

Clinical Study of Fuchs Corneal Endothelial Dystrophy Leading to Penetrating Keratoplasty

A 30-Year Experience

Natalie A. Afshari, MD; Aaron B. Pittard, MD; Adnan Siddiqui, BS; Gordon K. Klintworth, MD, PhD

Objective: To review 30 years' clinical experience with Fuchs corneal endothelial dystrophy leading to penetrating keratoplasty (PK).

Methods: We reviewed the clinical records of patients diagnosed histopathologically as having Fuchs corneal endothelial dystrophy who underwent PK at Duke University Medical Center between January 1, 1972, and December 31, 2001. This observational case series included 424 patients (546 eyes).

Results: Women represented 77.6% of patients. Mean age at the time of PK for all patients was 69.2 years. Bilateral PK was required in 28.8% of patients, and the mean interval between the 2 PKs was 3.2 years. There was no difference with regard to sex in the likelihood of requiring bilateral PK ($P=.59$). Among 376 documented family histories, 13.6% were known to be positive for Fuchs dystrophy. Patients with a positive family history underwent PK a mean of 5 years earlier ($P<.002$) and were more likely

to require bilateral PK ($P<.003$). Patients who underwent bilateral PK were twice as likely to have a positive family history compared with those undergoing unilateral PK ($P<.001$). Mean visual acuities at corneal thicknesses of 539 to 650 μm , 651 to 750 μm , and greater than 750 μm were 20/60, 20/60, and 20/80, respectively. Patients who underwent bilateral PK and had a preceding cataract extraction on 1 eye required PK of the pseudophakic eye on average 3.2 years earlier than the fellow eye. The mean time from cataract extraction to PK was 2.2 years.

Conclusions: This large study affirms that Fuchs dystrophy is a disorder of aging that predominantly affects women (3.5:1) and is often familial. Pachymetry-determined corneal thickness was a poor predictor of visual acuity until extreme levels of corneal edema were reached. Cataract extraction in an eye with Fuchs dystrophy leads to earlier PK.

Arch Ophthalmol. 2006;124:777-780

FUCHS CORNEAL ENDOTHELIAL dystrophy is a common disorder of aging characterized by central corneal guttae followed by stromal edema that may result in decreased visual acuity (VA) and pain.¹⁻³ Although the basic cause has yet to be determined, the principal defect is a decline in the number of functional endothelial cells.^{2,4} Other histopathologic findings may include subepithelial bullae and thickening of the Descemet membrane.^{2,5} The disorder is slowly progressive and bilateral but frequently asymmetric. Women are predominantly affected and familial clustering is common, suggesting an autosomal dominant inheritance and incomplete penetrance.⁶⁻⁸ The age distribution is wide, although the typical symptomatic onset is in the fifth or sixth decade of life, preceded several years earlier by clinical evidence of the disease.² Medical management may be attempted; however, most patients ultimately

require penetrating keratoplasty (PK).¹ Fuchs dystrophy accounts for a tenth to a quarter of all corneal transplantations.⁹⁻¹⁶

Because few studies of Fuchs dystrophy exist, we reviewed the clinical records on 546 eyes from 424 patients with Fuchs dystrophy who underwent PK at our institution during the past 3 decades.

METHODS

During the 30 years between January 1, 1972, and December 31, 2001, 710 patients with the histopathologic diagnosis of Fuchs dystrophy had undergone PK at Duke University Eye Center. All histopathologic diagnoses were confirmed by one ophthalmic pathologist (G.K.K.). The same criteria were used to diagnose each specimen: scant endothelial cells, corneal guttae, and thickening of the Descemet membrane. The medical records of 424 patients were available for review with institutional review board approval. This equated to reports on 546

Author Affiliations:
Departments of Ophthalmology (Drs Afshari, Pittard, and Klintworth and Mr Siddiqui) and Pathology (Dr Klintworth), Duke University Medical Center, Durham, NC.

