·Review·

Characteristics of corneal dystrophies: a review from clinical, histological and genetic perspectives

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Abstract

• **Corneal dystrophy is a common type of hereditary corneal diseases. It includes many types, which have varied pathology, histology and clinical manifestations. Recently, the examination techniques of ophthalmology and gene sequencing advance greatly, which do benefit to our understanding of these diseases. However, many aspects remain still unknown. And due to the poor knowledge of these diseases, the results of the treatments are not satisfactory. The purpose of this review was to summarize the clinical, histological and genetic characteristics of different types of corneal dystrophies.**

• **KEYWORDS:** corneal dystrophy; clinic; histology; gene mutation

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INTRODUCTION

Corneal dystrophies (CDs) are a group of commonly-occurring primary, progressive corneal diseases. Depending on the anatomical sites, CDs can be classified into 3 subtypes: 1) anterior CDs include anterior basement membrane dystrophy (ABMD) and Meesman's epithelial dystrophy; 2) stromal CDs include Reis-Bueckler's dystrophy, honeycomb dystrophy, lattice dystrophy, granular dystrophy, Avellino dystrophy, macular dystrophy, Schnyder crystalline dystrophy, Fleck dystrophy, and congenital hereditary stromal dystrophy; 3) endothelial CDs include Fuch's dystrophy, congenital hereditary endothelial dystrophy, and posterior polymorphous dystrophy. Most CDs are characterized with varied shapes of corneal opacities. CDs have been investigated by many ophthalmologists worldwide, but their mechanisms remain unclear in many cases. Although CDs are still enigmatic, our knowledge about them has been expanded greatly in recent years due to the development of gene sequencing techniques and ophthalmological examination advances [*e.g.* high-definition optical coherence tomography (OCT), confocal microscopy]. This review highlights the advances in our understanding of CDs based on researches in recent years.

MATERIALS AND METHODS

Search Strategy To identify the relevant studies, we searched PubMed for papers investigating the clinical manifestations, histology or genetics of CDs. The search was through May 2015 with no language restrictions. Each subtype of CDs was searched separately. For example, the searching key items of ABMD include: ABMD, epithelial basement membrane dystrophy (EBMD), Cogan microcystic dystrophy, map-dot-fingerprint (MDF) dystrophy, clinic, histology, genetics, gene mutation. The other CDs were searched with the same means. In addition, we manually reviewed the reference lists from the relevant articles.

Study Selection We aimed to identify all the relevant studies that investigate the clinical, histological or genetic aspects of each types of CDs. We applied the following exclusion criteria: 1) editorials or letters; 2) case series or case reports; 3) studies not investigating the clinic, histology or genetics of CDs; 4) studies not conducted in humans or mice. The first two authors independently reviewed all searched results to get the eligible articles. Discrepancies between the two authors were resolved by the consensus of the third author of this review. In the end, we identified 99 relevant articles, which were used as reference articles in our review.

Anterior (Epithelial and Bowman´s Membrane)

Anterior basement membrane dystrophy ABMD [online mendelian inheritance in man (OMIM) 121820] is also known as EBMD, Cogan microcystic dystrophy or MDF dystrophy. ABMD is characterized by subepithelial bleb-like microcysts, fingerprint lines, geographic map-like lines, and epithelial microcysts or dots, which are all bilateral and frequently asymmetric, revealed by slit-lamp examination. About 10% of ABMD patients develop painful recurrent epithelial erosions [1]. The cause of ABMD remains controversial. Though it is more likely to be age-related, the hereditary pathways in some cases are seemingly autosomal dominant or X-chromosome-related[2-3].

