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Fuchs' corneal dystrophy

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Abstract

Fuchs' corneal dystrophy (FCD) is a progressive, hereditary disease of the cornea first described a century ago by the Austrian ophthalmologist Ernst Fuchs. Patients often present in the fifth to sixth decade of life with blurry morning vision that increases in duration as the disease progresses. Primarily a condition of the posterior cornea, characteristic features include the formation of focal excrescences of Descemet membrane termed 'guttae', loss of endothelial cell density and end-stage disease manifested by corneal edema and the formation of epithelial bullae. Recent advances in our understanding of the genetic and pathophysiological mechanisms of the disease, as well as the application of new imaging modalities and less invasive surgical procedures, present new opportunities for improved outcomes among patients with FCD.

Keywords

Descemet membrane; DSEK; endothelium; Fuchs' corneal dystrophy; guttae

Discovery & description of Fuchs' corneal dystrophy

In 1910, Austrian ophthalmologist Ernst Fuchs (1851–1930) first reported 13 cases of central corneal clouding, loss of corneal sensation and the formation of epithelial bullae, which he labeled 'dystrophia epithelialis corneae'. It was characterized by late onset, slow progression, decreased visual acuity in the morning, lack of inflammation, diffuse corneal opacity, intense centrally, and roughened epithelium with vesicle-like features [1,2].

Treatments were soon developed, but without reported success. Knapp described topical application of dionin salve, mercury salve, subconjunctival injections, hot applications, bandaging, oral arsenic, strychnine and potassium iodide, without benefit [3]. A regimen of cod-liver oil, milk, butter, boric acid and holocain lotion, iron tonic, quinine and strychnia was

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also proposed to counter the low intake of fat and vitamin A considered by some to be the source of disease [4].

Within 5 years, the exacerbation of the disease after cataract surgery [5], the position of opacity in the bottom two-thirds of the cornea [6] and inheritability of the disease [7] were all noted.

A shift to the understanding of Fuchs' corneal dystrophy (FCD) as primarily a disease of the corneal endothelium resulted after a number of observations in the 1920s. Crystal-like features of the endothelium were noted by Kraupa in 1920, who suggested that the epithelial changes were dependent on the endothelium. Using a slit lamp, Vogt described the excrescences associated with FCD as drop-like in appearance in 1921 [8]. In 1924, Graves then provided a detailed explanation of the endothelial elevations visible with slit-lamp biomicroscopy [9]. A patient with unilateral epithelial dystrophy and bilateral endothelial changes was described by the Friedenwalds in 1925 [2]; subsequent involvement of the second eye led them to emphasize that endothelial changes preceded epithelial changes. As only a subset of patients with endothelial changes proceeded to epithelial involvement, Graves stated on 19th October 1925 to the New York Academy of Medicine that "Fuchs' epithelial dystrophy may be a very late sequel to severer cases of the deeper affection" [10]. In 1926, Gifford reported two patients with FCD in which such endothelial elevations were "unquestionably present" [11].

The term 'cornea guttata', as first used by Vogt to refer to these affected corneas of patients with FCD, has its origins in the 'tropfige' (German for drop-like) appearance of the endothelium. The singular term 'gutta' (plural, 'guttae') is the Latin noun for 'drop', with 'guttata' being the adjective describing the 'guttate' cornea. Vogt referred to individual excrescences as 'dew drops' in his report [8], suggesting that use of the noun would be appropriate. Nevertheless, it has been pointed out that adapting terminology in the field of ophthalmology is not a historically new development [12], as 'cornea' was initially an adjective (tunica cornea) used over 600 years ago to describe the hardness of this unique coat of the eye in similarity to a horn (cornu).

While the correlation between endothelial and epithelial findings became more widely accepted, the actual progression of endothelial pathology was first described by Graves in 1924. According to Graves, disease started with endothelial elevations at the central cornea, then continued with an increase in the number of central corneal elevations [9]. This was followed by uniform distribution of elevations across the cornea with rounded peripheral corneal elevations and increasing central involvement. Finally, transitory vacuoles would appear in the cornea.

The decades to come would bring more effective therapies and greater insight into the cause of disease. As stated by the Friedenwalds in the 1920s: "No light has as yet been thrown on the etiology of this particular condition … the fact that endothelial changes can exist for years before the epithelial changes develop would point, perhaps, to some other, as yet unknown factor, as cause for the whole disease process" [2]. Recent developments offer hope that such factors will be discovered.

Epidemiology

Prevalence

Few studies have examined the prevalence of FCD on a large scale. First assessed in a clinical setting, Fuchs himself estimated the occurrence of dystrophia epithelialis corneae to be one in every 2000 patients; a rate that is likely reflective of those who progress to advanced disease [7]. In 1922, Moeschler examined 176 eyes among 94 individuals, showing eight eyes affected with 'tropfige endothelprominenzen', a prevalence of 4.5% among patients over 50 years of

age and 10.5% of patients over 60 years of age [2]. In 1934, Goar examined 800 eye patients in his office and reported an incidence of 6.62% [13].

In 1967, in order to assess a broader sample, Lorenzetti conducted a study of 1016 individuals at an outpatient medical center in Florida, USA, examining individuals who presented for office visits for a variety of medical complaints and those who accompanied them. In this study, approximately 3.9% of individuals over 40 years of age demonstrated confluent guttae [14].

