Demographic Profile and Clinical Course of Fuchs Endothelial Corneal Dystrophy in Mexican Patients.

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Research Article

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Abstract

Purpose

To describe the demographic characteristics and clinical course of Fuchs endothelial corneal dystrophy (FECD) in a Mexican-mestizo population.

Methods

A retrospective observational and longitudinal study was performed in consecutive patients with the clinical diagnosis of Fuchs endothelial corneal dystrophy seen at our institution. Initial and last follow-up best corrected visual acuity, slit-lamp findings, and specular microscopy endothelial morphometric parameters were analyzed.

Results

One hundred and two eyes belonging to 51 patients were included in the analysis. Median age at the time of diagnosis was 69 years (range, 25–87 years) with a female-to-male ratio of 3.3:1. Visual loss (59.8%) and fluctuating matutine vision (7.8%) were the most common complaints at presentation. Regarding FECD staging, 65 (63.7%) were classified as stage-I FECD, 21 (20.6%) stage-II, and 15 (14.7%) as stage-III. A high percentage of eyes (44%) presented visual impairment ($\leq 20/40$) at presentation, and the presence of isolated corneal guttata was the most common stage of presentation (64%) at slit-lamp examination. Fifty-nine (57.8%) eyes did not require any medical or surgical management, and 17% of the evaluated eyes finally required a corneal transplantation, being penetrating keratoplasty with 8 (44.4%) eyes the most frequent technique performed.

Conclusion

Demographical characteristics of Fuchs dystrophy regarding age at presentation, gender distribution, and clinical stage at the time of diagnosis did not differ significantly from other international reports. Almost 20% of these patients will require keratoplasty during the disease, emphasizing the need for safer and more reproducible keratoplasty techniques.

Introduction

Fuchs endothelial corneal dystrophy (FECD) is a common aging disorder of the corneal endothelium. It is the most frequent endothelial dystrophy and the leading indication for corneal transplantation worldwide [1]. FECD is a hereditary condition characterized by the progressive decline of corneal endothelial cell density (ECD) with extracellular matrix (ECM) deposition on Descemet's membrane (DM) in the form of guttae [2]. When the number of functional endothelial cells becomes critically low, fluid permeates the

corneal stroma leading to edema and decreased vision [3]. Persistent stromal edema results in subepithelial and epithelial bullae, which eventually migrate anteriorly and rupture through the corneal epithelium, causing episodes of sharp pain, tearing, and foreign body sensation [4]. Worsening of stromal edema results in keratocyte apoptosis and subepithelial fibrosis with severe vision impairment due to loss of corneal transparency [5].

Despite being a significant cause of visual loss in elderly patients and the first indication of corneal transplantation worldwide, the incidence and prevalence of FECD are challenging to obtain since many patients present with non-progressing corneal guttae, and most patients with FECD have signs and symptoms that manifest late in life, requiring surgical intervention after the sixth or seventh decades [6].

The clinical and demographical descriptions of FECD patients are based mainly on the experience of analyses performed on Caucasian and Asian populations [7-13]. To date, there is no information regarding the epidemiological characteristics of FECD in Hispanics. We analyze the demographical characteristics, clinical findings, disease stage, clinical course, and visual outcomes from FECD in a Mexican-mestizo population in the present study. According to an extensive literature search, this is the largest case series of FECD reported in Latin America.

Methods

We conducted a retrospective, observational, and longitudinal case series study of FECD patients seen at the Cornea and External Disease Service of our institution between January 2002, and November 2020. The study was previously approved by the Ethics (License No. P000355-CCEDFM-CEIC-CR002) and Research (License No. P000355-CCEDFM-CI-CR002) Committees of our institution (License No. CONBIOETICA 19 CEI 011-2016-10-17 and COFEPRIS 20 CI 19 039 002, respectively), following the tenets of the Declaration of Helsinki.

All patients included in this study were diagnose and classified according to Adamis et al.'s staging system (Table 1) [2, 5]. The classification of the FECD stage was based on clinical features (Figure 1). The main characteristic distinguishing corneal guttae from FECD is corneal edema developing in the latter [14].