ABMD is histologically characterized by the thickened epithelial basement membrane (EBM) which duplicates and/or insinuates into the corneal epithelium, and the presence of hyperreflective dots, which result in the classical manifestation of MDF opacities in the cornea on slit-lamp examination. More recently, a more finest ultrastructure of ABMD in some cases was studied with confocal microscopy[4] and standard-definition (SD)-OCT [2]. The ABMD lesions have variable shapes (*e.g.* map-, dot-, fingerprint- or bleb-like). In the superficial/basal epithelium and Bowman's membrane under microscopy, the map-like lesion of the cornea presents a different shape of high-reflective extracellular deposits, while the fingerprint-like lesion presents multiple dark striae[4]. Both lesions show a thickened EBM, which invaginates into the epithelium in the form of multi-sheet fibrogranular material [5-8]. The dot-like lesion has 2 subtypes: Cogan cysts and the cysts reported by Bron and Brown [7]. Cogan cysts are the cell degeneration products that aggregate in the form of cyst underneath an intraepithelial sheet. The second subtype is a sheet of fibrogranular material in the EBM and Bowman's membrane. Besides the classical MDF type, there are also some other subtypes, such as Band-shaped and whorled microcystic dystrophy. Under light microscopy, the scraped epithelium shows a transition of normal corneal epithelium into the zone where the cytoplasm is distended with abundant fine vacuoles. Swollen cells are present at all levels of epithelium, and neither periodic acid-Schiff (PAS) nor Alcian blue acid mucopolysaccharide stain shows cytoplasmic positivity[3].

Gelatinous drop-like dystrophy (GDLD) (OMIM 204870), or familial subepithelial corneal amyloidosis, which has an autosomal recessive hereditary pattern, was first reported in 1914 [9]. Though the incidence rate was about 1 in 30 000 in Japan, it is very rare in other countries [10]. GDLD is characterized by an accumulation of amyloid substances in the subepithelial region of the cornea, which have several shapes (yellowish-white, mulberry-like, gelatinous) (Figure 1). In the first decade of life, the accumulation of these substances leads to vision disturbance, foreign-body sensation, photophobia, and lacrimation. In the later stages, neovasculation may occur in the subepithelium and superficial stroma [11]. Surgical intervention is temporally effective, but recurrence within a few years has been reported[12-13].

GDLD is correlated with the gene mutations on the tumor-associated calcium signal transducer 2 (TACSTD2)[14]. The TACSTD2-encoded protein is a monomeric cell surface glycoprotein expressed in the cornea, trophoblasts, and most carcinomas [15-16]. To date, more than 20 mutations in TACSTD2 have been identified [11]. In Japan, the major mutation identified in GDLD cases is Q118X in TACSTD2[17].

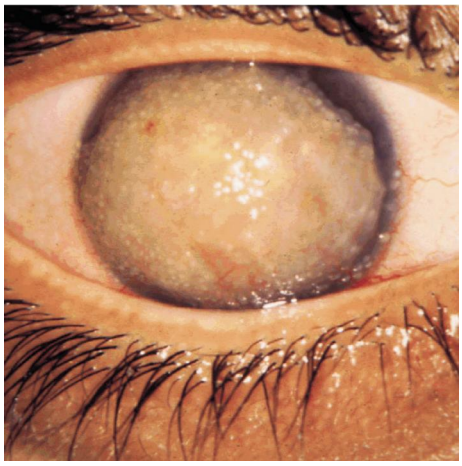

Figure 1 Gelatinous drop-like dystrophy, courtesy of Dr. GK Klintworth.

Histological biopsy reveals a thinned corneal epithelium with an incompletely destroyed Bowman's membrane and subepithelial and stromal amyloid deposits, partially arranged in a band-shape [12]. Immunohistochemical and proteomic analyses reveal that amyloid fibril formation may be attributed to abnormal accumulation of lactoferrin and transforming growth factor beta-induced protein (TGFBIp)[18-19]. Amyloid nodules in the subepithelial layer and the anterior corneal stroma are stained with Congo red to form apple-green birefringence when combined with polarized light[20].

Despite the discovery of many gene mutations, the mechanism of amyloid formation remains unclear [11]. As reported, the abnormal proteins found in the amyloid lesions of GDLD are rich in advanced glycation end (AGE) products and D-b-aspartic acid. It is proposed that the amyloid fibril formations in GDLD may be caused by the non-enzymatic post-translational modifications of proteins, including AGE formation and isomerisation of aspartyl residues[21].

Meesmann´s epithelial corneal dystrophy Meesmann's epithelial corneal dystrophy (MECD) (OMIM 122100) is a rare bilateral disorder confined to the corneal epithelium. Its symptomatic intraepithelial microcysts appear in the first few years of life and can be seen under a slit lamp [22]. Under slit-lamp biomicroscopy, the lesions appear as punctate, bubble-like, round or oval opacities in the corneal epithelium[23]. Nevertheless, vision is usually not affected [24]. MECD is mostly considered as an autosomal dominant inherent disease, but an autosomal recessive form is also reported[23]. MECD has been linked to gene mutation in K3 and K12, which are expressed in the corneal epithelium[25-26].

