Atopy and keratoconus: a multivariate analysis

Ahmed M Bawazeer, William G Hodge, B Lorimer

Abstract

***Background/aims*—The primary goal of this study was to determine if atopy is a risk factor for keratoconus. Other potential risk factors were also studied and included age, sex, race, eye rubbing, mitral valve prolapse, handedness, collagen vascular disease, ocular trauma, pigmentary retinopathy, Marfan's syndrome, Down's syndrome, and a history of contact lens wear.**

***Methods*—A case-control study was designed (n=120) with incident cases assembled from the years 1985–99. Controls were chosen from the same person-time experience as cases and were picked from a source population with multiple outcomes ensuring that none was knowingly related to any of the potential exposures being studied. Atopy was defined based on the UK working group 1994 definition (at least 4/6 criteria = complete, 3/6 criteria = incomplete, and at least 1/6 criteria = partial). Keratoconus was defined based on clinical criteria and previously published I-S values. Multiple logistic regression was used in the analysis to obtain the odds ratios as the measure of association.**

***Results*—In the univariate associations, there was an association between keratoconus and atopy as well as eye rubbing and family history of keratoconus. However, in the multivariate analysis, only eye rubbing was still a significant predictor of keratoconus (odds ratio = 6.31 p = 0.001).**

***Conclusions*—This study supports the hypothesis that the most significant cause of keratoconus is eye rubbing. Atopy may contribute to keratoconus but most probably via eye rubbing associated with the itch of atopy. No other variable measured was significantly associated with the aetiology of keratoconus.**

(*Br J Ophthalmol* 2000;**84**:834–836)

University of Ottawa Eye Institute, Ottawa, Ontario, Canada
A M Bawazeer
W G Hodge
B Lorimer

Correspondence to:
Dr William Hodge, University of Ottawa Eye Institute, 501 Smyth Road, Ottawa, Ontario, Canada K1H 5P6
whodge@ogh.on.ca

Accepted for publication
18 April 2000

Keratoconus is a progressive non-inflammatory corneal ectasia characterised by central corneal thinning, corneal scarring, corneal protrusion, and progressive irregular myopic astigmatism.[1] Classically, the onset of this disorder starts at puberty and it is progressive until the third to fourth decade of life, when it usually arrests.[2] The reported incidence of keratoconus is approximately 1 per 2000 per year, and the prevalence is 54.5 per 100 000.[2] The cause of this condition is still largely unknown. A positive association between keratoconus and many conditions has been suggested, including atopy, eye rubbing, contact lens wear, handedness, cardiovascular disease (especially mitral valve prolapse), ocular trauma, collagen vascular disorders, pigmentary retinopathy, Marfan's syndrome, and Down's syndrome.[2] The association between atopy and keratoconus has been reported since the beginning of the 20th century in a number of descriptive studies. The first reported association was described by Hilgartner *et al* in 1937.[3] Since then, many conflicting reports have been published. Brunsting *et al* in 1955,[4] Galin and Berger in 1958,[5] Spencer and Fisher in 1959,[6] and Roth and Kierland in 1964[7] diagnosed keratoconus only in only a small number of patients from a large series of atopic individuals. Furthermore, Lowell and Carroll in 1970[8] in an analytical study, found no significant difference between the incidence of atopic traits in keratoconus patients when compared with a group of controls. Despite the low rate of keratoconus in these published reports, Copman in 1965[9] reported 32% of patients with keratoconus had eczema compared with a 3% incidence of eczema in the general population. However, two thirds of these patients admitted that they rubbed their eyes excessively making it unclear whether atopy itself or the eye rubbing was the most important factor in the aetiology of keratoconus. Davies *et al* in 1976,[10] in a controlled study, reported a history of atopy in 35% of cases of keratoconus, compared with 12% in the control group. In a large controlled study, Rah *et al*[11] found a positive association between atopy and keratoconus. A definite history of atopy was found in 35% compared with 12% in the matched control group. Gasset *et al*,[12] in a survey of 162 keratoconus patients found that the prevalence of asthma was 1% in the control group compared with 17.9% in the keratoconus group. Finally, Harrison *et al* in 1989[13] found a positive association between atopy and keratoconus.