Cross-sectional studies suggest a relatively higher prevalence of disease in European countries relative to other areas of the world. Slit-lamp examination and noncontact specular microscopy of 774 participants in the Reykjavik Eye Study in 2005 revealed 11% of females and 7% of males with guttae [15]. An examination of 107 patients with cataract in Japan revealed four (3.8%) with 'primary cornea guttata', described as early signs of FCD [16]. A comparison of the prevalence of cornea guttata between Japan and Singapore found a significantly increased prevalence of disease in Singapore (8.5 vs 5.5%) and decreased mean endothelial cell count among its affected individuals relative to Japan [17].

Studies that have examined indications for penetrating keratoplasty (PK) at various institutions confirm a generally higher proportion of patients in Europe and the USA that receive transplants secondary to FCD (Table 1). However, a direct comparison is limited by regional differences in frequency of various indications such as trauma or infection. These studies suggest a lower prevalence in South America, Asia and Australia, with no reports known to us of prevalence studies conducted in Africa.

While clinical experience in the USA suggests a significantly decreased prevalence of FCD among individuals of African–American, Latin–American or Asian origin, a greater understanding of the genetic basis of disease is needed to determine the extent to which a lower rate of clinical presentation may simply represent decreased progression of disease among these populations. In Lorenzetti's study, black and white study participants demonstrated a similar overall likelihood of demonstrating a guttate cornea ($p < 0.54$), but with corneas of white individuals significantly more likely to demonstrate findings of confluence ($p < 0.0001$) [14]. The presence of FCD in an African–American patient was reported in 1924 [18]. Differences between populations in the endothelial cell density (ECD) may contribute to differences in barrier function, as suggested by a study showing increased ECD in a Japanese cohort compared with eyes in an American cohort [19]. Thus, it may be that corneas of populations generally associated with an increased prevalence of FCD are more likely to progress to a clinically significant state of disease if affected.

Risk factors

Identification of risk factors associated with FCD would be of great benefit to both patients and clinicians who seek to prevent the onset or advancement of disease.

The role of UV radiation in the pathogenesis or exacerbation of FCD is not yet clear. Guttae in FCD often appear in an inter-palpebral distribution, suggesting a role for environmental exposure. In addition, the higher prevalence of disease in Singapore over Japan may suggest a role for proximity to the equator [17]. However, assessment of solar UV exposure among participants in the Reykjavik Eye Study found no significantly different risk from increased exposure to UV light during the third, fourth or fifth decades of life [15]. This latter study found that higher bodyweight and BMI were associated with a lower risk of cornea guttata [15]. Why this may be the case has yet to be elucidated, although increased body mass is often correlated with alterations in hormone levels.

A smoking history of more than 20 pack-years was found to be associated with a twofold increase in the risk of developing cornea guttata [15]. Ocular effects of tobacco use include increased molecular oxidation damage and changes in aqueous outflow dynamics.

Association of FCD with other diseases

An association of FCD with increased intraocular pressure was first noted by Fuchs in his original report; a correlation that he personally attributed to chance [1]. A link with axial hypermetropia, shallow anterior chamber and angle closure glaucoma was suggested in a series of 24 patients with FCD [20] and a subsequent series of 23 patients [21], but another study of 22 patients found no significant difference in aqueous outflow between patients and controls [22].

An increased prevalence of age-related macular degeneration among 55 patients with primary central cornea guttata was found relative to a control group [23], although this correlation was not supported by the Reykjavik Eye Study [15].

In a series of corneas with keratoconus and concurrent corneal dystrophies, 27 out of 51 patients (52.9%) were affected with FCD [24]. It is unknown whether a correlating factor increases susceptibility to both diseases or whether this pattern simply represents an increased frequency of FCD relative to other corneal dystrophies. To date, no common pathway has been identified to link the pathophysiology of these two diseases.

Development of FCD was suggested to correlate with an increased rate of cardiovascular disease in a series of 27 patients [25], but this has not since been confirmed. In addition, the mesodermal source of vascular endothelium in contrast to the derivation of corneal endothelium from neural crest cells suggests that these two processes may in fact be separate.

A case of FCD was reported in a young female with rare, mis-sense mitochondrial DNA mutations [26]. Corneal abnormalities beginning in her teenage years resulted in corneal edema and endothelial degeneration, which later required bilateral keratoplasty. These mutations also resulted in glaucoma, progressive hearing loss, dysarthria, rhythmic alternating movements, unsteady gait and hyper-reflexia. The cause of such an association is unclear, although the significant energy requirement of the corneal endothelial layer would require effective mitochondrial energy regulation and its disruption may contribute to processes in the FCD pathway.

To date, reports of the association of FCD with other diseases have been generally limited by small sample size. Definitive conclusions will require future studies with adequate power to determine causal or correlative relationships.

Clinical presentation

The clinical development of disease spans a course from early endothelial changes when patients are asymptomatic to the severe epithelial form of FCD first described by Fuchs, a progression that generally begins in early middle age, often in women, and occurs over the course of two to three decades. Symptoms at presentation may include painless decrease in visual acuity, photophobia, glare and halos around lights that are worse in the morning.