The dystrophic epithelium is histologically characterized by cellular swelling, cyst-like inclusions, and cytoplasmic vacuoles. The cysts contain PAS-positive degenerated cell debris [27] and are a dense intracellular substance of unknown composition [28]. Electron microscopy has revealed an electron-dense and amorphous "peculiar substance" in the

cytoplasm of epithelial cells. Deposition of the peculiar substance in the epithelium leads to cyst formation and cell death, followed by rapid epithelial regrowth[27].

Stromal Corneal Dystrophies

Reis –Bückler corneal dystrophy Reis-Bückler corneal dystrophy (RBCD) (Corneal Dystrophy of Bowman's I, CDB1, OMIM 608470) was first reported in 1917 by Reis and elaborated in 1949 by Bücklers[29-30]. The affected patients experience recurrent painful erosions of corneal epithelium within the first few years and moderate impairment of visual loss. With aging, however, map-like and ring-like opacities appear in Bowman's membrane, and these lesions become denser and irregular. After the second decade, patients may feel less pain due to the decrease of corneal sensitivity [31]. RBCD is associated with the R124L mutation in transforming growth factor, beta-induced (TGFBI) gene or with atypical cases of F540, H626R, G623D or R124C mutations[32]. However, there are rare reports on RBCD in Chinese patients.

The materials in the opacities are eosinophilic, congophilic and are not stained with PAS on histopathological examination [30]. Light microscopy reveals rod-shaped and trapezoidal deposits in the Bowman's layer and between epithelial cells[32]. This pathological finding is consistent with the superficial granular dystrophy[31].

Avellino Dystrophy Avellino dystrophy, also known as Granular corneal dystrophy type II (GCD2, OMIM 607541), was first reported in patients from Avellino, Italy [33]. GCD2 belongs to the stromal CDs, which also include GCD and lattice corneal dystrophy (LCD). The classical manifestations of GCD2 combine the characteristics of GCD and LCD with discrete granular and lattice opacities. The granular opacities appear earlier and more commonly than the lattice opacities[34]. The opacities could lead to the disturbance of visual acuity, but their location and severity decide the final outcomes [34]. The onset seems to be earlier in homozygote than in heterozygote patients[35]. GCD2 is associated with Arg124His mutation in TGFBI, mapped to chromosome 5q, and has an autosomal dominant pattern [34]. It is proposed that the pathogenesis of GCD2 may be critically related to defective autophagy [36]. However, its mechanism is still poorly understood.

Histologically, GCD2 patients have both hyaline granular deposits, which are located superficially, and amyloid lattice deposits, which appear at deeper sites [35]. The hyaline granules and amyloid lattice lines are stained with Congo red and Masson's trichrome, respectively. Depending on the shapes, GCD2 lesions can be divided into 3 types: 1) type 1, diffuse hazy deposits are superficially located in an irregular soft pattern; 2) type 2, granular deposits are subdivided into superficial round granular deposits (type 2a) and superficial round spiculated ones (type 2b). In GCD2 linear (lattice) deposits, the branches radiated out from the main deposit or trunks are well below the Bowman layer and appear dense and white; 3) some deposits have short side branches (type 3a, <trunk width), while others have long side branches (type 3b, > trunk width) [34].

Central cloudy dystrophy of Francois Central cloudy dystrophy of Francois (CCDF), first reported in 1955 [37], is characterized by polygonal cloudy gray stromal opacities separated by relatively clear lines, which creates a leather-like crocodile appearance in the central cornea. Under the slit lamp, CCDF is larger and more numerous in the posterior part of the stroma and becomes smaller and less frequent in the anterior part. The anterior layers are unaffected in some cases, but the grey patches reach the Bowman's membrane in other cases. The corneal endothelium and epithelium are unaffected[38]. This condition is presumably an autosomal dominance, but its detailed mechanism is unknown [39]. In contrast, similar corneal opacities located at either the central or peripheral cornea in the deep stromal layer are known as "posterior crocodile shagreen" and are usually considered as age-related corneal degenerations. The distinction between two entities is an inheritant pattern[40].

