Epithelial And Subepithelial Corneal Dystrophies

Corresponding Author:
Dr. Shveta J Bali,
Senior Resident, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences,
9/43, Ladies Hostel, AIIMS, 110029 - India

Submitting Author:
Dr. Shveta J Bali,
Senior Resident, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences,
9/43, Ladies Hostel, AIIMS, 110029 - India

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Author(s): Sachdev R, Bali S J, Gupta N

Abstract

Corneal dystrophies are a heterogenous group of rare, inherited corneal diseases that are typically bilateral, symmetric, non-inflammatory, slowly progressive, and usually bear no relationship to environmental or systemic factors. The word dystrophy is derived from Greek literature (dys = wrong, difficult; trophe = nourishment). Clinically, the corneal dystrophies are divided into three groups based on the principal anatomical location of the abnormalities. Some affect primarily the corneal epithelium and its basement membrane or Bowman layer and the superficial corneal stroma (anterior corneal dystrophies), the corneal stroma (stromal corneal dystrophies), or Descemet membrane and the corneal endothelium (posterior corneal dystrophies). Most corneal dystrophies have no systemic manifestations and present with variable shaped corneal opacities in a clear or cloudy cornea and they affect visual acuity to different degrees.

Section I: Introduction

Corneal dystrophies are a heterogenous group of rare, inherited corneal diseases that are typically bilateral, symmetric, non-inflammatory, slowly progressive, and usually bear no relationship to environmental or systemic factors. The word dystrophy is derived from Greek literature (dys = wrong, difficult; trophe = nourishment). Clinically, the corneal dystrophies are divided into three groups based on the principal anatomical location of the abnormalities. Some affect primarily the corneal epithelium and its basement membrane or Bowman layer and the superficial corneal stroma (anterior corneal dystrophies), the corneal stroma (stromal corneal dystrophies), or Descemet membrane and the corneal endothelium (posterior corneal dystrophies). Most corneal dystrophies have no systemic manifestations and present with variable shaped corneal opacities in a clear or cloudy cornea and they affect visual acuity to different degrees.

Classification of corneal dystrophies

The increasing availability of genetic analyses highlighted the shortcomings of the phenotypic method of classification of corneal dystrophy. Abnormalities in different genes may produce a single phenotype, whereas various defects in a single gene can manifest as varying phenotypes. The International Committee for Classification of Corneal Dystrophies (IC3D) was developed to incorporate the traditional classification of corneal dystrophies with new genetic, clinical, and pathologic information. The anatomic classification continues to group dystrophies according to the structures predominantly involved. Each dystrophy carries a template summarizing genetic, clinical, and pathologic information. A category number from 1 through 4 is assigned depicting the level of evidence supporting the existence of the particular dystrophy. The most defined dystrophies belong to category 1 (a well-defined corneal dystrophy with a gene that has been mapped, identified and specific mutations are known) and the least defined belong to category 4 (a suspected dystrophy without substantial genetic evidence).

Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and specific mutations are known.

Category 2: A well-defined corneal dystrophy that has been mapped to 1 or more specific chromosomal loci, but the gene(s) remains to be identified.

Category 3: A well-defined corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus.

Category 4: This category is reserved for a suspected new, or previously documented, corneal dystrophy, although the evidence for it, being a distinct entity, is not yet convincing.

The category assigned to a specific corneal dystrophy can be expected to change over time as knowledge progressively advances. Eventually, all valid corneal dystrophies should attain the classification of category 1.

THE IC3D CLASSIFICATION (C = CATEGORY)

Epithelial and Subepithelial Dystrophies
1. Epithelial basement membrane dystrophy (EBMD)—majority degenerative, some C1
2. Epithelial recurrent erosion dystrophy (ERED) C4, (Smolandiensis variant) C3
3. Subepithelial mucinous corneal dystrophy (SMCD) C4
4. Mutation in keratin genes: Meesmann corneal dystrophy (MECD) C1
5. Lisch epithelial corneal dystrophy (LECD) C2
6. Gelatinous drop-like corneal dystrophy (GDLD) C1

Bowman Layer Dystrophies
1. Reis–Bucklers corneal dystrophy
(RBCD)—Granular corneal dystrophy type 3 C1
2. Thiel–Behnke corneal dystrophy (TBCD) C1, potential variant C2
3. Grayson –Wilbrandt corneal dystrophy (GWCD) C4

Stromal Dystrophies
1. TGFBI corneal dystrophies
A. Lattice corneal dystrophy
a. Lattice corneal dystrophy, TGFBI type (LCD): Classic lattice corneal dystrophy (LCD1) C1, variants (III, IIIA, I/IIIA, and IV) are C1
b. Lattice corneal dystrophy, gelsolin type (LCD2) C1 (This is not a true corneal dystrophy but is included here for ease of differential diagnosis)
B. Granular corneal dystrophy C1
a. Granular corneal dystrophy, type 1 (classic) (GCD1) C1
b. Granular corneal dystrophy, type 2 (granular-lattice) (GCD2) C1
c. Granular corneal dystrophy, type 3 (RBCD) = Reis–Bucklers C1
2. Macular corneal dystrophy (MCD) C1
3. Schnyder corneal dystrophy (SCD) C1
4. Congenital stromal corneal dystrophy (CSCD) C1
5. Fleck corneal dystrophy (FCD) C1
6. Posterior amorphous corneal dystrophy (PACD) C3
7. Central cloudy dystrophy of Francois (CCDF) C4
8. Pre-Descemet corneal dystrophy (PDCD) C4

Descemet Membrane and Endothelial Dystrophies
1. Fuchs endothelial corneal dystrophy (FECD) C1, C2, or C3
2. Posterior polymorphous corneal dystrophy (PPCD) C1 or C2
3. Congenital hereditary endothelial dystrophy 1 (CHED1) C2
4. Congenital hereditary endothelial dystrophy 2 (CHED2) C1
5. X-linked endothelial corneal dystrophy (XEDC) C2

Section II: Epithelial and Subepithelial Dystrophies

Epithelial Basement Membrane Dystrophy (EBMD)
Alternative Names: Map-dot-fingerprint dystrophy, Cogan microcystic epithelial dystrophy, Anterior basement membrane dystrophy, Dystrophic recurrent erosion.

