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The Relationship between Fuchs' Endothelial Corneal Dystrophy Severity and Glaucoma and/or Ocular Hypertension

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Abstract

Objective—To investigate if Fuchs' Endothelial Corneal Dystrophy (FECD) severity is associated with glaucoma and/or ocular hypertension (G/OHTN).

Methods—A subset of eyes (n=1610) from the FECD Genetics Multi-Center Study were examined to estimate the association between FECD severity (grades 0–6 based on guttae confluence) and G/OHTN. Logistic regression models were fit that accounted for the correlation between eyes and adjusted for age, sex, central corneal thickness, intraocular pressure, presence of diabetes, and time of day of initial evaluation.

Results—107 eyes (6.6%) had G/OHTN based on the study definition. The prevalence of G/OHTN in the control group was 6%. Prevalence was lower in index cases with an FECD grade of 1 through 3 and family members with a grade of 0 or 1 through 3 (0% and 2%, respectively) but higher in index cases and family members with a grade of 4 through 6 (11% and 9%, respectively). Adjusting for covariates, eyes with a grade of 4 through 6 were more likely to have concurrent G/OHTN than eyes with no FECD (index cases vs. controls: OR=2.10, p=0.04; affected vs. unaffected family: OR=7.06, p=0.07). Age (OR=1.06 per 1 year increase, p<0.001) and intraocular pressure (OR=1.15 per 1 mmHg increase, p<0.001) were also associated with an increased prevalence of G/OHTN. Sex, diabetes, time of day of evaluation, and central corneal thickness were not associated with the prevalence of G/OHTN (p>0.15).

Conclusions—Glaucoma and/or ocular hypertension occurs more often in eyes affected with severe FECD compared to unaffected eyes. Therefore, it may be beneficial to monitor for the development of glaucoma in these patients.

Introduction

Fuchs' Endothelial Corneal Dystrophy (FECD) is a common ocular condition with a prevalence of approximately 4% in the United States. [1] It can result in visual loss through progressive stages of endothelial dysfunction and corneal edema.[2] Prior studies have

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demonstrated the close association of FECD with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma.[3] Additionally, recent high-resolution corneal shape analyses identified posterior corneal thickness and elevation into the anterior chamber angle in FECD eyes[4,5] presumably contributing to a narrow or crowded angle and a resulting glaucomatous process. In a similar fashion, an acute primary angle-closure glaucoma attack may result in changes to corneal structure with the loss of endothelial cells and degeneration.[6] In a retrospective analysis, Loewenstein et al[7] suggested an association between the development of FECD and glaucoma through a common genetic link.

In this study, we performed a secondary analysis from the FECD Genetics Multi-center Study[8] of 1610 eyes from 969 individuals with varying degrees of FECD to investigate the relationship between FECD severity and prevalence of glaucoma and/or ocular hypertension (G/OHTN).

Methods

Study Population

Subjects were selected from the FECD Genetics Multi-Center Study cohort.[8] Families with FECD traits, unrelated FECD cases and control subjects were recruited in that study to identify genetic risk factors for FECD. Demographic information and ocular and systemic medical histories were obtained through a standardized questionnaire administered to the patient. Each eye was examined separately for inclusion into the study. The control subjects were described previously[8] and included pseudophakic eyes with surgery dates at least 1 year from the time of enrollment. Exclusion criteria for this study included those eyes that 1) had undergone penetrating or endothelial keratoplasty; 2) had cataract surgery within 1 year of the study examination; 3) had a history of blunt, penetrating or perforating trauma; or 4) had evidence of another corneal endothelial dystrophy. The diagnosis of G/OHTN for each eye was established subjectively through a physician-guided patient-completed survey as well as identifying a history of previous glaucoma surgical and/or laser procedures or current use of ocular hypertensive medications. Subject age, time of examination, sex, and presence of diabetes were also recorded. Cornea-fellowship trained ophthalmologists examined eyes for evidence of FECD signs, obtained intraocular pressure (IOP) measurements by applanation tonometry, and recorded the time of the measurement.

FECD grade and central corneal thickness determination

The degree of FECD was graded according to a modified semi-quantitative 7-point severity scale based on guttae confluence previously described.[8] The FECD grades were as follows: 0, no guttae; 1, 1 to 12 central or paracentral non-confluent guttae; 2, more than 12 central or paracentral non-confluent guttae; 3 (1–2 mm of confluent central/paracentral guttae); 4, more than 2 to 5 mm of confluent central or paracentral guttae); 5, more than 5mm confluent central or paracentral guttae); and 6, more than 5 mm of confluent central or paracentral guttae with stromal and/or epithelial edema). Central corneal thickness (CCT) was measured 3 times using an ultrasonic pachymeter that had been internally calibrated. Pachymeters were used from the following manufacturers: Accutome, Bausch and Lomb Surgical, DGH Technology, KMI Surgical, Eye Technology, Inc., Haag-Streit, Sonogage, Sonomed, and Tomey. Each instrument internally calibrates and takes repeated measurements to determine the thickness ultrasonically. Given the difficulty in defining the exact center of the cornea, 3 separate readings were obtained immediately after each other and the mean of these measurements was used as the CCT.