In this study we attempted to study the atopy-keratoconus association while also controlling for eye rubbing and other factors that have been associated with the aetiology of keratoconus.

Patients and methods

STUDY DESIGN

A case-control study was designed with cases recruited from the cornea service of the University of Ottawa Eye Institute. Incident cases were chosen from the years 1985 to 1999. To ensure that controls were sampled from the same study base, they were also chosen from the same years and service.

STUDY VARIABLES

The outcome variable studied was keratoconus which we purposely defined strictly so that no misclassification would occur. To that end,

patients needed at least four of the following five criteria to be diagnosed with keratoconus: Munson's sign, Fleisher ring, stress lines, inferior steepening on corneal topography, and a positive I-S value (greater than 1.26 dioptres).[14]

The main predictor variable defined a priori was atopy. We used the 1994 UK working group guidelines for the diagnosis of atopy.[15] Atopy was defined as a history of itchy skin plus three or more of the following: history of involvement of skin creases, a personal history of asthma or hay fever (or a history of atopic disease in a first degree relative), a history of general dry skin in the past year, visible flexural eczema, and onset under the age of 2. In this study we further subdivided atopy into complete (four or more out of the six criteria), incomplete (three out of six), partial (one or two out of six), and none (none out of six). Other covariates measured were based on literature evaluation of other keratoconus associations and included: age, race, sex, contact lens wear, eye rubbing, cardiovascular disease, Marfan's syndrome, Down's syndrome, handedness, systemic collagen vascular disease, ocular trauma, and pigmentary retinopathy.

INCLUSION AND EXCLUSION CRITERIA

To be included in this study patients had to be at least 18 years of age and be a patient at the cornea service of the University of Ottawa Eye Institute. Patients had to be willing to fill out a questionnaire and to give informed consent. Patients were excluded if they had any eye conditions positively or negatively associated with the main predictor variable including bacterial keratitis, herpes simplex blepharoconjunctivitis, or herpes simplex keratitis.

INTERVENTION

Clinical examination and topography were used to establish a diagnosis of keratoconus. The predictor variables and covariates were determined via a questionnaire closely patterned after the UK working group atopy questionnaire. Because this questionnaire has already been developed and tested with respect to reliability, validity, and responsiveness we did not re-evaluate the questionnaire. However, we did administer the questionnaire before the study began to 20 patients randomly chosen from the cornea clinic as a trial and no problems were encountered. For other clinical information (such as a history of a medical condition), the patient's medical record was used to confirm the information from the questionnaire whenever possible.

SAMPLE SIZE AND STATISTICAL ANALYSIS

Based on an expected odds ratio of 3/1 and with a two sided alpha of 0.05 and a power of 80%, the total sample size estimated from this study was 116.[16] In order to maintain the power of the study while recognising that controls would be easier to find than cases, we used a 1.5/1 control to case ratio. Using the method described by Hulley and Cummings,[16] with the above mentioned variables, 47 cases and 71 controls would be needed. For the statistical analysis, first univariate associations between the covariate and keratoconus were determined. For continuous variables such as age, this was done with analysis of variance after checking for normality via an inverse normal plot. For discrete outcomes such as sex, the χ^2 test with one degree of freedom was employed using the Yates's correction where appropriate. Any association with a p value less than 0.15 was then included in the multivariate model. The multivariate model was constructed with both the likelihood method and the Pearson expected value approach. Quadratic terms were employed where there were non-linear trends and centring was used to avoid collinearity. A p value less than or equal to 0.05 was considered significant.

Results

A total of 49 cases and 71 controls were recruited into the study.

BACKGROUND VARIABLES

Table 1 summarises the demographic characteristics among cases and controls: there was no difference among the cases and controls with respect to these variables.