Histologically, light microscopy reveals stromal staining for acid mucopolysaccharide [39]. Transmission electron microscopy (TEM) identifies extracellular vacuoles, some of which have fibrillogranular substances and electron-dense deposits. The opacities result from the extracellular accumulation of mucopolysaccharide and lipid-like material[39].

Schnyder´s central crystalline dystrophy Schnyder's central crystalline dystrophy (SCCD) (OMIM 121800), first described by Schnyder and van Went, has an autosomal dominant inherited pattern. SCCD is characterized by a bilateral clouding of the central cornea, arcus lipoides and/or visible crystalline deposits of cholesterol in the stroma. There is accumulation of phospholipid, unesterified cholesterol and cholesterol ester in the corneal stroma [41]. The precise mechanism remains unclear. Gene mutations are considered to be localized at 1p34.1-p36 interval and in some candidate genes: *FABP3*, *CTPS*, *SCP2*, *COL8A2*, *GALE* and *MTHFR* [41]. To date, mutations of *UBIAD1* have been identified in 28 unrelated families with SCCD [42-45]. Common systemic findings associated with SCCD include hypercholesterolemia and hyperlipidemia, but their presence is not mandatory for the pathogenesis of SCCD.

Histologically, diagnosis of SCCD is confirmed by the lipid and cholesterol deposits in the corneal stroma on oil red O staining under corneal biopsy. Under *in-vivo* confocal microscopy, superficial epithelial cells appear in normal limits, while the basal cell layer is poorly visualized and presents crystalline deposits extending from the anterior stroma. Moreover, large or multiple deposits of brightly reflective crystalline material extend from the anterior stroma

to the middle part, while the regularity and density of keratocytes are remarkably decreased. Although poorly visualized because of the increased reflectivity of the anterior cornea, the posterior stroma shows fine needle-shaped deposits in the posterior stromal matrix, but number decreases with depth and the brightness is reduced compared with the deposits in the anterior stroma[46].

Congenital stromal corneal dystrophy Congenital stromal corneal dystrophy (CSCD) (OMIM 610048) is very rare. Its clinical manifestations include the diffused, bilateral and corneal clouding of flake-like whitish opacities throughout the stroma. The lesions appear shortly after birth and progress with age. Some affected patients also suffer from strabismus or nystagmus. Most patients undergo a penetrating keratoplasty in early adulthood with good outcomes[47]. CSCD is the only known human disease associated with the mutated gene of decorin, a small leucine-rich proteoglycan (SLRP)[48]. Decorin is involved in the control of fibrillogenesis and fibril organization, which contribute to corneal transparency and refractive stability [49]. It is proposed that a truncated SLRP protein core is retained and accumulates intracellularly. This process triggers endoplasmic reticulum stress, which leads to abnormal synthesis and secretion of SLRP and ultimately to impairment of stromal structure and corneal transparency[48].

Histologically, epithelial cells are normal under confocal microscopy, but the reflectivity is increased throughout the stromal layer. In CSCD patients, the lamellar stromal structure is disrupted, which is more severe in the anterior and posterior central stroma. The Fourier-domain OCT images also show higher diffuse reflectivity in the stroma than in the normal cornea. Under electron microscopy, the electron-lucent zones in the corneal stroma are located between the normal lamellae of collagen fibrils with thinned filaments in haphazard arrangement[47].

Francois-Neetans Fleck corneal dystrophy Fleck corneal dystrophy (FCD), also called Francois-Neetens FCD (OMIM 121850), is very rare and first described in 1956[50]. Slit-lamp examination reveals bilateral, flat, gray-white, oval or round discrete opacities throughout the corneal stroma. No systemic abnormality has been reported[51]. FCD occurs early in life but then progresses slowly, and visual acuity is not greatly disturbed. Thus, treatment is not necessary in most cases. Recurrence was not reported in a 10-year follow-up after penetrating keratoplasty [52]. FCD is caused by mutations in PIP5K3 and has an autosomal dominant pattern [53-54]. PIP5K3 gene is responsible for intracellular accumulation and engorgement and the reported mutations result in truncation of PIP5K3 protein before its structure is formed, leading to the abnormal activity of PIP5K3 protein. Further studies are needed to elucidate the function of PIP5K3 protein in FCD patients and normal persons[55].

Histopathologically, some keratocytes contain fibrillogranular material in relatively large intracytoplasmic vacuoles, while some keratocytes contain pleomorphic electron-dense and membranous intracytoplasmic inclusions [56]. The materials were predicted to contain lipids and acid mucopolysaccharides[54].