Statistical Analyses

Study groups were defined by a combination of FECD grade and how the subjects were sampled, resulting in 6 defined groups. Subjects who were identified for the study due to presence of FECD were broken down into two groups (index cases): those with an FECD grade of 1through 3 and those with an FECD grade of 4 through 6. Subjects who were identified for the study due to a family relation of an index case were broken down into 3 groups: those with no FECD [an FECD grade of 0 (unaffected family member)], those with mild or moderate FECD (an FECD grade of 1 through 3), and those with severe FECD (an FECD grade of 4 through 6). Finally, unrelated and unaffected controls with an FECD grade of 0 were independently recruited.

Based on eye-level data, univariate and multivariable logistic regression models were used to estimate the odds ratios (OR) of G/OHT among the levels of various covariates. Because some subjects contributed 2 eyes to the analyses, the eye-level data was not independent. Although a generalized estimating equations approach is a standard method for modeling correlated data within the same subject, some study groups had a 0% prevalence of G/OHT; thus a generalized estimating equations approach could not be used because it resulted in a complete separation of data points. One solution to this problem is the method for penalized maximum likelihood estimation by Firth[9]. However, because this approach is applicable only to independent data, multiple outputation was used to repeatedly sample from the clustered data to produce independent data sets, fit a logistic regression model with Firth's approach to each data set, and then aggregate the results[10]. Note that although multiple outputation does allow for computation of ORs and p-values, it does not allow computation of confidence intervals and so none are given. For consistency, all models (including those that did not suffer from complete separation) used this approach.

Results

A total of 1610 eyes from the 969 subjects were analyzed in this study. Of the 1610 eyes, 107 (6.6%) eyes carried a diagnosis of G/OHTN based on the patient-physician completed survey (Table 1). The prevalence of G/OHT in the control group was 6%. Index cases with an FECD grade of 1 through 3 and family members with an FECD grade of 0 or 1 through 3 had lower observed prevalences (0%, 0%, and 2%, respectively), whereas those with an FECD grade of 4 through 6 had higher observed prevalences (11% for index cases and 9% for affected family members) (Table 2). Among those without FECD, unaffected family members were found to have decreased odds of G/OHT relative to controls (OR=0.11, p=0.02), but this result did not hold up in multivariable analysis (OR=0.23, p=0.21). Index cases with severe FECD were found to have increased odds of G/OHT relative to controls (univariate OR=1.82, p=0.05, multivariable OR=2.10, p=0.04), but those with mild to moderate FECD were not found to be different from controls. Similarly, affected family members with severe FECD were found to have increased odds of G/OHT relative to unaffected family members (univariate OR=12.14, p=0.01; multivariable OR=7.06, p=0.07), but no such difference was found for those with mild FECD. No difference in the prevalence of G/OHT was found between index cases and affected family for either mild/moderate or severe FECD. Among the other covariates of interest, age and IOP were found to be positively associated with G/OHT (Table 3 and Table 4).

Discussion

To our knowledge, this study is the largest of its kind to report an association between the degree of FECD based on extent of guttae and presence of corneal edema and G/OHTN established historically. In our study, we found evidence that index cases and affected family members with severe FECD (grade 4–6) had a higher prevalence of G/OHTN relative to

controls or unaffected family members. In order to strengthen the validity of the study and eliminate confounding effects that could elevate IOP, patients were excluded if they had prior keratoplasty, cataract surgery within 1 year of the study examination, or history of trauma.[11–16] Additionally subjects were excluded if they had evidence of other corneal endothelial dystrophies besides FECD to better identify a relationship between FECD and G/OHTN. Eyes from patients with FECD and control subjects consisted of both phakic and pseudophakic eyes. Pseudophakic eyes were treated as control eyes as long as they did not show evidence of guttae on corneal examination and if they had undergone their cataract surgery more than a year from the time of study enrollment. If the subject had undergone their cataract surgery within a year from the time of study enrollment, they were excluded from the study, regardless of their FECD status. While we are able to report an association between the 2 diseases, it becomes difficult in establishing causality. Pitts and Jay[3] identified FECD with axial hypermetropia and shallow anterior chamber depths through biometry analyses. Brunette et al[4] and Shousha et al[5] noticed a change in posterior corneal curvature with thickening into the anterior chamber angle in FECD patients, possibly contributing to elevated IOPs.