Without a known family history of disease, the presence of guttae may be first discovered as an incidental finding during routine ophthalmological examination. Examination of the offspring of patients with FCD has revealed progression from subclinical to overt disease and demonstrates that early changes are represented by few central guttae that increase in number over time. Some patients with a strong family history of disease may seek evaluation before

the development of symptoms, especially if both parents are affected, in which case this dual genetic contribution can result in increased severity at an earlier age [27,28].

Patients often first present to clinic with painless, blurry morning vision, as movement of water through the cornea is altered at night during sleep. In the intact cornea, corneal hydration depends on a balance in the transfer of fluid between two corneal planes: the epithelium through which water is transported to the exterior surface [29] and the endothelium through which water enters the anterior chamber [30]. During sleep, the closure of eyelids and subsequent decreased tear film evaporation place increased stress on the endothelial layer, which must accommodate the demand for regulating corneal water content. With decreased pump function, fluid is unable to effectively leave the cornea at night, leaving glare and blurriness of vision upon waking. This pattern of visual changes in the morning was identified in the initial description of disease by Fuchs, who repeatedly examined one individual over several hours [1].

As disease advances, corneal edema results in the development of painful subepithelial and epithelial bullae, and if untreated, may progress to loss of corneal sensation, visual acuity and, ultimately, the development of corneal opacification and pannus formation.

This process may be exacerbated by trauma [31], surgery [32,33], toxic exposure [34] or infection [35–37].

Pathophysiology of FCD

Hereditary transmission of FCD

In 1915, J Gray Clegg presented to the Ophthalmological Society of the UK a pair of sisters who presented at 44 and 47 years of age with a condition similar to what was described by Fuchs. In addition to his description of these two individuals, he stated that a third younger sister was similarly affected, along with a paternal grandmother who “had a film in one eye and was told nothing could be done” and a paternal uncle with unilateral blindness at 80 years of age. He concluded that this was the result of a “familial variety” of corneal dystrophy [7].

Subsequent studies suggested an autosomal dominant pattern of inheritance of this disease. Cross described this trend across several pedigrees in 1971 [38]. In 1978, Krachmer described 64 families with FCD, examining 228 relatives and finding a pattern consistent with autosomal dominant inheritance [39]. In 1980, Rosenblum described a similar pattern [40].

While not all patients with FCD are aware of a family history of disease, it is plausible that some sporadic cases may represent the first clinically significant presentation in a family of subclinically affected individuals. Alternatively, these patients may be recipients of two different genes, one from each parent, which would contribute individually to a subtle disease state; it has been shown that the transmission of two different genotypes to one individual may accelerate the onset of disease [28]. Further understanding of the genetic basis of FCD will assist in determining the proportion of cases which in fact are of familial origin.

Families with a disease of early onset

In 1979, Malcolm Magovern described a family with corneal guttae which displayed, similar to previous reports, an autosomal dominant pattern [41]. However, in contrast to the typical female-predominant disease of late onset, men and women in this family were equally affected, with the majority of affected individuals under 40 years of age and four individuals yet to reach their teens. Approximately 25 years later, structural mutations in the *COL8A2* gene were correlated with a disease of early onset. Linkage was found by Biswas to a 1p34.3-p32 interval and implicated a Q455K mutation at position 1364 in the *COL8A2* gene to the pathogenesis of disease [42]. Gottsch and colleagues revisited the family studied by Magovern and identified

a L450W mutation in the collagen-repeat domain of this protein among affected family members [43]. A family in the UK was identified by Liskova with the L450W mutation and early onset of disease [44].

Pathologic mutations in *COL8A2* may appear in specific populations, with a Q455V mutation shown to be present in a cohort of Korean patients with FCD [45]. This gene, however, does not appear to be associated with the typical late-onset FCD in Caucasian patients [46], and cases are rare.

In early-onset disease, Descemet membrane is markedly thickened, leading to corneal decompensation at an early age. In contrast to normal corneas in which Descemet membrane is approximately 5–10 μm in total thickness [47], a histological study of three eyes with early-onset disease revealed Descemet membrane thicknesses of 25, 31 and 38 μm correlated with the L450W mutation in *COL8A2* [48].

Ultrastructural changes secondary to this mutation are present throughout Descemet membrane. The anterior banded layer, which develops before birth and maintains a thickness of 3 μm over the lifetime of an individual [47], has been shown to increase up to three times in magnitude in early-onset disease, a distinguishing feature from late-onset FCD in which increased overall thickness of Descemet membrane is generally a postnatal process resulting in posterior structural abnormalities [49]. A posterior nonbanded layer is present, which is produced by the normal endothelium and which generally increases from 2 to 10 μm during a lifetime [47]. However, the additional formation of a thin, 2-μm internal layer of wide-spaced collagen, 120 nm in periodicity and containing collagen VIII, has been demonstrated and is unique to cases of early onset [49]. A posterior striated layer, not present in normal corneas, contributes approximately 40% of the total thickness in these cases and is also rich in collagen VIII [49]. Immunohistochemistry studies show segregation of the two collagen VIII subtypes (collagen VIII α1 and α2) into fibrillar structures, with stains for collagen IV, fibronectin and laminin resulting in thick, intensely labeled bands in the posterior aspect of Descemet membrane [49]. Notably, posterior excrescences in early-onset disease may be absent upon histological examination; these may be buried within Descemet membrane or may appear as the result of an optical aberration secondary to altered collagen deposition [48]. These differences suggest that the disease, called early-onset FCD, may, in fact, represent a different disease process altogether, rather than the classic, late-onset disease described by Fuchs.