Relevant clinical information was retrieved from the medical records, including demographics, stage of FECD, best-corrected visual acuity (BCVA), main complaint at presentation, slit lamp biomicroscopic evaluation, lens status, posterior segment evaluation, including the retina and optic nerve, and medical and/or surgical management. Cataract was graded according to the Lens Opacities Classification System III (LOCS III) [15]. Specular microscopy (Tomey EM-3000, Nagoya, Japan) was performed to obtain the corneal morphometric analysis in all cases. Data retrieved included endothelial cell density (ECD, average number of CECs per mm^2), pleomorphism (percentage of hexagonal cell), polymegathism (CEC size variations), or the coefficient of variation (variation in cell area), and central corneal thickness (CCT). An ECD $<1,000$ cells/ mm^2 , a pleomorphism $<50\%$, and a polymegathism >0.40 renders the cornea

a significant risk for endothelial decompensation after anterior segment surgery [16]. Initial and final BCVA were classified into four groups according to the International Classification of Diseases (ICE)-11 (2018): (1) mild, presenting BCVA worse than 6/12 (Snellen 20/40); (2) moderate, presenting BCVA worse than 6/18 (Snellen 20/60); (3) severe, presenting visual acuity worse than 6/60 (Snellen 20/200); and (4) blindness, presenting visual acuity worse than 3/60 (counting finger at 1-meter). A BCVA better than 6/12 (Snellen 20/40) was considered optimal. To assess the visual acuity of our study group, we first excluded patients with significant cataract defined as any LOCS III grading ≥ 2 , posterior capsular opacification, macular pathology (age-related macular degeneration, choroidal neovascularization, macular edema, vitreoretinal traction, epiretinal membrane formation, atrophy, among others), proliferative diabetic retinopathy, advanced glaucoma, and high myopia (six diopters or greater).

At last consultation, follow-up time, BCVA, lens status, medical and/or surgical management required to control the disease, and disease progression according to the Adamis et al.'s staging system were recorded [2, 5]. In patients with specular microscopy available at the last follow-up visit, the ECD loss was analyzed. The initial and final BCVA was measured with the Snellen visual acuity chart under standardized conditions and converted into the LogMAR scale for statistical purposes.

Statistical analyses were performed using IBM SPSS v.24 (IBM Inc., Armonk, NY, USA). Frequencies and percentages were used to describe categorical variables. Normality was evaluated with the Shapiro-Wilk test. Normally distributed variables were described with means and standard deviations (SDs), while non-normally distributed variables were described with medians and interquartile ranges (IQR).

Results

Fifty-one Mexican-mestizo patients (102 eyes) with a clinical diagnosis of FECD were included in the study. A total of 39 (76.5%) were women and 12 (23.5%) men, with a female-to-male ratio of 3.3:1 and aged between 25 and 87 years (median 69, IQR = 16.75). The sociodemographic characteristics of the study population are shown in Table 2.

A total of 32 (62.8%) patients were otherwise healthy at the first visit. Also, 86 (84.3%) eyes had no prior history of ocular disease; however, eight (7.8%) eyes had a confirmed diagnosis of non-proliferative diabetic retinopathy, six (5.9%) had glaucoma, and two (2.0%) eyes, age-related macular degeneration. Sixty-eight (66.7%) eyes had no previous history of ocular surgery. Phacoemulsification surgery with 25 (24.5%) eyes (Figure 2), followed by refractive surgery with 6 eyes (5.9%) were the prevailing ocular procedures reported during the follow-up time. While visual loss (59.8%) and fluctuating matutine vision (7.8%) were the most common complaints at presentation, 16.7% of eyes were asymptomatic at the first visit.

Table 3 outlines the clinical characteristics of all eyes included for analysis at the first visit. According to the ICE-11, 29 (55.8%) eyes had no visual impairment, while 15 (28.8%) eyes had mild, 5 (9.6%) moderate, and 1 (1.9%) severe visual impairment. Two eyes (3.8%), classified as stage-III FECD, were blind at presentation due to corneal opacity. The overall mean BCVA was 0.33 ± 0.54 . While thirty (29.4%) eyes

had a clear lens and healthy optic nerve and retina at the initial examination, 72 (70.6%) eyes had either cataract, optic nerve and/or retinal abnormalities. Regarding corneal findings, 65 (63.7%) were classified as stage-I FECD, 21 (20.6%) stage-II, and 15 (14.7%) as stage-III FECD according to the Adamis and coworkers classification [5]. One eye had a prior history of penetrating keratoplasty (PKP). Eighty-seven (85.3%) eyes had specular microscopy performed at the diagnosis. The corneal morphometrical analysis, age, and the clinical FECD stage at presentation (Figure 3) are shown in Table 4.