The results of our study may conflict with other studies. Krachmer et al[1] performed a similar study involving 64 families, with each individual graded with varying degrees of FECD. In their analysis, only 1 out of 71 subjects (1.4%) with corneal edema had open-angle glaucoma with documented visual field loss. A major limitation of their study, however, is the relatively small sample size of FECD patients. In another retrospective analysis of 430 eyes, Ali et al[17] found no significant risk of open-angle glaucoma in patients with corneal endothelial dystrophy; however, they did note a higher incidence of ocular hypertension and secondary glaucoma in patients with corneal endothelial dystrophy undergoing corneal transplantation. Given the high association we found between severe FECD and G/OHTN in index cases and affected family members, a genetic link initially postulated by Loewenstein et al[7] between the 2 processes may be plausible.

As shown in Tables 3 and 4, older age and higher IOPs were also associated with G/OHTN. Both results are well supported in the literature.[18–20] With increasing age, FECD severity may likewise also advance.[21] Because study group comparisons between less and more severe FECD showed an increased odds of G/OHTN after adjusting for age, our analysis suggests that age alone is not enough to explain the relationship between FECD severity and the prevalence of G/OHTN.

A significant association between diabetes and G/OHTN was not found (univariate analysis OR: 0.8, p-value 0.59; multivariate analysis OR: 0.56, p-value 0.19). Various clinical and population-based studies have been performed to identify a link between the two diseases, although the results vary.[22–24] Additionally, time of day of examination did not bear a significant relationship to G/OHTN in univariate and multivariable analysis (OR: 1.39, p-value 0.19 and OR: 1.43, p-value = 0.17). Studies have demonstrated a diurnal relationship with IOPs, but this association is not universal among all patients with glaucoma. For instance, while some individuals have peak IOPs in the morning, others may peak in the afternoon.[25,26] In our study, IOP was measured only once and at varying times of the day; thus, it is possible that some of our patients may have had higher recorded IOPs in the morning and others in the afternoon, resulting in variability and preventing a significant association between time of day and G/OHTN.

We did not find an association between higher CCT and G/OHTN. Other studies, such as the Ocular Hypertension Treatment Study, found that lower CCT measurements were positive risk factors for the development of glaucoma, while higher CCT measurements tended to result in falsely elevated IOP readings and a lower prevalence of glaucoma.[27–29] Patients in

this latter group had thicker, healthy corneas. On the other hand, patients with severe FECD tend to have higher CCT measurements due to corneal edema. Diagnosing G/OHTN in patients with severe FECD should not be done based solely on CCT and IOP measures. Eyes with thicker CCT measurements due to corneal edema should be treated differently than eyes such as those examined in the Ocular Hypertension Treatment Study. As demonstrated in prior studies, the IOP readings by applanation in patients with corneal edema may be inaccurate.[8,30,31] Thus, it is more important to identify glaucoma in such patients by other means, such as visual field testing and optic nerve analysis.

Our study had several limitations. This was a post hoc analysis of the previously reported FECD Genetics Multi-Center Study[8], a study conducted to identify genetic factors of FECD. Because the data collected for the FECD Genetics Multi-Center Study was not collected to address this study, this may have resulted in residual confounding because data on all possible confounding factors of the association between FECD and G/OHT was not obtained. For instance, subjects were denoted as having glaucoma through a physician-guided, subject-completed questionnaire, rather than the traditionally defined “optic neuropathy associated with progressive loss of peripheral vision.”[32] The questionnaire asked subjects if they were diagnosed with glaucoma, whether they were currently receiving medications to treat glaucoma, and if they received any form of laser or surgical treatment for their glaucoma. The diagnoses of glaucoma and ocular hypertension were combined for this study due to the variability in responses from the subject-completed survey. For example, many subjects identified themselves as having glaucoma because they were using glaucoma eye drops; however, the use of topical glaucoma medications alone cannot be used to diagnose a patient with glaucoma as patients with ocular hypertension have similar needs for the medications.