Classic late-onset FCD

The disease commonly referred to as FCD is one of late onset. To date, four chromosomal loci and one known genetic mutation have been implicated in the disease. In 2005, FCD in a large family was found to be linked to a 13pTel-13q12.13 locus, labeled as *FCD1* [27]. An additional *FCD2* locus at 18q21.2-q21.32 was subsequently identified in multiple families [50]. A third locus, *FCD3*, was recently described at 5q33.1-q35.2 [51], and *FCD4* at 9p [52].

In this latter study, a missense Q840P mutation in *TCF8* was causally associated with disease, shown to be sufficient but not necessary for pathogenesis. Moreover, the concurrence of both *FCD4*- and *TCF8*-related disease haplotypes were correlated with a specifically poor prognosis. Notably, a null mutation of *TCF8* had previously been causally associated with posterior polymorphous corneal dystrophy, suggesting that genetic interaction between different genes modulates the phenotypic manifestation of disease in FCD [53]. Future studies will be needed to determine the role of *TCF8* in causing FCD among the general population; in a study of Chinese individuals with 74 affected and 93 age- and race-matched controls, Mehta and colleagues found one patient with a missense mutation in *TCF8* [54].

This recent discovery of more loci associated with late-onset FCD suggests that the disease commonly manifested in the general population is likely an outcome of the interaction of multiple genes. The presence of such interaction is supported by a genome-wide scan among 92 individuals that described peaks on five chromosomes [55].

As other common corneal dystrophies and FCD may to some extent bear similar pathological features, a role has been put forward for genetic mutations previously associated with these hereditary conditions. Besides *TCF8*, the gene *SLC4A11* is associated with autosomal recessive congenital hereditary endothelial dystrophy [56,57] and associated loss of function [58]. We have previously described the expression of this gene in the corneal endothelium and demonstrated significantly lower expression in FCD endothelial cells [59]. In one study of 89 FCD patients, four heterozygous mutations were found in *SLC4A11* that were absent in ethnically matched controls [60]. Further studies will be needed to establish the significance of *SLC4A11* mutations in FCD.

In all clinical cases of late-onset FCD, structural abnormalities of Descemet membrane are present in a pattern that is generally distinct from early-onset disease and normal corneas. Overall thickness of Descemet membrane is increased, with a range of 14–46 μm in one study of 47 FCD corneas [61]. However, anterior layers of Descemet membrane in late-onset FCD appear relatively intact, with wide-spaced, irregular collagen deposited posterior to Descemet membrane in the form of posterior banded and fibrillar layers [62]. Immunohistochemistry reveals strong staining of collagen IV, laminin and fibronectin in the posterior layer of Descemet membrane and its excrescences, with collagen VIII α1 localized more strongly in the posterior fibrillar layer relative to collagen VIII α2 [49]. In one study, corneas with increased stromal and epithelial edema demonstrated a thicker fibrillar layer, suggesting a role for dysfunction of this layer in the pathophysiology of endothelial decompensation [62].

The loss of corneal endothelial function in FCD may be secondary to changes in Descemet membrane or coincide with primary failure of the endothelial cells, although the identification of a causative structural mutation in early-onset disease suggests that the former may be an integral component of this process, with endothelial abnormalities further exacerbating disease. Certainly, the density of corneal endothelial cells in patients with FCD is markedly reduced. In the normal cornea, the endothelial layer density peaks *in utero* and is reduced rapidly until birth, measured among 81 corneas to decrease from 16,105 cells/mm [2] to 6167 cells/mm [2,63]. After this, ECD is gradually diminished over the lifetime of an individual to approximately 2000–3000 cells/mm [2,64–66]. This is decreased in FCD, with an average ECD of 1202 cells/mm [2] among patients between 41 and 86 years of age in a study of 17 eyes with this condition [67]. As the number of endothelial cells decrease, remaining cells increase in area to maintain the barrier function of this layer; in one study, this resulted in a doubling of size for each cell between the age of 20 and 80 years [68]. Pleomorphism results as the remaining cells change in shape from their original hexagonal form.

The premature decrease of ECD in FCD relative to normal corneas may be due to a decreased ability to withstand oxidative stress and an increased susceptibility to apoptosis. An investigation of FCD using serial analysis of gene expression (SAGE) demonstrated a significant decrease in expression levels of several genes associated with oxidation and apoptosis, including nuclear ferritin, glutathione *S*-transferase-π and heat-shock 70-kDa protein [59]. A significant decrease in the expression of Prx-2, -3 and -5 has also been found in FCD, which may be consistent with a reduced ability of endothelial cells to tolerate oxidation-associated damage [69].

Recent studies suggest that pathways associated with apoptosis may be reflected not only in posterior layers, but also throughout the cornea. Apoptotic cells were identified in the basal

epithelial cell layer with nucleus labeling, TUNEL and transmission electron microscopy in an examination of FCD corneas, a finding not found in the study control group [62]. Another study identified a significant increase in apoptotic cell numbers in three layers in corneas of eyes with FCD [70]. In one study, keratocytes from patients with FCD demonstrated increased Bax levels and decreased Bcl-2 levels following camptothecin exposure, a pattern distinguished from normal keratocytes [71]. Another study identified p27, cathepsin and survivin pathways to be involved with cell death in FCD [72].