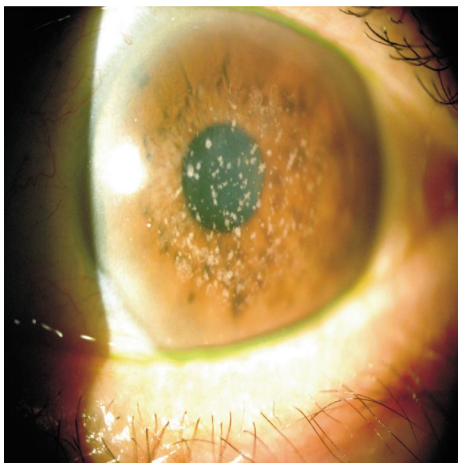

Figure 2 Granular corneal dystrophy (Groenouw type I).

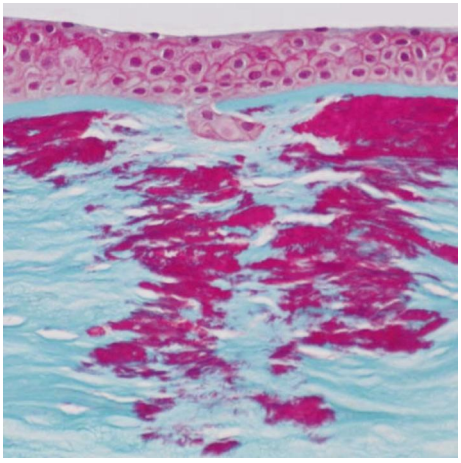

Figure 3 Light microscopy of GCD I. Masson Trichrome stain, courtesy of Dr. GK Klintworth.

GCD I (Groenouw type I) belongs to the TGFBI-associated CDs, which also include RBCD, Thiel-Behnke corneal dystrophy (TBCD), LCD, and GCD II. GCD I is characterized by the discrete opacities in the corneal stroma, which are irregularly crum- or flake-like and appear slightly whitish or glassy (Figure 2). Though most patients are asymptomatic, some patients develop recurrent erosions. The lesions become more numerous and severe with time, leading to visual acuity impairment. Some patients may require keratoplasty in the fifth decade or later[31]. GCDI is autosomal dominant and associated with the mutations on TGFBI. The predominant one of the varied mutations is Arg555Trp [57]. The Arg555Trp mutation will lead to the abnormal degradation/turnover of corneal TGFBIp, and finally to the accumulation and increased propensity to aggregate through electrostatic interactions[58].

Histologic findings with Masson Trichrome red staining and without Congo red staining were tested (Figure 3). Electron

microscopy shows eletron-dense rod-like deposits and microfibrils in keratocytes and epithelial cells. The materials are ascribed to phospholipid [31]. Though the lesions affect mostly the stroma, they do occur within the whole depth of the cornea in some cases.

Lattice corneal dystrophy LCDs are a subgroup of stromal CDs. All LCDs have amyloid accumulation in the stroma and are often arranged in a branching pattern [31]. LCDs have an autosomal dominant pattern and is related to the mutations on the TGFI gene, which encodes keratoepithelin, an extracellular matrix that mediates cell adhesion [59]. LCDs are classified into 3 subtypes: LCD I (OMIM 122200), LCD Ⅱ (OMIM 105120), and LCD Ⅲ and LCD Ⅲ A (OMIMs 204870 and 608471). LCD I is most commonly-seen. The abnormalities of LCD I occur in the first or second decade of life and progress over time. Its anterior stroma has rod-like or linear opacities. Recurrent erosions are common and central anterior stromal haze may develop with age. The lesions usually affect the anterior and central corneas, leaving a relatively normal periphery cornea. The mutation at codon 124 of TGFBI, where the amino acid arginine is replaced by cysteine, is previously considered as the most frequent defect of LCD I. LCD Ⅱ is associated with systemic amyloidosis type V (Meretoja syndrome/Finnish type), which is an autosomal dominant systemic disease. LCD Ⅱ occurs in the early adulthood and affects cornea, skin, and cranial nerves[60]. LCD Ⅲ is clinically manifested as the presence of thick ropy lattice lines in the cornea compared with other subtypes. LCD Ⅲ has an autosomal recessive inheredance pattern and rare corneal erosions. Its lesions appear usually in the fourth decade of life. LCD Ⅲ A has almost the same changes, except that it has recurrent erosions and a dominant inheritance pattern[31].