Fifty-nine (57.8%) eyes did not require any medical or surgical management. Seventeen (16.7%) eyes received medical management with hypertonic saline eyedrops alone (15 eyes) or in combination with a bandage contact lens (BCL, 2 eyes). On the other hand, 18 (17.6%) eyes required corneal transplantation. Of those, 8 (44.4%) eyes were managed with PKP, 3 (16.7%) with a triple procedure (PKP + cataract extraction and intraocular lens implantation), and 2 (11.1%) eyes with Descemet membrane endothelial keratoplasty (DMEK). The remaining 5 (27.8%) eyes are currently waiting for a corneal donor. Complications arising from any form of corneal transplantation were present in 38.9% of the eyes, including 4 eyes with allographic rejection, 2 eyes with ocular hypertension (OHT), and one eye with FECD recurrence.

After a median follow-up of 60 months (range: 24 – 180; IQR 78), we could retrieve specular microscopy data in a subgroup of 26 (25.49%) of the eyes. Table 5 shows the disease stage and age at the last visit and the comparative corneal morphometric analysis of eyes at initial and final visits.

Discussion

The demographic profile, corneal morphometric characteristics, clinical course, and therapeutic outcome of Latin American patients with FECD have not been previously described. We analyzed 102 eyes from 51 Mexican-mestizo patients with FECD. Females predominated males by three to one, comparable to other Caucasian series showing a similar female predominance [4, 7, 8]. However, in a study performed in the United States, Rosenblum et al. reported a much larger female predominance (7.3:1) [17]. Another Caucasian study of 32 patients from Tangier found a female-to-male ratio of 2.6:1 [9], while data from Asians on predominantly corneal guttae stage I of FECD reported a ratio of 2.8:1 [11]. On the other hand, Lorenzzetti et al. found no significant differences in the incidence of corneal guttae between Caucasians and African-Americans [8].

Regarding the development of advanced FECD, female sex and age are the most significant risk factors for severe FECD requiring corneal transplantation [4, 18, 19]. Afshari et al. and Chan et al. reported a female prevalence of 77.6% and 61.8%, respectively, in FECD patient candidates for corneal transplantation [4, 18]. Contrary to these reports, only 17 eyes (16.67%) required corneal transplantation in our study. Of those, 64.7% were female patients. The reason for this gender-based disparity remains elusive. However, a recent murine study found that ultraviolet-A (UVA) light triggers estrogen-metabolizing enzymes and forms reactive estrogen metabolites and estrogen-DNA adducts in females but not male mice [20]. Moreover, UVA light also results in greater CEC loss and edema due to loss of tight-junction

proteins (e.g., ZO-1) [16]. UVA exposure, however, might not fully explain the higher prevalence of FECD in women. In a study measuring the amount of ultraviolet radiation dose received by United States citizens, Godar et al. reported that males received higher doses [21]. Castanedo-Cazares et al. reported similar results in a Mexican-mestizo population [22]. The same author reported in another study that Mexicans disregard the potentially harmful effects of sun exposure, despite being aware of such effects [23]. Although UVA light damage seems a plausible explanation for the presence of FECD in our population, the gender-based disparity cannot be explained on this basis. More extensive studies are required to establish such a potential association.

Like previous studies, the average age of affected individuals was 65.35 years [11, 17]. Early-onset FECD, described as disease development before 40, occurred in only 3 (5.89%) of our patients. Such finding differs from other registries reporting a prevalence of up to 31.5% of FECD patients aged 10 to 39 [8]. So far, only the presence of the *COL8A2* gene is associated with the early-onset form of FECD [24]. A variant presenting in the first decade of life has been described in patients with the *COL8A2* gene mutations [25].

After excluding eyes with other potential causes of vision loss, the mean baseline BCVA in our study was 0.32 LogMAR (20/43 Snellen eq.), which differs from other studies reporting better visual acuities (0.08 LogMAR, 20/24 Snellen eq.) in patients with FECD at diagnosis [26]. Of those, 12 (23.01%) and 6 (11.54%) eyes were classified at presentation as FECD stage 2 and 3, respectively. Thirty-four eyes (65.4%) were classified as stage 1.