The corneal guttae, excrescences of Descemet membrane which are the hallmark of FCD, link the two posterior layers of the cornea in the pathology of disease. Investigation into the structure and pattern of guttae can offer insight into the mechanisms associated with FCD. Histological and specular microscopy analyses of guttae formed in an early-onset pattern of disease demonstrated an intra- and intercellular pattern of guttae that was distinct relative to the more common late-onset type [49]. Recent examination of the structural abnormalities within guttae have identified a role for clusterin, a proaggregative protein found among FCD-affected eyes, and co-localized in guttae with TGF-βIp [73].

In addition to the structural abnormalities in FCD, a number of genes may be associated with corneal edema, a process that represents advancement towards the final stages of disease. Disruption of aquaporins has been associated with edema in both FCD and PBK/ABK corneas, with decreased AQP1 in both conditions, and increased AQP3 and AQP4 in the latter [74]. The SAGE analysis referenced earlier also found altered expression of genes associated with pump function [59]. Additional solute transporters have also been suggested to correlate with FCD [60].

Documentation & imaging of FCD

Initial diagnosis and assessment of FCD is generally accomplished through slit-lamp microscopy in the clinical setting, either in patients demonstrating symptomatology or as an incidental finding during evaluation of other complaints. Commonly described as having a ‘beaten silver’ appearance, the varying images of guttae and methods of illumination by slit lamp were described in detail by Graves in 1924, including direct illumination, marginal illumination, specular reflection and retro-illumination [9].

In the clinical setting, quantitative measurement of disease progression is often performed through the documentation of corneal pachymetry measurements over time. This technique is advantageous in its decreased time required for completion, lower cost to the patient and decreased equipment costs for the clinician. Furthermore, it does not require extensive training for its administration or in the interpretation of results. However, cyclic variability in corneal thickness may decrease the reliability of results from this test [75,76].

If documentation of the presence of guttae is required, specular microscopy offers a magnified view of the corneal endothelium in which guttae appear as hyporeflective images with an occasional central highlight. Quantitative evaluation with this modality includes measurement of the cell density of the endothelial layer, which decreases over time in eyes with FCD. However, the decreased scope of the view in specular microscopy limits its use in quantitative analysis of the distribution of corneal guttae and provides a challenge to the clinician who seeks to obtain serial images of a specific location on the cornea. Scales developed to assess progression of disease using specular microscopy may progress across all stages before clinical signs are present [77].

An alternative to specular microscopy is confocal microscopy of the cornea, which could be particularly useful for patients whose endothelial cells cannot be effectively imaged with noncontact specular microscopy [78]. Similar to specular microscopy, this technique offers a

view of the cornea in which guttae may be distinguished as hyporeflective regions in the imaged endothelial background [79]. In one study of 17 eyes affected with FCD, comparison of endothelial cell counts between confocal and specular microscopy revealed a strong correlation ($r = 0.95$) [67]. It has also been suggested that confocal microscopy allows improved imaging of FCD within the swollen cornea, which is of particular use in FCD [80]. One study comparing the use of confocal biomicroscopy and noncontact specular microscopy in 28 normal eyes and 11 eyes with FCD suggested equivalence of cell count measurements in normal eyes with both instruments, but reportedly better visualization of FCD corneas with the confocal technique [81].

Recent advances in optical coherence tomography (OCT) and its application to anterior segment imaging have offered promise for the use of this modality to document FCD, at this point in conjunction with other forms of imaging [82]. As some OCT machines already in distribution can be adapted to new anterior segment settings, this technique could serve as an efficient, non-invasive tool to document disease in patients with FCD. Similar to specular microscopy, the width of each image is currently restricted to a small area of the central cornea, limiting the ability to compare serial images, which would require a larger area of image capture. Moreover, while current resolution settings allow for visualization of guttae, effective quantitative analysis would require a significantly higher level of detail. Nevertheless, the 830-nm spectral domain OCT has been reported to be able to demonstrate three different levels of severity in eyes with FCD [83]. Given the ubiquitous presence of OCT in current clinical settings for retinal evaluation, this may be an area of significant potential for imaging of the cornea if the necessary resolution can be achieved.

Viewing the FCD cornea with a slit lamp utilizing retro-illumination allows the observer to view the pattern and distribution of guttae across the cornea for an overall assessment of the severity and progression of the disease. As such, photography of the cornea using retro-illumination to capture an impression of guttae across the surface of the cornea can also be utilized to objectively describe the distribution and progression of guttae over time [84]. Using landmarks and unique patterns of gutta distribution to align consecutive images, progression of FCD was demonstrated in one family with a specific FCD genotype [28]. Although quantitative analysis is currently utilized in research settings, subjective comparison of serial photographs may be feasible for clinical application.

Medical intervention

Medical treatment of FCD is utilized to treat symptoms of early disease such as blurry vision in the morning. By increasing external osmolality, hypertonic sodium chloride (Muro 128®) drops or ointment can be given to extract water from the cornea. It is typically administered at bedtime and waking.

A hairdryer is sometimes used to increase evaporation at the corneal surface, but caution should be exercised to avoid damaging the corneal surface by holding it at arm's length and at a low heat setting.

A greater understanding of FCD pathophysiology may assist in the future with the development of treatments to prevent progression of disease. At this point in time, definitive treatment requires surgery.