Histologically, LCD I is considered to affect both the stroma and the epithelium[61]. The stroma show dense deposits, which can be stained with Congo red, PAS, and Masson's trichrome. Dichorism and birefringence appear under polarized light, and fluorescence occurs with thioflavin-T[31]. In LCD Ⅱ, the amyloid marker, Congo red, will show material deposition under Bowman's layer and sometimes at the EBM level [60]. Histopathologically, amyloid deposits of LCD Ⅲ are located in the middle and superficial stromata beneath the Bowman's membrane [31]. In LCD Ⅲ A, the deposits can be stained by Congo red and display red-apple green birefringence under polarized light, thus showing an amyloid component. They are also stained partially positive with Masson trichrome, suggesting the presence of hyaline components in the deposits. The lattice deposits are immunoreactive with the anti-TGFBIp antibody. The epithelium shows dehiscence from the Bowman layer. No abnormality is found in Descemet's membrane (DM) or the endothelium[62].

Macular corneal dystrophy Macular corneal dystrophy (MCD) (OMIM 217800) is very rare and has an autosomal recessive inheritance pattern. Its prevalence rate varies among different countries [63]. MCD begins in early years of life with superficial gray-white opacities concentrated in the middle cornea. With aging, the lesions spread to the periphery and involve the entire corneal stroma. Another characteristic manifestation is corneal thinning [64]. The opacities and abnormal structure of the cornea can lead to severe visual impairment [65]. MCD is associated with the mutations on the CHST6 gene, which encodes corneal N-acetylglucosamine 6-O-sulfotransferase (C-GlcNAc6ST), an enzyme that transfers sulfate to the unsulfated keratan chains on lumican. Lumican helps to maintain the crucial size and ordered structure as well as corneal transparency. It also influences corneal hydration and therefore corneal transparency [66]. MCD can be classified into subtypes I and II, defined by the absence or presence of sulfated keratan sulfate (KS) in the serum. A third subtype, type IA, with KS present in the keratocytes but absent in the cornea and the serum, has been described in MCD patients from Saudi Arabia[65].

Histologically, the cornea in MCD is characterized by the accumulation of extracellular deposits in the stroma and DM as well as by intracellular storage of similar material in the keratocytes and corneal endothelium. The deposits stain with Alcian blue and other histochemical methods for glycosaminoglycans (GAGs). Biochemical studies based on organ cultures of corneas as well as serum analyses of MCD patients suggest that the basic defect in MCD lies in a sulfotransferase, which is specific for sulfation of KS proteoglycan. Molecular genetic studies on MCD contribute to the mapping of the MCD gene and then to the identification of the carbohydrate 6-sulfotransferase (*CHST6*) gene, which codes corneal N-acetyl glucosamine 6-sulfotransferase, as the cause for MCD[67].

Pre –Descemet´s corneal dystrophy Pre-Descemet's corneal dystrophy (PDCD), or deep filiform dystrophy, is very rare. PDCD was first described and called as cornea farinata in 1923 [68]. To date, little research is done in PDCD. It is characterized with fine morphological opacities in the posterior stroma. The lesions are composed of lipids [69]. PDCD is age-related, but the pathology remains unclear [70]. The affected patients are usually asymptomatic, and their visual acuity is very rarely affected [71]. The onset time is usually the fourth to seventh decade. PDCD can be subdivided into deep filiform dystrophy, deep punctiform dystrophy, polychromatic dystrophy, and corneal farinata. These dystrophies have similar essential characteristics, but they differ in color under direct and indirect slit-lamp illumination. Since the deposits are uniform throughout the cornea, they present a variety of colors that are constant[68].

Histopathologic examination of one PDCD patient demonstrates that the pathologic findings are limited to the keratocytes of the posterior stroma [72]. The keratocytes are cytoplasmic vacuoles containing lipid-like materials, which on electron microscopy consist of fibrillogranular and electron-dense lamellar inclusions. No extracellular deposition of a similar material was noted. These findings suggest that the accumulated materials are most likely lipofuscin, a degenerative pigment that accumulates in aged cells[70].