Although variable, a cutoff value $\geq 2,500$ endothelial cells/mm² has consistently been reported as normal [26-30]. In FECD patients, such values significantly decrease as the disease progresses. In a study performed in Asians, Kobashi et al. found a mean ECD of 1,893 cells/mm² in patients with FECD [26]. In the present study, we report an even lower ECD (1,516.69 cells/mm²). Such difference might be explained by ethnicity but also by a delayed diagnosis. Previous studies have shown significant differences in the corneal ECD among different racial and ethnic groups and ages [27, 29]. McGlumphy et al. reported that, compared with Caucasians, African Americans and Asians had increased values of ECD, Hispanics had lower values [27]. A decrease in ECD occurred in our series with the increasing severity of FECD and age (Table 5). Corneal thickness represents an important parameter to measure disease progression and aid in surgical decision-making [16]. The mean CCT was 523.92 μ m in stage-I, 564.08 μ m in stage-II, and 607.40 μ m in stage-III in our study population. Kopplin et al. evaluated the relationship between CCT and FECD severity [31]. They found that with the increasing severity of FECD, an increase in CCT occurred. Such findings were also observed in patients without clinically visible edema [31]. Moreover, a study of 259 eyes managed with PKP found that a preoperative corneal thickness of 775 μ m or greater was a significant risk factor for a BCVA of 20/100 or worse, while below that level, BCVA was 20/60 [4].

Seventeen percent of eyes required corneal transplantation. Only two out of seven eyes (28.6%) managed with PKP or triple procedure achieved a BCVA better than 20/200. However, the two eyes managed with DMEK achieved a final BCVA of 20/20 and 20/40. A recent study performed by Castellucci et al. compared the visual outcomes and quality of life after bilateral ultrathin Descemet's stripping automated

endothelial keratoplasty (UT-DSAEK) with bilateral PKP for FECD [32]. Corneal high-order aberrations (HOAs), contrast sensitivity, BCVA, and quality of life were measured. After a mean follow-up of 32 months, all outcomes significantly favored UT-DSAEK. Only posterior HOAs were similar among groups. This study, however, was retrospective and included a small sample (13 in the UT-DSAEK group vs. 11 in the PKP group) [32]. Regarding graft clarity and ECD, Price et al. demonstrated that DSAEK and PKP were comparable after 3-years. Notwithstanding, a 3.2-mm DSAEK incision width was associated with significantly less ECD than a 5.0-mm incision [33].

The limitations to this study have to do with its retrospective nature, limiting the availability of standardized and complete clinical data and, a reasonable number of eyes analyzed had other ocular comorbidities that precluded an accurate analysis. Strengths include the fact that this is the first study evaluating the clinical profile of FECD patients in a Latin American population.

Conclusions

The characteristics of Fuchs dystrophy in Mexican-mestizo patients, regarding gender distribution, age at presentation, and early detection, do not vary significantly from other international reports. Almost 20% of these patients will require keratoplasty during the clinical course of the disease. Therefore, appropriate surgical indication and timing are crucial to avoid late-stage complications, including mature cataract formation, prominent stromal edema, and scarring resulting in significant visual impairment affecting the patient's quality of life. Furthermore, late surgical intervention conditions the patient to penetrating keratoplasty instead of a less invasive and much quicker visual rehabilitating procedure such as endothelial keratoplasty (DSAEK or DMEK). This study increases the awareness of the occurrence of FECD in Latin American patients and contributes to improving our understanding of the clinical behavior of this visual disabling disease in this ethnic group.

Declarations

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Conflict of interest: The authors declare no conflicts of interest nor financial disclosures.

Availability of data and material: Data of this study is available upon request from the corresponding author. The data are not publicly available because the study was approved under informed consent for research purposes, protecting the participants' privacy, prohibiting sharing information with third parties according to the Mexican General Law for the Protection of Personal Data in Possession of Obligated Parties.

Code availability: Not applicable.