We also did not have access to the subject's visual field testing or optic nerve analyses. Clinical optic nerve findings, such as presence of disc hemorrhages, nerve fiber layer loss, and increased cupping as well as optical coherence tomography and visual field changes have been shown to be useful diagnostic modalities for assessing progression of glaucoma.[33,34] Access to such information would have been useful in determining a more conclusive association between FECD severity and G/OHTN. Furthermore, we could not accurately establish which form of glaucoma (i.e., primary or secondary open angle vs narrow angle) each subject had. While the survey asked subjects which form of glaucoma they were diagnosed with, the question was open-ended and was often left unanswered by the subject. A prospective study evaluating patients with FECD in combination with glaucoma-related diagnostic testing will be useful in addressing this issue.

Despite these study limitations, given the large sample size and strong correlation in our study, an association between severe FECD and G/OHTN was found. Thus, while monitoring FECD progression, particularly with moderate to advanced disease, periodic glaucoma assessments should also be considered. More detailed studies including gonioscopy, subjective visual field testing, and objective optical coherence tomography readings of such patients may be prudent in further understanding the 2 processes and their genetic relationship.

Acknowledgments

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Table 1

A: Baseline characteristics at the subject level.

Variable	Summary statistics (n=969)
Age, mean ± SD, y	66.4 ± 12.2
Male, No. (%)	336 (34.7)
Diabetes, No. (%)	105 (10.8)

B: Baseline characteristics at the eye level.

Variable	Summary statistics (n=1610)
Grade time in the PM, No. (%)	739 (49.4)
CCT, mean ± SD, μm	581.0 ± 53.2
IOP, mean ± SD, mm Hg	15.5 ± 3.2
FECD group, No. (%)	
Control	551 (34.2)
Unaffected family	121 (7.5)
Index cases (1–3)	16 (1.0)
Index cases (4–6)	276 (17.1)
Affected family (1–3)	187 (11.6)
Affected family (4–6)	459 (28.5)
G/OHTN	107 (6.6)

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure; FECD, Fuchs' Endothelial Corneal Dystrophy; G/OHTN, Glaucoma and/or Ocular Hypertension

Table 2

Prevalence of Glaucoma and/or Ocular Hypertension by study group.

FECD grade	Controls	Unaffected family
0	33/551 = 6.0%	0/121 = 0.0%
FECD grade	**Index cases**	**Affected family**
1–3	0/16 = 0.0%	4/187 = 2.1%
4–6	31/276 = 11.2%	39/459 = 8.5%

Abbreviation: FECD, Fuchs' Endothelial Corneal Dystrophy

Table 3

Univariate associations between each covariate and the prevalence of Glaucoma and/or Ocular Hypertension

Effect Estimated		Raw Prevalence		Model Results	
Comparative	**Reference**	**Comparative**	**Reference**	**OR**	**p-value**
Unaffected	Control	0/121 = 0.0%	33/551 = 6.0%	0.11	0.02
Index (1–3)	Affected (1–3)	0/16 = 0.0%	4/187 = 2.1%	1.21	0.96
Index (4–6)	Affected (4–6)	31/276 = 11.2%	39/459 = 8.5%	1.42	0.24
Index (1–3)	Control	0/16 = 0.0%	33/551 = 6.0%	0.49	0.59
Index (4–6)	Control	31/276 = 11.2%	33/551 = 6.0%	1.82	0.05
Affected (1–3)	Unaffected	4/187 = 2.1%	0/121 = 0.0%	3.86	0.31
Affected (4–6)	Unaffected	39/459 = 8.5%	0/121 = 0.0%	12.14	0.01
1-y increase in Age				1.06	<.001
Male	Female	29/541 = 5.4%	78/1069 = 7.3%	0.63	0.08
Diabetes	Not	9/171 = 5.3%	98/1439 = 6.8%	0.80	0.59
Grade time in PM	Grade time in AM	57/739 = 7.7%	45/757 = 5.9%	1.39	0.19
1-μm in CCT				1.00	0.30
1-mm increase in IOP				1.11	0.004

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure

Table 4

Multivariable associations between each covariate and the prevalence of Glaucoma and/or Ocular Hypertension

Effect Estimated		Model Results	
Comparative	**Reference**	**OR**	**p-value**
Unaffected	Control	0.23	0.21
Index (1–3)	Affected (1–3)	0.71	0.85
Index (4–6)	Affected (4–6)	1.28	0.45
Index (1–3)	Control	0.38	0.46
Index (4–6)	Control	2.10	0.04
Affected (1–3)	Unaffected	2.30	0.56
Affected (4–6)	Unaffected	7.06	0.07
1-y increase in Age		1.06	<.001
Male	Female	0.66	0.15
Diabetes	Not	0.56	0.19
Grade time in PM	Grade time in AM	1.43	0.17
1-μm in CCT		1.00	0.41
1-mm increase in IOP		1.15	<.001

Abbreviations: CCT, central corneal thickness; IOP, intraocular pressure