Table. Findings in Patients With Fuchs Dystrophy

Criteria	Patient Group						
	All Patients	Women	Men	Positive Family History	Bilateral PK	Unilateral PK	Previous Cataract Extraction
Patients, No.	424	329	95	51	122	302	NA
Eyes, No.	546	426	120	72	244	302	187
Women, No.	77.6*	41	97	232	156
Men, No.	22.4*	10	25	70	31
Age at first PK, mean, y	69.2	70.2	66.3	64.8	65.6	70.8	73.5
BCVA <20/40, %	83.1	85.7	74.1	75.4	78.0	87.9	73.0
BCVA <20/100, %	36.3	37.8	31.6	18.8	29.6	41.9	35.7
Positive family history, %	13.6	14.4	12.8	...	21.1	9.2	7.4
Bilateral PK, %	30.0	29.3	26.5	41.2	10.4

Abbreviations: BCVA, best-corrected visual acuity; PK, penetrating keratoplasty, ellipses, not applicable.

*Given as percentage of patients.

eyes because some of these patients had undergone bilateral PK. From these records, the following data were extracted: (1) age of the patient at the time of PK in each eye; (2) sex; (3) preoperative VA; (4) date of previous cataract extraction (CE), if done; (5) family history, defined as the presence of Fuchs dystrophy in any member who is genetically related to the patient; (6) pachymetry findings; (7) preoperative clinical diagnosis; (8) histopathologic diagnosis; and (9) time interval between bilateral PKs. Family history and pachymetry results were not always available, particularly in older records.

We analyzed the records of patients who had undergone previous CE to help determine whether this procedure plays a role in accelerating the progression of Fuchs dystrophy. One group consisted of patients who underwent bilateral PK and a preceding unilateral CE. In that group, the time from CE to PK was recorded. Another group consisted of patients who underwent unilateral PK and a preceding unilateral CE. From these patients we determined the percentage of cases in which the CE was performed in the eye that later required PK.

We analyzed preoperative age, VA, number of eyes requiring PK, and family history and compared the results between men and women. We examined the same data in patients with a documented family history of Fuchs dystrophy to determine whether these patients were more severely affected. Having a blood relative who had known Fuchs dystrophy or had undergone PK was considered a positive family history.

When pachymetry data were available, readings were compared between the eyes that had and had not undergone operation. Eyes with previously grafted corneas were excluded.

RESULTS

Our findings are summarized in the **Table**. A single ophthalmic pathologist (G.K.K.) confirmed the diagnosis of Fuchs dystrophy in all 546 eyes using the same pathologic criteria. In 64 (11.7%) of the 546 eyes studied, the patient was clinically diagnosed as having pseudophakic or aphakic bullous keratopathy.

SEX COMPARISON

Of the 424 patients studied, 329 (77.6%) were women, which equated to a female-male ratio of 3.5:1. At the time of PK, the mean ages for men and women were 66.3 and 70.2 years, respectively, which was a statistically significant

difference of 4 years ($P=.002$). There was no difference with regard to sex in the likelihood of requiring bilateral PK ($P<.59$) or having a family history of Fuchs dystrophy ($P<.72$). The mean preoperative corneal thickness was greater in men by 23 μm .

FAMILY HISTORY

Family histories of 376 patients (88.7%) were documented in the medical records for review. Among those documented, 51 (13.6%) were positive for 1 (33 patients [65%]) or more (18 patients [35%]) blood relatives who had known Fuchs dystrophy or had undergone PK. Within this group with a positive family history, 41 (80%) were women and 10 (20%) were men. In addition, 21 patients in this group (41%) required bilateral PK, and the total number of eyes in this group was 72 (56 eyes in women and 16 eyes in men). The mean age at first PK was 64.8 years. Visual acuity was less than 20/40 in 75.4% and less than 20/100 in 18.8%. Pachymetry of the cornea indicated a corneal thickness of 679 μm in the operated-on eye and 652 μm in the fellow eye.

These 51 patients underwent PK a mean of 5 years earlier (at 64.8 vs 69.8 years; $P<.002$) and were more likely to require bilateral PK (21 patients [41.2%] vs 71 [21.8%]; $P<.003$) than were patients with no family history of Fuchs dystrophy. Patients who underwent bilateral PK were twice as likely as those who underwent unilateral PK to have a positive family history (21.1% vs 9.2% of patients; $P<.001$) (Table).

BILATERAL VS UNILATERAL PK

Of the 424 patients studied, the mean age at the time of the first PK was 69.2 years. One hundred twenty-two patients (28.8%) required bilateral PK; 97 (79.5%) of them were women. Their mean age was 65.6 years at the time of the first PK and 68.7 years at the time of PK in the second eye. The mean interval between the 2 procedures was 3.2 years. Of the remaining patients who underwent a unilateral PK, 76.8% were female and the mean age at PK was 70.8 years.

