4%
No difference	115	54%	157	44%
Sleep position				
Front	76	38%	82	23%
Back	9	5%	78	22%
Side	117	58%	195	55%
Side of head				
Right	65	32%	76	21%
Left	51	25%	61	17%
No difference	86	43%	218	61%
Allergies				
Yes	122	60%	129	36%
No	80	40%	226	64%
Night-time work				
Yes	32	16%	11	3%
No	170	84%	344	
Dry eye syndrome				
Yes	144	71%	126	35%
No	58	29%	229	65%
Family history of keratoconus				
Yes	14	7%	4	1%
No	188	93%	351	99%
Screen-time				
>60%	162	80%	177	50%
<60%	40	20%	178	50%

may contribute to keratoconus but most probably through the eye rubbing associated with the irritation of atopy. To explore this known risk factor in greater detail, we aimed to elucidate the particular patterns of eye rubbing most strongly associated with keratoconus.

There is increasing evidence to suggest that eye rubbing may contribute to the development of keratoconus by activating inflammatory mediators and that the pathogenesis of keratoconus progression may involve chronic inflammatory events. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are seen to be overexpressed in the tears of subclinical and keratoconus eyes, even in patients diagnosed as having unilateral KC.[20] Increased levels of IL-6, AQ:3 TNF-α, and matrix metalloproteinase-9 have been measured in the tears of patients with keratoconus.[21] McMonnies[14] showed that eye rubbing increases the corneal temperature, as well as ocular inflammatory and enzymatic activity, and reduces the epithelial thickness and viscosity of the extracellular matrix. Eye rubbing performed through the eyelids has been shown to produce a localized inflammatory response, which in turn produces a reduction in corneal resistance and peripheral displacement of ground substance from the corneal apex. A study by Balasubramanian et al[22] demonstrated an AQ:4 increase in inflammatory proteins such as IL-6, TNF-α, and metalloproteinases matrix metalloproteinase-13 in tears after

TABLE 3. Odds-Ratio in Univariate Analysis

Variables	Odds-Ratio	2.50%	97.50%	*P*
Male gender	3.9	2.62	5.79	<0.001
Eye rubbing	192	33.29	7343.3	<0.001
Type of rubbing				
Knuckle rubbing	30.9	12.45	94.38	<0.001
Type of rubbing				
Pulps of fingers	15.9	6.27	49.23	<0.001
Type of rubbing				
Beneath the eyes	3.4	2.42	8.13	<0.001
Night-time work	5.9	2.8	13.23	<0.001
Dry eye	4.5	3.05	6.69	<0.001
Side sleep position	2.2	1.39	3.3	0.005
Prone sleep position	8	3.94	18.2	0.005
Supine sleep position	0.25	0.13	0.46	<0.001
% screen time	1.03	1.02	1.03	<0.001
Family history of keratoconus	6.5	2.01	27.56	0.0058
Allergy	2.7	1.84	3.87	<0.001

TABLE 4. Odds-Ratio Using Mulivariate Regression

Variable	Odds-Ratio	2.50%	97.50%	*P*
Male gender	3.32	1.19	9.42	0.02
Type of eye-rubbing				
Beneath the eyes	0.31	0.09	0.97	0.06
Type of eye-rubbing				
Knuckles	8	3.76	17.74	<0.001
Type of eye-rubbing				
Pulps of fingers	5.79	2.64	13.27	<0.001
Night-time work	2.61	0.95	7.86	0.24
Dry eye	4.09	2.26	7.6	0.02
Side sleep position	0.85	0.44	1.65	0.21
Supine sleep position	0.12	0.04	0.36	0.02
% screen time	1.02	1.01	1.04	<0.001
Family history of keratoconus	1.88	0.34	15.7	0.52
Allergy	1.47	0.82	2.62	0.5

TABLE 5. Odds-Ratio Final Model

Variables	Odds-Ratio	2.50%	97.50%	*P*
Male gender	4.16	1.47	11.89	<0.001
Type of rubbing				
Beneath eyes	0.29	0.06	0.71	0.016
Type of rubbing				
Knuckle rubbing	8.29	3.92	18.26	<0.001
Type of rubbing				
Finger tips	5.34	2.44	12.21	<0.001
Night-time work	3.40	1.25	10.03	0.020
Dry eye syndrome	4.16	2.30	7.70	<0.001
Side sleep position	10.17	3.84	33.73	<0.001
Prone sleep position	11.63	3.88	38.16	<0.001
% screen time	1.02	1.01	1.04	<0.001

Baseline continuous variables were compared between cases and controls using the Mann–Whitney *U* test, and baseline categorical variables were compared between cases and controls using χ^2 or Fisher exact tests as appropriate. Odds ratios were calculated using univariate and multivariate logistic regression. The final model was adjusted for age. Generalized variance inflation factor was used to check for multicollinearity. $P < 0.05$ was considered significant. All statistical analyses were performed using R version 3.6.1.