UNIVARIATE ASSOCIATIONS

The first step of the multivariate analysis was to study whether there were any univariate associations between the variables measured and keratoconus. Table 2 summarises the univariate associations between keratoconus and (1) other illnesses, (2) ocular trauma, (3) a family history of keratoconus, (4) atopy, and (5) eye rubbing. We included any risk factor with a p value less than 0.15 to be included in the multivariate analysis. As can be seen from the univariate analysis, there is a suggestion of association between keratoconus and family history of keratoconus as well as atopy (in all its definitions) and eye rubbing. There was no difference between the cases and controls with respect to previous contact lens wear, handedness, Marfan's syndrome, or Down's syndrome.

Table 1 Demographic characteristics among cases and controls

	Cases (n=49)	*Controls (n=71)*	*p Value*
Age (years)	32.7	31.1	0.32
Male	26 (53.1%)	39 (54.9%)	0.84
White	44 (89.8%)	59 (83.1%)	0.31

Table 2 Univariate associations for keratoconus among cases and controls

	Cases (n=49)	*Controls (n=71)*	*p Value*
Cardiac disease	3 (6.1%)	3 (4.2%)	0.64
Joint disease	1 (2.0%)	5 (7.0%)	0.23
Retinal disease	1 (2.0%)	0 (0.0%)	0.34
History of ocular trauma	5 (10.2%)	10 (14.1%)	0.53
Family history of keratoconus	4 (8.2%)	0 (0.0%)	0.01
Complete atopy	10 (20.4%)	3 (4.2%)	0.01
Incomplete atopy	3 (6.1%)	2 (2.8%)	0.14
Partial atopy	5 (10.2%)	2 (2.8%)	0.11
Eye rubbing	22 (44.9%)	8 (11.2%)	0.001

Table 3 Risk factors for keratoconus from the multivariate analysis

	Odds ratio	*p Value*	*95% CI*
Complete			
Atopy	3.67	0.08	0.85–15.82
Eye rubbing	5.38	0.001	2.06–14.05
Family history of keratoconus	6.31	0.12	0.60–65.96
Incomplete			
Atopy	1.11	0.41	0.59–19.99
Eye rubbing	7.05	0.001	2.67–18.65
Family history of keratoconus	5.75	0.141	0.56–59.10
Partial			
Atopy	3.68	0.16	0.61–22.24
Eye rubbing	6.18	0.001	2.40–15.89
Family history of keratoconus	6.66	0.112	0.64–69.20

MULTIVARIATE ANALYSIS

Table 3 summarises the multivariate analysis using atopy, eye rubbing, and family history of keratoconus in the multivariate model. Given that this was a multivariate analysis, the odds ratio is the measure of association. In the analysis, three separate models were created first with atopy defined as complete atopy, then as partial atopy, then as incomplete atopy. Regardless of how atopy is defined, the results are the same: only eye rubbing remains significant in the multivariate model. Atopy is no longer significantly associated with keratoconus and family history is not significant either.

Discussion

Based on the clinical sample obtained from this study, the most important risk factor for the development of keratoconus is eye rubbing. This was the only risk factor that was significant at both the univariate and multivariate level. Atopy as defined in this study was significant only in the univariate analysis. This fact raises the possibility that atopic patients who develop keratoconus may do so because of the eye rubbing that atopic individuals inevitably have from severe itching. These conclusions held whether atopy was defined as complete, incomplete, or partial based on the UK working group definition. The conclusion that eye rubbing may be the most important risk factor for keratoconus is supported by others. Karseras and Ruben elicited a history of eye rubbing in two thirds of their keratoconus patients who went on to need hard contact lens wear.[17] In a case report, Coyle[18] prospectively followed a patient who could neutralise a cardiac arrhythmia by vigorously rubbing his eyes and eventually developed keratoconus without any other risk factors. Gritz and McDonnell also prospectively followed a patient who developed keratoconus over an 11 month period and his only risk factor was ocular massage.[19]

An inherited component to keratoconus has been postulated by some authors. Our data support this possibility as the odds ratio with respect to this variable comparing cases with controls was 6.09 (composite odds ratio, data not in a table). However, the odds ratio was not statistically significant. This may be because there is no true association. Alternatively, this study was powered to study the atopy-keratoconus association and hence it may be underpowered to determine if an inherited component to keratoconus exists. A larger sample size purposely calculated for this association may have revealed a significant and more stable odds ratio.