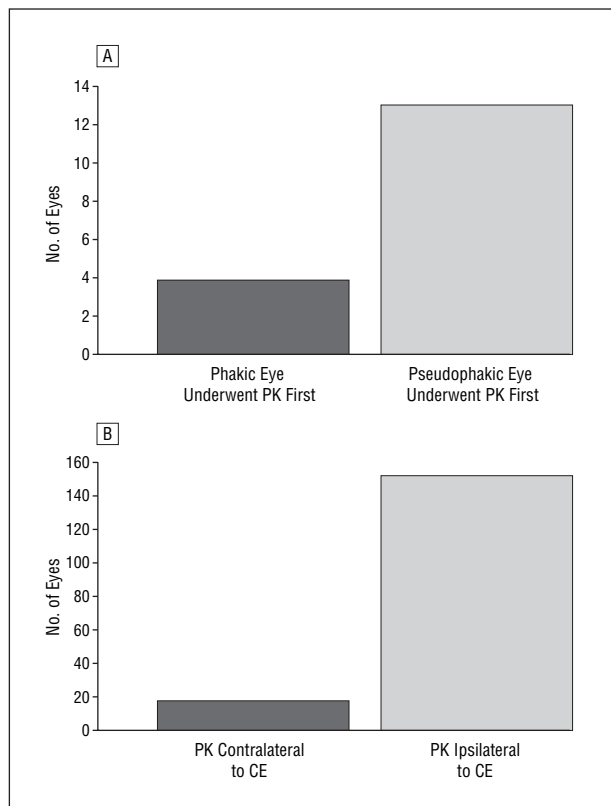


Figure 1. Relationship of cataract extraction (CE) and penetrating keratoplasty (PK). A, In patients who had bilateral PK and unilateral CE, the pseudophakic eye was more likely to undergo PK first. B, The likelihood of PK being performed ipsilateral to a preceding CE among eyes that underwent unilateral PK and a preceding unilateral CE.

CATARACT EXTRACTION

We identified 17 patients who had undergone bilateral PK and unilateral CE. In 13 (76%) of these patients, the eye that underwent CE required PK earlier than the fellow eye by a mean of 3.2 years. The mean interval between CE and PK was 2.2 years. One hundred seventy patients underwent unilateral PK and an earlier unilateral CE. In 152 (89.4%) of these patients, the CE was performed in the eye that later required PK. Overall, of the 424 clinical charts reviewed, 187 (34.2%) of the 546 eyes had undergone a previous CE (**Figure 1**).

VISUAL ACUITY

Best-corrected VA was measured at the last visit before corneal transplantation, and **Figure 2** illustrates the distribution of VAs among these patients. The mean VA overall was 20/64.

PACHYMETRY

Pachymetry measurements were available in 259 eyes (47.4%) (**Figure 3**). Corneal thickness ranged from 539 to 940 μm , with a mean of 681 μm at the time of PK and 618 μm in the fellow eye. Corneal thicknesses and corresponding mean VAs were: 539 to 650 μm , 20/60; 651 to 750 μm , 20/60; and greater than 750 μm , 20/80. In the overall analysis of pachymetry data and VA, we found

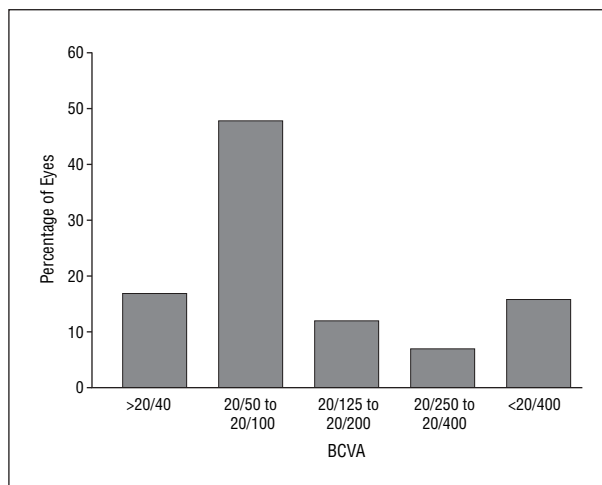


Figure 2. Distribution of best-corrected visual acuity (BCVA) in the operated-on eye at the time of penetrating keratoplasty.

