Case control study of risk factors for acute corneal hydrops in keratoconus

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Subtitle

In a case control study we have shown that in subjects with keratoconus vernal keratoconjunctivitis, asthma, visual acuity and steep keratometry values are independently associated with the odds of developing an acute cornea hydrops.

Abstract

Purpose: To determine risk factors for the development of acute corneal hydrops in keratoconus in the UK in a case controlled study.

Methods: Between November 2009 and December 2010 we prospectively identified 73 individuals who developed acute corneal hydrops. We then identified 174 controls from 9 regions in the UK with keratoconus who had not had hydrops. For cases and controls we recorded demographics and clinical features. Univariate and multivariable logistic regressions were performed to identify risk factors.

Results: Univariate analysis suggested strong associations between the odds of hydrops and each of vernal keratoconjunctivitis (OR 4.08, 95% CI 1.45-11.49, P=0.008), asthma (OR 2.70, CI 1.34-5.47, P=0.006), atopic dermatitis (OR 3.13, CI 1.50-6.56, P=0.002), learning difficulties (OR 7.84, CI 2.86-21.46, P<0.001), previous hydrops (OR 40.2; CI 6.2 to ∞, P<0.001), black ethnicity (OR 2.98, CI 0.98-8.99; P=0.05), visual acuity in the worse eye (OR 8.76 CI: 3.86, 19.88; P < 0.001) and minimum keratometry ≥ 48 dioptres prior to the hydrops (OR 4.91, CI 1.07-22.6, P=0.041). The use of a contact lens correction was also found to be associated with the odds of hydrops (OR 0.08; CI 0.03 to 0.19, P<0.001). Multiple variable regression indicated that having vernal keratoconjunctivitis (adjusted odds ratio [AOR] 15, 95% CI 1.30-173.7; P=0.03), asthma (AOR 4.92, CI 1.22-19.78; P=0.025), visual acuity in worse eye (AOR 4.11, CI 1.18, 14.32; P = 0.026 and a high keratometry value (AOR 4.44, CI 0.85-23.18; P=0.077) were independently associated with the odds of hydrops in subjects with keratoconus.

Conclusions: Some individuals with keratoconus are at especial risk of developing acute corneal hydrops. These patients could be managed more aggressively to reduce their risk of developing this complication of their disease.

Introduction

Keratoconus is characterised by thinning and ectasia of the cornea that causes irregular astigmatism, myopia and blurred vision. The majority of cases appear to be sporadic although multiple genetic and environmental factors are thought to contribute to the development of disease.[1] In the majority of cases the refractive error can be corrected with glasses or contact lenses, but as the disease progresses vision can be further reduced as a result of stromal scar. In hospital based populations approximately 10% of patients require a keratoplasty to improve their vision within 10 years of diagnosis,[2] the proportion increasing with further follow up,[3] and in developed countries keratoconus is the most common indication for keratoplasty.[4] In a minority of cases an acute corneal hydrops develops following a split in Descemet's layer, which allows aqueous fluid to enter the stroma with gross epithelial and stromal oedema.[5-8] Vision can be severely reduced during the hydrops but improves as the oedema resolves over 3 to 4 months, although a visually significant scar usually persists. Complications of hydrops such as perforation, infection and vascularisation are uncommon but have been reported particularly in patients with chronic allergic eye disease.[7] The presence of corneal scar after the resolution of a hydrops may mean that a keratoplasty is required to restore vision. Compared to eyes with keratoconus without a prior hydrops, the risk of an allograft rejection after a hydrops is increased following a penetrating keratoplasty,[7 9] possibly as a result of associated ocular allergy, although the prospect for long-term graft survival is still good.[9]

We recently published a population based survey of acute corneal hydrops in the UK in which we reported the incidence of the condition as well as the strong association between black and South Asian ethnicity.[5] As an extension of that survey we have

conducted a case controlled study to identify factors associated with the development of acute corneal hydrops. The anticipation is that this information may improve the management pathway for patients with keratoconus.