60 seconds of eye rubbing in healthy volunteers. These findings suggest that keratoconus may not be entirely a noninflammatory disorder.

Our study also demonstrated significant associations between prone and side sleep positions, and keratoconus. One potential explanation is that a sleep position resulting in direct contact between eye and pillow can generate substantial mechanical stress as well as being a significant source of local irritation. Conversely, the supine sleep position is seen to be a protective factor, possibly linked to the lack of direct mechanical pressure between eye and pillow, as well as associated local irritant and thermal effects.

Night-time work and screen time have not previously been implicated as risk factors in keratoconus studies. Increasing use of computer screens and hand-held devices has resulted in increasing reports of "computer vision syndrome" which results in fatigue, dry eye, and ocular itch[24,25] factors which lead to an increased rate of eye rubbing. Our study found a strong association between night-time work and keratoconus. Studies on night shift workers have shown that these patients are susceptible to occurrence or an increase in dry eye symptoms. A study by Lee on sleep deprivation and another one by Makteb on night-time workers, both revealed a reduced tear film break-up time and Schirmer test, as well as an increase in tear osmolarity and subjective pain measured on a visual analogue scale.[26,27]

TABLE 6. Eye Rubbing: Adjusted for Age

Eye Rubbing	Mean Age (Yrs)	Median Age (Yrs)
Yes	31.54 ± 8.02	30 (IQR 26–26)
No	30.93 ± 7.39	30 (IQR 26–35)

Mann–Whitney *U* test 0.402; no significant difference.
IQR, interquartile range.

In our final analysis, no link was found between a family history of keratoconus and risk of developing keratoconus. Indeed, specific genetic risk factors for keratoconus have proven difficult to identify.[11] A meta-analysis regarding the genetics of keratoconus did not find any argument in favor of a specific genetic link in keratoconus.[28] Studies on "zinc finger protein 469" polymorphisms identified corneal thinning and reduction of corneal hysteresis, but no significant association with keratoconus.[29,30] A twin study carried out by Tuft et al[31] did not identify any significant difference between the development of keratoconus in monozygotic or dizygotic twins, suggesting certain environmental factors need to be present to develop keratoconus. Genetic factors control certain anatomical corneal characteristics such as thickness, but also hysteresis, as demonstrated in a twin study by Carbonaro et al,[32] showing a genetic influence in the corneal hysteresis values. We suspect that these parameters may explain why certain eyes are more vulnerable to mechanical trauma such as repeated eye rubbing.

This study emphasizes the importance of eye rubbing and supports the notion of a primary role of mechanical factors in the pathogenesis of keratoconus. Studies on Marfan syndrome show a reduction in corneal hysteresis and progressive thinning[33]; however, in these patients, the cornea undergoes regular and symmetrical flattening as opposed to the steepening seen in patients with keratoconus.[34] This suggests that a reduction in corneal hysteresis and corneal pachymetry alone is not enough to explain the cone shaped corneal deformation found in keratoconus.

This study highlights patients who may be more susceptible to keratoconus: patients with ocular allergies, dry eyes, blepharitis, eye strain, night-time work, and prolonged screen time. These patients should be explicitly informed of the risk of repetitive eye rubbing, particularly the more damaging patterns such as rubbing with the knuckles or fingertips. Furthermore, it highlights to clinicians that patients should be carefully questioned on the subject of eye rubbing during history taking because patients often underestimate and underreport the extent to which they rub their eyes.

We acknowledge that there are limitations to this study. Most of our data are based on the patients' verbal history which is dependent on accurate patient recollection and response and is subject to recall bias. In particular, it can be notoriously difficult to elicit an accurate eye-rubbing history. We did not address other issues which may influence the sleep position, such as obstructive sleep apnea requiring the use of a mask at night.[35] Our control group consisted of eyes with normal topographical examinations at the time of study inclusion; however, because these eyes were not followed in time, we can only assume the likelihood that these eyes did not go on to develop keratoconus. Owing to the nature of this study, selection bias may affect the results, although we attempted to control for this where possible.

In conclusion, using multivariable analysis in this case-control study, we found that eye rubbing, prone sleep position, night work, and screen time were significantly associated with KC. We recommend that patients at risk should be specifically counseled on the risks of eye rubbing and evaluated for these newly identified risk factors with the aim of reducing the risk of keratoconus.

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