Surgical treatment of FCD

Surgery in FCD is performed for advanced disease resulting in loss of daily function, low visual acuity and/or pain secondary to epithelial bulla formation. PK has traditionally been the mainstay of surgical treatment, but the recent addition of Descemet stripping endothelial

keratoplasty (DSEK) and other endothelial keratoplasties of the cornea offer new alternative procedures that are less invasive.

Penetrating keratoplasty

Considered decades ago as a 'very unfavorable' factor for surgical outcomes in PK [85], FCD has since become a common indication for this procedure throughout North America and Europe (Table 1). Successful transplantation was described by Stocker in 1952 [86], and replaced the full thickness of the FCD cornea.

Patients may choose to undergo PK when visual function has decreased to an unsatisfactory level. The risk of cataract in this population, however, adds an additional factor to be considered when choosing when and whether to undergo corneal transplantation.

In patients with asymptomatic corneal disease, but advanced cataract causing significant visual dysfunction, cataract surgery may be conducted alone with the possibility of future transplantation as needed. Current research suggests that patients with corneal thickness of up to 640 μm may be able to undergo cataract surgery without significant increased risk of requiring PK in the immediate future [87]. In a retrospective study of 136 patients with FCD undergoing cataract surgery alone, 90% of patients with corneal thickness measuring at least 600 μm did not require PK within 1 year of surgery, compared with 83% of patients with corneal pathymetry measurements of at least 640 μm, suggesting that this latter level of thickness may serve as an effective cut-off point [87].

In patients with mild cataract and significant corneal pathology from FCD, several factors play into the decision of whether to proceed with PK alone or with concurrent cataract surgery. Generally, outcomes appear to be similar: in one study of 93 patients at Wills Eye Hospital undergoing the triple procedure (PK, cataract extraction and intraocular lens implantation) and 32 patients with nonsimultaneous procedures (PK, followed by future cataract surgery), no significant difference was found after 6–8 years in the rate of clarity among grafts and refractive status between the two groups, suggesting that the triple procedure may be more cost effective given such similar outcomes [88]. Patient age may also serve as a significant factor: FCD patients undergoing PK at an advanced age experience an increased likelihood of undergoing subsequent cataract surgery, which also occurs earlier after the procedure than patients who are relatively younger [89]. In addition, taking into account the increased perioperative risks specific to the elderly population, it may be advantageous for FCD patients with cataract to undergo the triple procedure.

Endothelial keratoplasty

In 1954, while still an ophthalmology resident, Charles Tillett performed the first posterior lamellar keratoplasty in a 68-year-old man with bilateral endothelial decompensation after cataract extraction. Despite utilizing 6-0 silk sutures and working without viscoelastics or an operating microscope, a 10-mm graft persisted without corneal edema 1 year after surgery. However, vision was lost after air caught behind the iris contributed to angle closure glaucoma [90].

A modern application of this procedure was realized in 1998 with the development of deep lamellar endothelial keratoplasty, in which a limbal incision and mid-stromal pocket was utilized to transplant posterior corneal tissue [91]. This new technique was demonstrated in one study of FCD patients to result in more rapid vision recovery, relatively less astigmatism and decreased change in spherical equivalent compared with PK, with endothelial cell loss similar between groups [92].

This new movement towards selectively transplanting the posterior cornea became increasingly adopted with the addition of DSEK, in which the recipient's Descemet membrane and endothelium are stripped and replaced with healthy donor tissue that includes the endothelial cell layer, Descemet membrane and posterior stroma. Unlike PK, DSEK does not expose the intraocular contents of the eye or require long-term sutures. Additional advantages of DSEK include its successful use in a new triple procedure (DSEK, cataract extraction and intraocular lens implantation) [93] and the ability to maintain PK as a back-up procedure in the event that grafts do not restore vision successfully. The most common complication of DSEK is graft detachment [94]. An increase in intraocular pressure may be present, a process secondary to intra-operative factors such as air displacement [95] or correlated with steroid administration [96].

In a recent report by the American Academy of Ophthalmology, a review of the literature on DSEK confirmed that this procedure offers earlier visual recovery and improved refractive outcomes and stability relative to PK, and reduced risk of intraoperative or late suprachoroidal hemorrhage, as well as decreased wound- and suture-related complications [97]. Graft survival, visual acuity and endothelial cell loss do not appear to differ between the two procedures. More recently, Melles reported the use of Descemet membrane endothelial keratoplasty (DMEK) in 2006, in which surgeons transplant donor Descemet membrane and endothelium cultured from corneoscleral rims through a clear corneal tunnel incision [98]. Reported outcomes after 2 years suggest an initial degree of endothelial cell loss similar to other endothelial keratoplasty techniques [99], with a report of 50 cases in which over half of patients achieved vision of 20/25 or better [100]. In these cases, DSEK can then be used as a back-up if graft detachment or failure occurs [101].

Over time, the further refinement and development of techniques in endothelial keratoplasty may offer advantages among these factors as well.

Refractive surgery in FCD

Published reports of outcomes of refractive surgery among patients with FCD are few. In one report, seven eyes with early guttate changes and a family history of FCD were followed for 1 year after undergoing laser-assisted *in situ* keratomileusis (LASIK). Despite an uneventful course of events at the time of the procedure, patients experienced a loss of ECD, increase in corneal thickness and myopic shift, which were statistically significant 1 year after the procedure [102]. In another report, a patient with guttae, but without symptoms or corneal edema, developed corneal decompensation after LASIK [32]. Large-scale studies would be required to better understand refractive surgery outcomes in patients with FCD.