Several authors have reported associations between keratoconus and systemic disorders especially in subgroups of patients such as those with trisomy 21. No such associations could be found in our study. However, it should be pointed out that while the case-control design is ideally suited to study rare outcomes such as keratoconus, it is a weakness of this design to study rare exposures such as systemic diseases that can occur in trisomy 21 patients. Hence we would not want to conclude that these previous associations which have been reported are erroneous.

Some of the weaknesses of the case-control design are selection bias, misclassification bias, and confounding bias. We attempted to reduce selection bias by ensuring that the cases and controls were chosen from the same study base; in other words from the same clinical population over the same time period. Misclassification bias was reduced by using a modified questionnaire that had already been developed and validated. Confounding bias was reduced by ensuring that an appropriate multivariate model was constructed. Of course residual confounding bias by unknown confounders is always a possibility in observational studies and can only be eliminated with a randomised clinical trial. However, a randomised trial to study risk factors for a rare disease such as keratoconus would be a completely unrealistic endeavour.

Supported by the University of Ottawa Medical Research Fund.

1 Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol* 1984;**28**:293–322.
2 Rabinowitz YS. Keratoconus. *Surv Ophthalmol* 1998;**42**: 297–319.
3 Hilgartner HL, Hilgartner HL Jr, Gilbert JT. A preliminary report of a case of keratoconus successfully treated with organotherapy, radium and shortwave dithermy. *Am J Ophthalmol* 1937;**20**:1032–9.
4 Brunsting LA, Reed WB, Blair HL. Occurrence of cataract and keratoconus with atopic dermatitis. *Arch Dermatol* 1955;**72**:237–41.
5 Galin MA, Berger R. Atopy and keratoconus. *Am J Ophthalmol* 1958;**45**:904–6.
6 Spencer WH, Fisher JJ. The association of keratoconus with atopic dermatitis. *Am J Ophthalmol* 1959;**47**:332–4.
7 Roth HL, Kierland RR. The natural history of atopic dermatitis. *Arch Dermatol* 1964;**89**:209–14.
8 Lowell FC, Carroll JM. A study of the occurrence of atopic traits in patients with keratoconus. *J Allergy Clin Immunol* 1970;**46**:32–9.
9 Copeman PWM. Eczema and keratoconus. *BMJ* 1965;**2**: 977–9.
10 Davies PD, Lobascher D, Menon JA, *et al.* Immunological studies in keratoconus. *Trans Ophthalmol Soc UK* 1976;**96**: 173–8.
11 Rah A, Davies P, Ruben M, *et al.* Keratoconus and coexisting atopic disease. *Br J Ophthalmol* 1977;**61**:761–4.
12 Gasset AR, Hinson WA, Frias JL. Keratoconus and atopic disease. *Ann Ophthalmol* 1978;**10**:991–4.
13 Harrison RJ, Klouda PT, Easty DL, *et al.* Association between keratoconus and atopy. *Br J Ophthalmol* 1089;**73**: 816–22.
14 Rabinowitz YS, Nesburn AB, McDonnell PJ. Videokeratography of the fellow eye in unilateral keratoconus. *Ophthalmology* 1993;**100**:181–6.
15 Williams HC, Burney PGJ, Pembroke AC, *et al.* The UK working party's diagnostic criteria for atopic dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994;**131**: 406–16.
16 Hulley SB, Cummings SR eds. *Estimating sample size and power in designing clinical research.* Baltimore: Williams and Wilkins, 1988:139–50.
17 Karseras AG Ruben M. Aetiology of keratoconus. *Br J Ophthalmol* 1976;**60**:522–4.
18 Coyle JT. Keratoconus and eye rubbing. *Am J Ophthalmol* 1984;**97**:527–8.
19 Gritz DC, McDonnell PJ. Keratoconus and ocular massage. *Am J Ophthalmol* 1988;**106**:757–8.