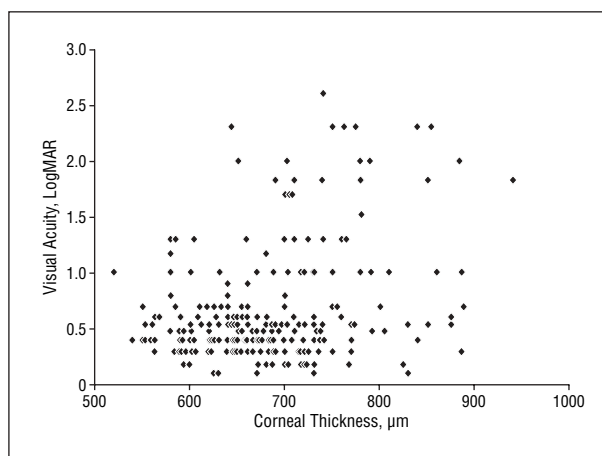


Figure 3. Correlation of pachymetry findings and visual acuity at the time of penetrating keratoplasty. LogMAR indicates logarithm of the minimal angle of resolution.

no linear decline in VA, as one might expect with increasing corneal thickness. However, at corneal thicknesses of approximately 775 μm and greater, the mean VA was 20/100, compared with 20/60 below that level ($P<.004$).

COMMENT

Fuchs dystrophy is a disorder predominantly affecting women, as demonstrated in studies beginning with Ernst Fuchs' original description of the disease.¹⁷ Our finding of a female-male ratio of 3.5:1 confirms that observation. The reasons behind this sex-based discrepancy have not been established, although a few theories have been postulated, including embryological and hormonal mechanisms.¹ To draw conclusions about sex and disease severity, we analyzed age at first PK and mean preoperative VA. Although men were an average of 4 years younger than women at the time of PK, and although the preoperative corneal thickness was slightly greater in men (by 23 μm), the mean preoperative VA was somewhat better in men. It is possible that the PKs were performed at

an earlier stage of this disease in men. However, there was no difference with regard to sex in the likelihood of requiring bilateral PK or of having a family history of Fuchs dystrophy.

Although corneal thickness is commonly used as a measurement of disease progression, pachymetry findings are highly variable and do not seem to be a reliable indicator of VA. A linear correlation between VA and pachymetry values was not found. However, there was a statistically significant decline in VA at extreme levels of corneal edema (ie, at $\geq 775 \mu\text{m}$). There may be a critical level of corneal edema beyond which VA drops off precipitously.

Familial clustering of Fuchs dystrophy is well documented.⁶⁻⁸ Of the 424 patients studied, 376 had family histories documented in the medical records. Among those documented, it is impossible to know the extent to which the issue of family history of Fuchs dystrophy was pressed. Also, some negative family histories turned out to be positive when the issue was explored more thoroughly in recent follow-up clinic visits. For these reasons, the factor of 13.6% of patients having positive family histories, although significant, is probably artificially low. Two observations suggest that patients with a family history of Fuchs dystrophy may be more severely affected. First, PK was performed on average 5 years earlier in patients with a positive family history. Second, patients with bilateral PK were twice as likely as those with unilateral PK to have a positive family history. We found no sex-specific difference in the likelihood of having a family history of the disease.

This 30-year study includes extracapsular CE as well as phacoemulsification, and we did not account for surgical method in our analysis. Nevertheless, the role of CE in the progression of corneal decompensation in patients with Fuchs dystrophy was significant. One third of the eyes studied had undergone a previous CE. Of those patients who underwent bilateral PK and a preceding unilateral CE, the eye that underwent CE was 3 times more likely to require PK before the fellow eye by a mean of 3.2 years. Among patients who underwent unilateral PK and a preceding unilateral CE, 89.4% of the CEs were performed on the eye that later required PK. The small but significant percentage of patients with a preoperative diagnosis of pseudophakic bullous keratopathy underscores the difficulty in diagnosing Fuchs dystrophy in a patient after CE. Clearly, CE remains a method of unmasking Fuchs dystrophy.