Posterior Corneal Dystrophies

Congenital hereditary endothelial dystrophy Congenital hereditary endothelial dystrophy (CHED) is a rare inherited disorder of the corneal endothelium and characterized by corneal opacification and nystagmus. The onset time of CHED is usually at birth and shortly thereafter. The malfunction and degeneration of the corneal endothelium lead to corneal edema, especially the stroma, and make the cornea appear as ground glass. The condition is known to occur in two genetic forms: autosomal dominant (CHED1, OMIM 121700) and autosomal recessive (CHED2, OMIM 217700). CHED1 is more rare and has some clinical similarities with the posterior polymorphous dystrophy (PPMD)[73], while CHED2 is more severe and usually more common. CHED1 and CHED2 have been mapped to chromosome 20 at two distinct loci: 20p11.2-q11.2 for CHED1[74] and 20p13 for CHED2[75].

Histopathological analysis identified a markedly thickened DM and an atrophied endothelium in CHED2 patients. Additionally, the patient's cornea also had amyloid deposition and spheroidal degeneration. The presence of amyloid was confirmed based on the presence of apple green birefringence viewed under a polarizing filter[76].

Fuchs endothelial corneal dystrophy (FECD) (OMIM 136800) is the most common type of endothelial CD. Bilateral, non-inflammatory and progressive loss of endothelium results in visual loss. FECD is characterized by guttata within cornea (Figure 4), stromal edema, and microcystic epithelial edema. The primary defect is corneal endothelial degeneration, and the secondary defect is corneal edema. Associated manifestations include prominent corneal nerves, stromal opacification, recurrent corneal erosions, open angle glaucoma, female gender, and familial predisposition [77]. Most cases are sporadic, and autosomal dominant inheritance has been recognized in familial cases[78-79]. In summary, mutations in FECD have been found in two transcription factors (TCF4/E2-2 and TCF8/ZEB-1), one collagen subunit (COL8A2), and two membrane proteins (LOXHD1 and SLC4A11/NaBC1). Except LOXHD1, these mutations appear to converge on the collagen secretion and water pump functions of corneal endothelium[80].

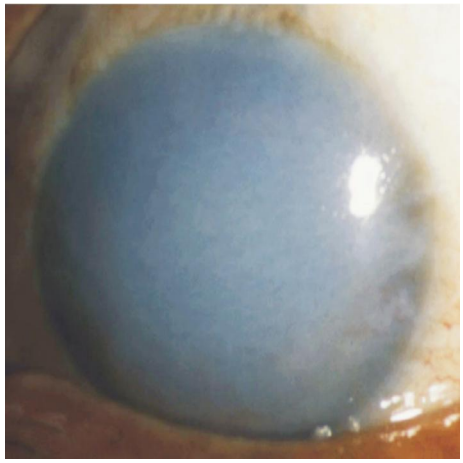

Figure 4 Fuchs endothelial corneal dystrophy, courtesy of Dr. GK Klintworth.

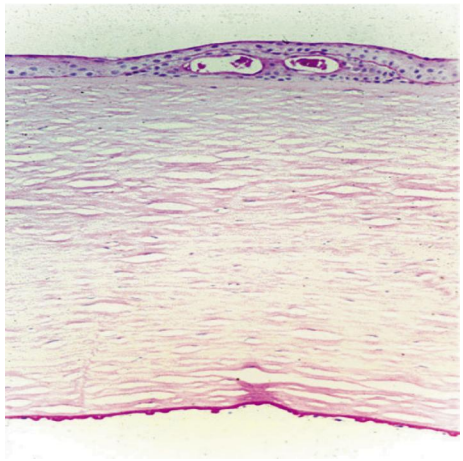

Figure 5 Light microscopy of FECD, PAS stain. Courtesy of Dr. GK Klintworth.

Histologically, some endothelial cells (ECs) are assumed to be fibroblast-like, including swollen mitochondria, dilated endoplasmic reticulum with granular material, increased number of cytoplasmic filaments, and phagocytosed pigment granules [81-83], especially when the posterior fibrillar layer (layer 4) of DM coveres the guttae in the posterior banded layer (layer 3)[83]. TEM and SEM present microvilli, increased number of hemi-desmosomes, and the positive immune-labelling of pancytokeratin and cytokeratin-7, which are markers usually present in almost all cells of epithelial origin [82]. Some FECD specimens had ECs with extremely long filopodia up to 100 mm long that were immuno-positive for KS and orientated in the same plane, giving the impression of mass cell migration in one direction (Figure 5)[84].