Authors' contributions: MBS: study protocol preparation, Ethics and Research Committees submission and revision, patients' assignment, data collection and analysis, manuscript writing and editing; JCHC: study design, statistical analysis, manuscript writing, and revision; RERL: data collection, manuscript writing and revision, tables, and figures editing; ARG: original idea, project coordination, study design, funds raising, manuscript writing and editing. All authors read and approved the final manuscript.

Ethics approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics (Registration No. P000355-CCEDFM-CEIC-CR002) and Research (Registration No. P000355-CCEDFM-CI-CR002) Committees of our institution (License No. CONBIOETICA 19 CEI 011-2016-10-17 and COFEPRIS 20 CI 19 039 002, respectively).

Informed Consent Statement: Informed consent by the patient was obtained to disclose health information and publish clinical images.

Consent for publication: Not applicable.

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Tables

Table 1 Grading of Fuchs endothelial corneal dystrophy. [5]

Grade	Vision loss	Symptoms	Clinical findings
I	None	None	Nonconfluent central corneal guttae, pigment deposition on the posterior corneal surface, and a grayish thickened Descemet membrane
II	Mild to moderate	Diurnal glare	Confluent central corneal guttae with spreading towards the periphery and varying degrees of stromal edema
III	Moderate to severe	Pain episodes	Stromal edema progresses towards the corneal epithelium leading to epithelial and subepithelial bullae formation, which may rupture
IV	Severe	None	Dense subepithelial scar tissue formation with corneal opacification and vascularization
Adapted from: Adamis AP, Filatov V, Tripathi BJ, Tripathi RC (1993) Fuchs' endothelial dystrophy of the cornea. Surv Ophthalmol 38:149-68. https://doi.org/10.1016/0039-6257(93)90099-s			

Table 2. Sociodemographic characteristics of Mexican-mestizo patients with Fuchs endothelial corneal dystrophy.

Characteristics	No patients (%)
Gender	
Female	39 (76.5)
Male	12 (23.5)
Age*	
Female	65.62 (22-83)
Male	64.50 (25-87)
Systemic disease	
None	32 (62.8)
Diabetes mellitus	6 (11.8)
Hypertension	4 (7.8)
Diabetes mellitus and hypertension	3 (5.9)
Hypothyroidism	3 (5.9)
Rheumatoid arthritis	2 (3.9)
Systemic lupus erythematosus	1 (2.0)
History of ocular disease	No. eyes (%)
None	86 (84.3)
Glaucoma	6 (5.9)
Non-proliferative diabetic retinopathy	8 (7.8)
Age-related macular degeneration	2 (2.0)
History of ocular surgery	
None	68 (66.7)
Phacoemulsification	25 (24.5)
Vitrectomy and phacoemulsification	2 (2.0)
Refractive surgery	6 (5.9)
Penetrating keratoplasty	1 (1.0)
Chief complaint	
No symptoms	17 (16.7)
Vision loss	61 (59.8)

Glare	4 (3.9)
Dry eye	2 (2.0)
Photophobia	3 (2.9)
Fluctuating vision	8 (7.8)
Floaters	4 (3.9)
Red eye	3 (2.9)
*Median (range)	

Table 3. Clinical features of Fuchs endothelial corneal dystrophy obtained at initial consultation.

Characteristics	No. eyes (%)
Snellen BCVA (52 eyes)^ß	
> 20/40	29 (55.8)
≤ 20/40 – 20/60	15 (28.8)
< 20/60 – 20/200	5 (9.6)
< 20/200 – CF 1-meter	1 (1.9)
< CF 1-meter	2 (3.8)
Lens status	
Clear	33 (32.4)
Cataract	42 (41.2)
Pseudophakia	26 (25.5)
Aphakia	1 (1.0)
Optic nerve appearance[¥]	
Normal	94 (92.2)
Glaucomatous damage	4 (3.9)
Retina & vitreous appearance[¥]	
Normal	79 (77.5)
Diabetic retinopathy	6 (5.9)
Macular disease ^α	13 (12.7)
Corneal findings [5]^{*,¶}	
Stage I: Corneal guttaes	65 (63.7)
Stage II: Corneal edema	21 (20.6)
Stage III: Bullous keratopathy	15 (14.7)
Stage IV: Corneal scarring	0 (0)
BCVA, best corrected visual acuity; CF, counting fingers.	
^ß After excluding for patients with significant cataract, posterior capsular opacification, macular atrophy, proliferative diabetic retinopathy, advanced glaucoma, and high myopia (six diopters or greater).	
[¥] In four eyes (3.9%) optic nerve evaluation was not possible due to opaque media.	