Methods

The study received local and regional ethics committee approval (09/H0706/5). We used the British Ophthalmological Surveillance Unit (BOSU) to identify new cases of acute corneal hydrops that occurred in the UK between November 2009 and December 2010.[5] Clinicians who reported a case were sent an initial questionnaire that requested information on patient demographics, the best corrected visual acuity before the onset of hydrops, previous keratometry values if available, and prior ophthalmic and medical history. Patients with a completed questionnaire were defined as cases and included for further analysis. Acute corneal hydrops was defined as the acute onset of bullous corneal edema with an identifiable break in the Descemet's layer in the presence of keratoconus. Keratoconus was confirmed using established criteria.[10] Keratometry was not an inclusion criterion for cases or controls but, when available, it could be performed using any method available. Minimum keratometry was taken as the last value recorded from the eye before the onset of hydrops. A diagnosis of asthma or eczema was based on self-reported symptoms and a diagnosis of venal keratoconjunctivitis was based on a clinical assessment. Learning difficulty was based on a review of the clinical record or a clinical assessment. Ethnic origin was categorized as White, South Asian (including Indian, Pakistani, Bangladeshi), Black, East Asian, Mixed race, or other ethnicity. We

chose not to include eye rubbing as a variable because we did not believe that it could be verified or quantified.

Controls with keratoconus who did not have a prior history of an acute corneal hydrops were identified from the public care hospital system from 9 ophthalmic centers in the UK selected by a clustered, stratified random sampling procedure. To do this we first divided the UK into nine regions and selected hospitals within each region using computer-generated random numbers with the probability of selection proportional to the number of ophthalmic consultants that worked in each hospital. A local investigator at each center then retrieved the case notes of 20 consecutive patients with keratoconus who had not had an acute corneal hydrops in the order they attended clinic. The same demographic and clinical data were collected for both cases and controls, with keratometry data recorded for the worst affected eye. All study patients were normally resident in the UK and there were no age restrictions. Potential risk factors for the development of acute corneal hydrops were obtained from previous reports.[7]

Statistical analysis

Summary measures were presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables. We used univariate logistic regression to examine associations between the development of acute corneal hydrops and each putative risk factor. We computed a correlation matrix to explore associations between factors. Backward stepwise multiple variable logistic regression was used to explore the independence of factors identified at univariate level ($P < 0.2$) to be associated with the odds of

hydrops. Approximate normality was assessed by visual inspection of histograms. All tests were 2-tailed and all analyses were performed in STATA (StataCorp LP, Tx, USA).

Results

A total of 73 individuals with an acute corneal hydrops were reported. The initial questionnaire was returned for 64 (88%) cases. The records of 179 controls were examined, of which 5 (1.5%) eyes that had a prior deep anterior lamellar keratoplasty (DALK) were excluded from the analysis. The mean age at diagnosis of hydrops in the 64 cases was 33.3 years (range 11 years to 78 years) compared to the mean age at examination of 36.4 years (range 12 years to 71 years) for the 174 controls (P= 0.09). There were 48 (75.0%) male cases compared with 115 (66.1%) male controls (P=0.19). None of the cases had corneal surgery prior to their acute corneal hydrops. In contrast, after exclusion of potential controls with keratoplasty, 10 of the 169 control eyes (3.5%) had an intrastromal corneal ring segment implant and 3 (0.9%) eyes had previous collagen cross-linking. Keratometry was recorded less frequently in cases (15 of 64, 23.4%) than in controls (144 of 174, 82.8%).

Risk factors

The results of the univariable analysis of potential risk factors are shown in Table 1. Patients with vernal keratoconjunctivitis had a 4-fold increase in the risk of developing acute corneal hydrops in comparison to the control group (OR 4.08, 95% CI 1.45-11.49, P=0.008). A self-reported history of asthma (OR 2.70, 95% CI 1.34-5.47, P=0.006) or atopic dermatitis (OR 3.13, 95% CI 1.50-6.56, P=0.002) were also significant risk factors. A minimum keratometry ≥48D (OR 4.91, 95% CI 1.07-22.6, 0.041) prior to the onset of hydrops and a history of a previous hydrops in either eye

were also associated with a significantly increased risk of acute corneal hydrops. We found a strong association between corrected visual acuity in the worse eye and the odds of hydrops (OR 8.76 (3.86, 19.88) $P < 0.001$). Patients with learning disabilities were at greater odds of developing hydrops than those without. Before the onset of hydrops a smaller proportion of cases than controls wore contact lenses for visual correction.