Future potential treatments

In corneas affected by FCD, a net decrease in ECD over time and subsequent loss of endothelial cell pump function is due in part to the inability of the corneal endothelium to regenerate itself. To counter this effect, investigations are underway to examine whether human cultured endothelial cells (HCECs) can be utilized to restore function to the corneal endothelium. In animal models, the application of a sheet of HCECs in rabbit corneas has been shown to result in decreased corneal edema and/or thickness after removal of the endothelium [103] or Descemet membrane [104], and has been shown to produce earlier resolution of corneal edema after insult [105]. A variety of novel mechanisms for developing and delivering HCECs have been reported, most recently including the use of the anterior lens capsule as a scaffold for cell expansion [106] and magnetic guidance of magnetite-incorporated endothelial cells to the posterior cornea [107]. Although still in its early stages, research into endothelial cell transplantation may offer a viable alternative or addition to current surgical techniques in the future.

Expert commentary

Although much progress has been made in the research and treatment of FCD, many questions remain to be answered. The exact causes of illness, the prediction of disease progression and delivery of an accurate prognosis, methods of prevention and effective nonsurgical treatment are all the subject of inquiries that necessitate an answer.

Increased attention must be given to research that can address the most basic questions of how disease develops: what is the biomolecular pathway implicated in disease, and what genetic or environmental factors contribute to its progression? In addition to shaping our understanding of FCD, identification of these factors would be essential for the prevention and management of this condition.

In the clinical setting, patients with advanced FCD should be aware of both PK and DSEK as treatment options, with referral if needed to a surgeon who can perform the less invasive procedure. The triple procedure may be utilized in patients with both clinically significant FCD and cataract, with DSEK now adopted in a new form of this surgery. The further development of endothelial keratoplasty procedures, which now constitute 90% of corneal transplants in the USA [201], will offer new avenues for treatment in the future and the opportunity for improved surgical outcomes.

Five-year view

Although it has been 100 years since *dystrophia epithelialis corneae* was first described by Fuchs, the development of our understanding of disease has perhaps progressed most rapidly during the past decade. The completion of the Human Genome Project and its implications for genetic research, the emphasis on minimally invasive techniques and endothelial keratoplasty in corneal transplantation, and research collaboration on an increasingly international level have all contributed to a setting ripe for scientific and clinical advancement in the research and treatment of FCD over the next 5 years.

The recent discovery of multiple chromosomal loci associated with FCD point to a perhaps yet unidentified, common pathway implicated in this condition. The further identification of related genes will allow us to understand this pathway in greater detail. Identification of phenotypic differences among various FCD genotypes may allow for more specific, accurate patient counseling in the future.

Further refinement of techniques in the transplantation of Descemet membrane and the corneal endothelium will allow for improved visual rehabilitation and a decreased rate of complications. As transplantation of corneal tissue occurs on a more selective scale, such as in the transition from DSEK to DMEK, methods of tissue delivery will be further refined to continue to improve surgical outcomes. Further research into the use of cultured endothelial cells to replace or repair the compromised endothelial layer in FCD would allow this technique to move from the laboratory closer to the bedside.

Key issues

- Fuchs' corneal dystrophy (FCD) is a progressive hereditary disease first described by Ernst Fuchs in 1910.
- It is a common indication for corneal transplantation in North America and Europe.
- Patients often present with blurry morning vision and physical findings of guttae, corneal edema and, in late stages, epithelial bullae.

- Changes in the structure of Descemet membrane and increased susceptibility to oxidative damage contribute to decreased endothelial cell density and pump function.
- Family studies reveal multiple chromosomal loci associated with common FCD, with inheritance of two separate genotypes shown to result in earlier onset of disease.
- In addition to the common use of corneal pachymetry and specular imaging, the use of optical coherence tomography and retro-illumination photography offer new alternatives for documenting and following progression of FCD.
- Preventative measures have yet to be identified, while smoking has been demonstrated to increase risk of developing disease.
- Medical intervention is limited to reducing symptoms of edema, but definitive treatment requires surgery.
- Descemet stripping endothelial keratoplasty and other endothelial keratoplasties offer new alternatives to Penetrating keratoplasty in the surgical treatment of FCD.

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Table 1

Proportion of penetrating keratoplasties indicated by Fuchs' corneal dystrophy, per institution or geographic location. Highest proportions were found in Europe and North America.