As a disorder of the elderly, Fuchs dystrophy will likely continue to increase in prevalence in an aging population. Several issues will require more investigation. Alternative therapies such as deep lamellar endothelial transplantation may provide promise in the advancement of treatment for these patients. Furthermore, the familial clustering of Fuchs dystrophy continues to suggest a ge-

netic predisposition for this disorder. One study¹⁸ found mutations in a gene encoding a portion of type VIII collagen, a component of endothelial basement membranes. Genetic and perhaps environmental factors may play a role in the relatively large number of individuals with Fuchs dystrophy at our institution. Further studies are needed to elucidate the cause of the disease as a possible guide for therapy or prevention.

Submitted for Publication: November 23, 2004; final revision received February 15, 2005; accepted February 15, 2005.

Correspondence: Natalie A. Afshari, MD, Department of Ophthalmology, Duke University Eye Center, Duke University Medical Center, DUMC Box 3802, Durham, NC 27710 (afsha003@mc.duke.edu).

Financial Disclosure: None.

Funding/Support: Dr Afshari has received a Career Development Award from Research to Prevent Blindness.

REFERENCES

1. Adamis AP, Filatov V, Tripathi BJ, Tripathi RC. Fuchs' endothelial dystrophy of the cornea. *Surv Ophthalmol*. 1993;38:149-168.
2. Borboli S, Colby K. Mechanisms of disease: Fuchs' endothelial dystrophy. *Ophthalmol Clin North Am*. 2002;15:17-25.
3. Wilson SE, Bourne WM, O'Brien PC, Brubaker RF. Endothelial function and aqueous humor flow rate in patients with Fuchs' dystrophy. *Am J Ophthalmol*. 1988;106:270-278.
4. Wilson SE, Bourne WM. Fuchs' dystrophy. *Cornea*. 1988;7:2-18.
5. Mustonen RK, McDonald MB, Srivannaboon S, Tan AL, Doubrava MW, Kim CK. In vivo confocal microscopy of Fuchs' endothelial dystrophy. *Cornea*. 1998;17:493-503.
6. Cross HE, Maumenee AE, Cantolino SJ. Inheritance of Fuchs' endothelial dystrophy. *Arch Ophthalmol*. 1971;85:268-272.
7. Magovern M, Beauchamp GR, McTigue JW, Fine BS, Baumiller RC. Inheritance of Fuchs' combined dystrophy. *Ophthalmology*. 1979;86:1897-1920.
8. Rosenblum P, Stark WJ, Maumenee IH, Hirst LW, Maumenee E. Hereditary Fuchs' dystrophy. *Am J Ophthalmol*. 1980;90:455-462.
9. Maeno A, Naor J, Lee HM, Hunter WS, Rootman DS. Three decades of corneal transplantation: indications and patient characteristics. *Cornea*. 2000;19:7-11.
10. Dobbins KRB, Price FW Jr, Whitson WE. Trends in the indications for penetrating keratoplasty in the midwestern United States. *Cornea*. 2000;19:813-816.
11. Lois N, Kowal VO, Cohen EJ, et al. Indications for penetrating keratoplasty and associated procedures, 1989-1995. *Cornea*. 1997;16:623-629.
12. Cursiefen C, Kuchle M, Naumann GOH. Changing indications for penetrating keratoplasty: histopathology of 1,250 corneal buttons. *Cornea*. 1998;17:468-470.
13. Brady SE, Rapuano CJ, Arentsen JJ, Cohen EJ, Laibson PR. Clinical indications for and procedures associated with penetrating keratoplasty, 1983-1988. *Am J Ophthalmol*. 1989;108:118-122.
14. Lois N, Kowal VO, Cohen EJ, et al. Indications for penetrating keratoplasty and associated procedures, 1989-1993. *Cornea*. 1997;16:623-629.
15. Al-Yousuf N, Mavrikakis I, Mavrikakis E, Daya SM. Penetrating keratoplasty: indications over a 10 year period. *Br J Ophthalmol*. 2004;88:998-1001.
16. Kang PC, Klintworth GK, Kim T, et al. Trends in the indications for penetrating keratoplasty, 1980-2001. *Cornea*. 2005;24:801-803.
17. Fuchs E. Dystrophie epithelialis corneae. *Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 1910;76:478-508.
18. Biswas S, Munier FL, Yardley J, et al. Missense mutations in COL8A2, the gene encoding the $\alpha 2$ chain of type VIII collagen, cause two forms of corneal endothelial dystrophy. *Hum Mol Genet*. 2001;10:2415-2423.