Table 1

Univariable analysis comparing 64 cases with keratoconus who developed and acute corneal hydrops and 174 controls with keratoconus who did not have hydrops. N= number, CI = confidence interval, VKC = vernal keratoconjunctivitis, K = keratometry, D = diopters, *seasonal or perennial allergic conjunctivitis. ** Including Down syndrome. ***minimum keratometry from 15 cases with acute corneal hydrops and 144 controls.

Risk Factor	Cases (N=64)	Controls (N=174)	Odds Ratio (95% CI)	P-value
Males, n (%)	48 (75.0)	115 (66.1)	1.54 (0.81 to 2.94)	0.191
Age at examination, Mean (SD)	33.3 (12.9)	36.4 (12.1)	0.98 (0.96 to 1.00)	0.088
Allergic conjunctivitis*	9 (14.3)	22 (12.8)	1.16 (0.51 to 2.69)	0.72
VKC	9 (14.8)	7 (4.1)	4.08 (1.45 to 11.49)	0.008
Asthma	22 (12.6)	18 (28.1)	2.70 (1.34 to 5.47)	0.006
Atopic Dermatitis	18 (10.3)	17 (26.6)	3.13 (1.50 to 6.56)	0.002
Previous hydrops in either eye	9 (14.7)	0 (0)	40.2 (6.2 to ∞)	< 0.001
Learning difficulties**	14 (21.9)	6 (3.4)	7.84 (2.86 to 21.46)	< 0.001
K ≥48D (%)***	13 (86.7)	82 (56.9)	4.91 (1.07 to 22.6)	0.041
Visual acuity (worse eye), mean (SD)	0.83 (0.63)	0.3 (0.36)	8.76 (3.86, 19.88)	< 0.001
Ethnicity				
White	41 (65.1)	122 (74.4)	-	
South Asian	14 (22.2)	28 (17.1)	1.49 (0.72 to 3.10)	0.29
Black	7 (11.1)	7 (4.3)	2.98 (0.98 to 8.99)	0.05
Other	1 (1.6)	7 (4.3)	0.43 (0.05 to 3.56)	0.43
Refractive Correction				
None	21 (38.9)	9 (5.2)	-	
Spectacles	10 (16.1)	13 (7.5)	0.33 (0.11 to 1.03)	0.06
Soft contact lens	4 (6.4)	33 (19.1)	0.05 (0.01 to 0.19)	< 0.001
Rigid contact lens	21 (33.9)	115 (66.5)	0.08 (0.03 to 0.19)	< 0.001
Scleral lens	6 (9.7)	3 (1.7)	0.86 (0.17 to 4.21)	0.85

Multivariable analysis

On multivariable analysis vernal keratoconjunctivitis, asthma, and visual acuity were independently associated with the odds of developing an acute corneal hydrops, while there was also strong evidence of an association with a steep minimum keratometry (⩾48D) (Table 2).

Table 2

Multivariable risk factor analysis of 15 cases with acute corneal hydrops and 144 controls with keratoconus who did not have hydrops. CI = confidence interval, VKC = vernal keratoconjunctivitis, K = minimum keratometry, D = diopters

Risk Factor	**Adjusted Odds ratio**	***95 % CI***	**P value**
VKC	15.00	1.30 to 173.70	0.026
Asthma	4.92	1.22 to 19.78	0.025
K ⩾48D	4.44	0.85 to 23.18	0.077
Visual Acuity worse eye	4.11	1.18 to 14.32	0.026