^a Age-related macular degeneration, macular edema, vitreomacular traction syndrome, atrophy

* Staging according to Adamis AP, Filatov V, Tripathi BJ, Tripathi RC (1993) Fuchs' endothelial dystrophy of the cornea. *Surv Ophthalmol* 38:149-68. [https://doi.org/10.1016/0039-6257\(93\)90099-s](https://doi.org/10.1016/0039-6257(93)90099-s)

[‡]One eye had previous history of penetrating keratoplasty.

Table 4. Disease stage, age, and corneal morphometric analysis at presentation.

FECD Stage	No. (%)	Age (yrs)*	ECD (mm ²)*	CV (%)*	6A (%)*	CCT (μm)*
I	59	64.0 ± 16.3	1719.1 ± 642.9	49.6 ± 12.8	36.8 ± 13.5	523.9 ± 46.8
II	17	66.5 ± 6.6	1266.0 ± 703.7	44.2 ± 13.6	29.0 ± 10.2	564.0 ± 72.2
III	11	76.0 ± 8.3	818.2 ± 285.2	53.9 ± 19.1	31.5 ± 6.6	607.4 ± 62.5
Total	87	66.0 ± 14.5	1516.6 ± 695.2	49.1 ± 14.0	34.7 ± 12.5	543.0 ± 61.6
* Mean ± standard deviation						
ECD, endothelial cell density; CV, coefficient of variation/polymegathism; 6A, hexagonality/pleomorphism; CCT, central corneal thickness						

Table 5. Disease stage, age, and comparative corneal morphometric analysis at last visit.

FECD Stage	No. (%)	Age (years)*	ECD (mm ²)*	CV (%)*	6A (%)*	CCT (μm)*
I	10	68.8 ± 22.3	1220.7 ± 516.4	52.1 ± 8.2	30.5 ± 5.1	510.8 ± 58.0
II	11	81.5 ± 9.8	1232.0 ± 710.6	54.6 ± 15.7	33.3 ± 8.8	571.7 ± 53.6
III	2	77.5 ± 0.7	1119.5 ± 738.9	50.5 ± 7.7	34.5 ± 6.3	567.0 ± 46.6
IV [‡]	3	76.3 ± 0.58	1083.3 ± 220.7	38.0 ± 18.1	-	519.6 ± 31.5
At presentation [¥]		69.1	1319.1	50.0	31.6	545.4
Last visit [¥]		75.5 ± 15.3	1201.85 ± 560.3	51.5 ± 13.13	32.2 ± 7.1	543.3 ± 57.5
% change from baseline [¥]		+8.48	- 8.89	+ 2.91	+ 1.89	- 0.39
<p>* Mean ± standard deviation</p> <p>[‡] The specular microscopy (Tomey EM-3000, Nagoya, Japan) was not able to obtain hexagonality values</p> <p>ECD, endothelial cell density; CV, coefficient of variation/polymegathism; 6A, hexagonality/pleomorphism; CCT, central corneal thickness</p> <p>[¥] Values from the 26 eyes with specular microscopy at initial and final visit</p>						

Figures

Figure 1

A. Fine endothelial guttae in a patient with stage I FECD; B. Direct and indirect transillumination of extensive corneal guttae; C. Stage III FECD with significant stromal edema and Descemet folds.

Figure 2

68 years-old-female with stage I FECD who developed a 3+ NS (A), decreasing her BCVA to 20/200 OD. The patient was successfully operated of clear cornea phacoemulsification with a PC-IOL implantation (B), regaining a BCVA of 20/25 (C). Footnote: FECD: Fuchs endothelial corneal dystrophy, NS: nuclear sclerosis, BCVA: best-corrected visual acuity, PC-IOL: posterior chamber intraocular lens.

Figure 3

A. High magnification slit-lamp specular reflection image of a cornea with FECD showing prominent guttae. B. Specular macroscopy of the same patient showing a CD = 1,106 cells/mm² with a high pleomorphism (only 18% hexagonal cells), and 66% polymegethism.