Posterior polymorphous corneal dystrophy Posterior polymorphous corneal dystrophy (PPCD) is a rare corneal disease and mainly affects the DM and the corneal endothelium. PPCD is characterized by the asymmetric patches of grouped vesicles, scalloped bands, geographic gray hazy areas, and epithelial-like endothelium (loss of contact inhibition with proliferation and growth over angle and iris). Some patients may develop stromal edema.

Moreover, iris and pupil may change similarly to those in iridocorneal endothelial syndrome. Broad peripheral anterior synechiae and glaucoma are also common. Patients may have symptoms of pains, foreign body sensation, tearing, photophobia, and decreased vision. PPCD is classified into 3 subtypes: PPCD1 (OMIM 122000), PPCD2 (OMIM 609140), and PPCD3 (OMIM 609141), which are associated with the gene mutations on VSX1, COL8A2 and ZEB1, respectively[85-89]. Histologically, the lesions of PPCD are located at the level of the endothelium and DM. The lesions have 3 types: vesicle-type lesions, band lesions and diffuse opacities. The former 2 types are more common than the last one[90-95]. Under slit-lamp, vesicles appear as blister or bleb-like, with an optically clear centre and a small halo of grey-white haze[93]. Previous studies show "epithelium-like" multilayered cells scattered in areas of normal endothelium and deposition of abnormal collagen material on DM, forming an abnormal posterior collagenous layer[90,94,96-97]. The 4 types of cells shown on the posterior corneal surface in PPCD are normal ECs, attenuated or degenerating ECs, fibroblast-like cells, and epithelial-like cells[95].

DISCUSSION

CDs include many subtypes. While some are age-related corneal diseases, most of them are associated with the gene mutations. They are different in causes, clinical manifestations, development, treatments and diagnosis.

The most common symptom may be visual loss. It appears in many types of CDs, such as ABMD, GDLD, RBCD, Avellino CD, GCD, MCD. Nevertheless, the severity of each type may be different, for example, MCD patients may suffer blindness with aging, which requires keratoplasty, the other patients' (PPCD, FCD *etc*) visual acuity remains quite stable in the most part of their lifes. Besides visual loss, foreign body sensation, recurrent erosions, lacrimation and photophobia are also commonly seen in patients. Some other symptoms like strabismus, nystagmus, glaucoma and synechiae are rare, but they may appear in PPCD or FECD.

Histological experiments done on the CDs also present varied findings. In most CDs, the lesions would lead to an abnormal corneal structure, especially in the lesions-concentrated field. However, the corneal structure shows no obvious changes in some types of CDs like CSCD. The lesions may locate in the cell or extracellular space. The substances of the lesions of different types of CDs may be lipid-like materials, acid mucosaccharide or abnormal proteins, which have distinct results after staining with PAS, Masson Trichrome, Congo red *etc*.

Thanks to the advances of gene sequencing techniques in recent years, more and more gene mutations associated with the CDs are identified. The mutated genes of CDs include: VSX1, COL8A2, ZEB1, TCF4/E2-2, TCF8/ZEB-1, COL8A2, LOXHD1, SLC4A11/ NaBC1, CHST6, TGFBI, PIP5K3, UBIAD1, K3, K1, TACSTD2 *etc*. According to the findings of histology and gene sequencing, the hypothesis of some special CDs were proposed by ophthalmologists. For example, Underhaug *et al* [58] thought that the gene mutations of the TGFBI may result in reduction of the proteolytic susceptibility of the mutated TGFBIp leading to the abnormal depositions of the TGFBIp in GCD. Morever, Choi *et al* [36] considered that autophagy may play an important role in the accumulation of the TGFBIp in GCD. However, the exact detailed mechanisms of most CDs remain unclear.

Because of the poor understanding of CDs, there are no efficient treatment methods. Among the treatments, keratoplasty is the ultimate chance to improve the visual acuity of severe patients. However, many patients undergoing keratoplasty may suffer from recurrence within a few years. Because the gene mutations play an important role in most types of CDs, gene research would greatly contribute to the understanding of CDs, leading to a new evolutionary treatment method. In recent years, *in-vitro* gene therapy experiments have already been done [98] and the results give us a perspective vision to cure CDs.

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