Discussion

Acute corneal hydrops occurs when there is a split in the Descemet layer that leads to gross bullous corneal edema. The natural history of a hydrops is for resolution of the edema over 3 to 4 months, although there may be a residual axial corneal scar that may require a subsequent keratoplasty for visual rehabilitation.[6 7] Hydrops only affects a minority of patients with keratoconus but the consequences for patients can be severe. Previous estimates of the prevalence of acute corneal hydrops in individuals with keratoconus, based on retrospective reviews in hospital practice, have ranged between 2.4% to 2.8%.[7 11 12] The incidence of an acute corneal hydrops in variants of keratoconus (pellucid marginal corneal degeneration and keratoglobus) may be substantially higher (11.4%).[12] However, our recent study indicates that the minimum estimated incidence of acute corneal hydrops in the UK is significantly lower than these previous reports at 2.35 (95% CI 1.84-2.95) per 1000 patients with keratoconus.[5]

In this study we have identified the local and systemic factors that may predispose an individual with keratoconus to develop an acute corneal hydrops. Because it is a rare event we used a case controlled design to compare the characteristics of patients who had an acute corneal hydrops with patients who had keratoconus but who had not had a hydrops. The results indicate that the major risk factors are the presence of atopic disease (asthma or VKC) as well as the severity of keratoconus, as indicated by a high keratometry value, and corrected visual acuity. An association between keratoconus and atopy (eczema, asthma, hay fever) has previously been reported.[13-16] Although the precise nature of the relationship between allergic eye disease and keratoconus is uncertain, eye rubbing has been reported to be a risk factor for the development of an acute corneal hydrops.[17]

Poor visual acuity, high keratometry values with astigmatism, ethnicity and age at presentation have previously been identified as risk factors for keratoplasty in patients with keratoconus.[2] Recently, morphometric features visualized with ocular coherence tomography in eyes with eyes with advanced keratoconus (epithelial thickening, stromal thinning, hyper-reflectivity of Bowman's layer and absence of stromal scarring) have been identified as risk factors for an acute corneal hydrops.[18]

Two previous studies have demonstrated that the prevalence of keratoconus is higher in South Asians than whites,[16 19] and we have also shown that the prevalence of acute corneal hydrops is higher in individuals of South Asian or black ethnicity compared to white individuals.[5] However, in the present study we did not observe that ethnicity was an independent risk for the development of an acute corneal hydrops.

The prevalence of keratoconus in patients with Down syndrome has been reported to be between 5.5% and 15%,[20-22] compared with 0.09% in the general population of Denmark.[23] Two previous case series of keratoconus reported that Down syndrome was present in 1.4[7] and 27%[24] of cases. In our study 8 (12.5%) of the 64 cases with acute corneal hydrops had Down syndrome, but there were no patients with Down syndrome in the control group. We speculate that this relative under-representation of individuals with Down syndrome in the control group may indicate that are rarely reviewed in the hospital service unless there is an acute problem.

The limitations of this study are that the control population was not matched for age of onset or duration of disease. These time points can be difficult to ascertain,

especially if there is asymmetric and slowly progressive disease. Although we used keratometry as the index of severity, other parameters such as astigmatism or corneal thickness may be relevant. The measurement was also based on a single observation; the rate of progression of the keratoconus is probably relevant but it could not be ascertained for this study. A small number of individuals who had previously had corneal cross linking of intracorneal ring insertion were included in the control group although the effect of these interventions on individual keratometry measurements or any risk of progression of keratoconus to acute corneal hydrops could not be determined. Although we suspected that keratometry was an important variable for the onset of hydrops, the low number of cases that had keratometry measurements before the onset of acute hydrops limited the power of the multi variable analysis. There are a number of factors that could have contributed to this; keratometry was not an inclusion criterion for the study, keratometry appears not to have been performed on all patients with keratoconus, and in some cases the onset of a hydrops may have prompted their first referral. Finally, the study was underpowered because, when we designed the study, we based our estimate of the incidence of acute corneal hydrops on previously reported series that were approximately an order of 10 higher than the incidence we observed in a prospective national survey.[5] The low number of cases means that the results of the multivariable analysis should be interpreted with caution.

In conclusion, we have identified several risk factors that are associated with an acute corneal hydrops in patients with keratoconus. Currently there are no universally agreed criteria to define which patients with keratoconus should undergo corneal collagen crosslinking to minimize the long-term consequences of this disease.[25 26] However, it is possible that an assessment of an individual’s

personal risk of having an acute corneal hydrops could be used to help determine whether they should be offered early treatment.

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