Author (year)	Procedure	Location	Years	Proportion (%)	Absolute	Ref.
North America						
Ghosheh *et al.* (2008)	Penetrating keratoplasty	Philadelphia, USA	2001–2005	10.8	126/1162	[108]
Cosar *et al.* (2002)	Penetrating keratoplasty	Philadelphia, USA	1996–2000	15.2	233/1529	[109]
Lois *et al.* (1997)	Penetrating keratoplasty	Philadelphia, USA	1989–1995	15.7	384/2442	[110]
Brady *et al.* (1989)	Penetrating keratoplasty	Philadelphia, USA	1983–1988	16	375/2299	[111]
Kang *et al.* (2005)	Penetrating keratoplasty	North Carolina, USA	1980–1981	15.6	29/186	[112]
Kang *et al.* (2005)	Penetrating keratoplasty	North Carolina, USA	1990–1991	13.0	41/316	[112]
Kang *et al.* (2005)	Penetrating keratoplasty	North Carolina, USA	2000–2001	23.8	89/374	[112]
Dobbins *et al.* (2000)	Penetrating keratoplasty	Indianapolis, USA	1982–1996	23.2	978/4217	[113]
Lindquist *et al.* (1991)	Penetrating keratoplasty	Washington State, USA	1980–1988	12.5	200/1594	[114]
Mamalis *et al.* (1992)	Penetrating keratoplasty	Utah, USA	1981–1990	5.8	11/199	[115]
Flowers *et al.* (1995)	Penetrating keratoplasty	Los Angeles, USA	1989–1993	4.8	53/1104	[116]
Mohamadi *et al.* (1989)	Penetrating keratoplasty	Los Angeles, USA	1984–1988	4.4	45/1019	[117]
Godeiro *et al.* (2007)	Specimens	Montreal, Canada	1999–2004	10.2	51/500	[118]
Dorrepaal *et al.* (2007)	Penetrating keratoplasty	Toronto, Canada	1996–2004	13.0	101/777	[119]
Liu *et al.* (1997)	Penetrating keratoplasty	Toronto, Canada	1986–1995	7.7	69/904	[120]
Maeno *et al.* (2000)	Penetrating keratoplasty	Toronto, Canada	1964–1997	9.56	592/6222	[121]
Europe						
Haamann *et al.* (1994)	Penetrating keratoplasty	Denmark	1984–1993	13.9	25/180	[122]
Wylegala *et al.* (2005)	Penetrating keratoplasty	Katowice, Poland	2000–2004	9.0	47/517	[123]
Poinard *et al.* (2003)	Penetrating keratoplasty	French Penetrating Keratoplasty Registry, France	2000–2001	9.1	1058/11,598	[124]
Legeais *et al.* (2001)	Penetrating keratoplasty	Paris, France	1980–1999	9.4	352/3736	[125]
Fasolo *et al.* (2006)	Penetrating keratoplasty	Italy	2001–2004	3.6	159/4415	[126]
Cursiefen *et al.* (1998)	Penetrating keratoplasty	Erlangen, Germany	1992–1996	14.9	186/1250	[127]
Lang *et al.* (1988)	Penetrating keratoplasty	Erlangen, Germany	1964–1986	11.0	178/1618	[128]
Kervick *et al.* (1990)	Penetrating keratoplasty	Belfast, Northern Ireland	1980–1988	9.7	17/175	[129]

Author (year)	Procedure	Location	Years	Proportion (%)	Absolute	Ref.
Morris *et al.* (1989)	Penetrating keratoplasty	London, UK	1985–1987	6.2	31/500	[130]
Al-Yousuf *et al.* (2004)	Penetrating keratoplasty	London, UK	1990–1999	9.3	73/784	[131]
Rahman *et al.* (2008)	Penetrating keratoplasty registry	UK	2007–2008	15.4	227/1478	[132]
South America						
Calix Netto *et al.* (2006)	Penetrating keratoplasty	Sorocaba, Brazil	6–12/2003	1.9	2/171	[133]
Sano *et al.* (2008)	Penetrating keratoplasty	São Paulo, Brazil	1996–2005	2.9	17/587	[134]
Sano *et al.* (2008)	Penetrating keratoplasty	São Paulo, Brazil	1991–1995	3.6	9/249	[134]
Oceania						
Edwards *et al.* (2002)	Transplants	New Zealand	1991–1999	4.4	58/1370	[135]
Australian Corneal Graft Registry (1993)	Corneal grafts	Australia	1985–1991	4.7	170/3608	[136]
Asia						
Chen *et al.* (2001)	Penetrating keratoplasty	Taiwan	1987–1999	4.5	35/770	[137]
Xie *et al.* (2007)	Penetrating keratoplasty	Qingdao, China	1997–2002	Corneal dystrophies 3.9	67/1702	[138]
Zhang *et al.* (2005)	Penetrating keratoplasty	Shanghai, China	1994–2003	Corneal dystrophies (non-Fuchs) 3.8	9/229	[139]
Chan *et al.* (1997)	Penetrating keratoplasty	Singapore	1991–1995	Corneal dystrophies 10.4	34/327	[140]
Tan *et al.* (2008)	Penetrating keratoplasty	Singapore	1991–2003	7.1	64/2100	[141]
Sony *et al.* (2005)	Penetrating keratoplasty	New Delhi, India	1997–2003	0.74	15/2022	[142]
Pandrowala *et al.* (2004)	Penetrating keratoplasty	Hyderabad, India	6 years	1.34	30/2244	[143]
Rao *et al.* (2001)	Bilateral penetrating keratoplasties	Tamil Nadu, India	1985–1997	5.3	2/38	[144]
Middle East						
Al Faran *et al.* (1991)	Keratoplasties	Riyadh, Saudi Arabia	1983–1988	0.6	12/2108	[145]
Yahalom *et al.* (2005)	Penetrating keratoplasty	Jerusalem, Israel	1981–2000	2.6	28/1057	[146]
Frucht-Pery *et al.* (1997)	Penetrating keratoplasty	Hadassah, Israel	1961–1990	3.1	32/1018	[147]