EBMD is characterized by recurrent corneal erosions as a result of abnormal epithelial-basement membrane adhesion complexes. This dystrophy is the most commonly encountered anterior corneal dystrophy in clinical practice.

Inheritance
Most cases have no definite hereditary pattern.

Autosomal dominant inheritance has been documented in a few cases. Genetic Locus 5q31; gene TGFBI in the minority of cases. Onset is in adult life around 30 years of age. Familial cases may manifest earlier in childhood.

Signs
Maps: appear as gray geographical patches, best observed on broad tangential illumination.

Dots (Cogan) are irregular round, oval or comma-shaped gray-white intraepithelial opacities; clustered like an archipelago in the central cornea. Occur in combination with other signs, especially with maps.

Dots (Blebs of Bron and Brown) are small clear round dots clustered together, visible only on retroillumination.

Fingerprint lines: Parallel, curvilinear branching lines with club shaped terminations. Refractile lines seen on retro illumination.

Combination of maps and dots are noted most frequently, followed by maps alone.

Symptoms
Patients may remain asymptomatic or develop recurrent erosions with pain, lacrimation, and blurred vision. Visual acuity is usually not affected. Irregular astigmatism and increase in higher-order aberration may cause blurred vision.

Histopathology
The major pathology lies in the abnormal synthesis of the epithelial basement membrane. Recurrent erosions occur due to lack of hemidesmosomal connections between the epithelial cells and the abnormal basement membrane.

Maps are areas of projections of the abnormal multilamellar basement membrane into the epithelium; fingerprint lines represent rib-like intraepithelial extensions of basal laminar material; dots represent intraepithelial pseudocyst containing cytoplasmic debris.

In vivo confocal microscopy images document the abnormal epithelial basement membrane protruding into the corneal epithelium, epithelial cell abnormalities, and microcysts. No abnormalities were observed in superficial epithelial cells or the stroma. Confocal microscopy has been reported to assist in the diagnosis of EBMD in patients suffering from recurrent erosion syndrome, particularly in patients with no corneal changes visible biomicroscopically.

Management
Corneal scraping may be performed in cases of recurrent corneal erosions. Following the procedure, a soft contact lens is placed for 24-48 hours and topical antibiotics instilled. A five-year cumulative probability
of recurrence up to 44.7% has been reported following epithelial debridement for anterior basement membrane dystrophy.9

Conservative therapy with hypertonic sodium chloride (to dehydrate the epithelium, allowing it to adhere better) along with lubricating eye drops may be useful in reducing the frequency and severity of attacks. Torres Pérez JD et al suggested that treatment of recurrent corneal erosions with erosion debridement may be better than stromal punctures with a 23- to 25-gauge needle since it implies less potential risks.10

Anterior stromal puncture by Nd:YAG laser has been reported to be an effective and simple procedure to treat recurrent corneal erosion with minimal complications.11

Phototherapeutic keratectomy using an excimer laser with low pulse energy and low number of pulses has been reported as an effective and minimal invasive treatment modality to achieve a fast and durable epithelial closure, to prevent recurrent corneal erosions, and to increase visual acuity in most patients. A success rate of 84.6% to 100% has been reported by various authors 10-13. Shallow ablations (mean ablation depth 4.6 microns) have been recommended by Zaidman et al in view of decreased complications.13,14

Epithelial Recurrent Erosion Dystrophy (ERED)
Alternative name: Franceschetti recurrent epithelial dystrophy.16
Variant: Dystrophia Smolandiensis.
Inheritance: Autosomal dominant; genetic locus remains unknown.17

Signs
Recurrent corneal erosions present typically at 4 –6 years of age but occasionally as early as 8 months of age. These may be precipitated by minimal trauma or may be spontaneous. The cornea may develop subepithelial haze or blebs between attacks. The Smolandiensis variant is characterized by recurrent corneal erosions, followed by the formation of central corneal keloid like opacities.18

Symptoms
Most patients experience attacks of redness, photophobia, epiphora, and ocular pain due to corneal erosions. Some may complain of sensitive eyes for years. Exposure to sunlight, dust and smoke and lack of sleep can precipitate attacks. Attacks generally decline in frequency and intensity and cease by the age of 50 years.

Histopathology
Light microscopic examination reveals epithelial hyperplasia, absence of Bowman's layer and subepithelial fibrosis in cases with Dystrophia Smolandiensis; the specimen being positive for Congo red, suggesting an amyloid deposit. The general morphological pattern of pathology (true keloid formation, absence of Bowman's layer, subepithelial fibrosis and abnormal subbasal nerves) probably reflects a novel phenotypic expression of the healing response to recurrent erosion of the corneal epithelium.18

Management
Recurrent erosions are managed similar to cases with epithelial basement membrane dystrophy.

In the Smolandiensis variant, a quarter of patients eventually require corneal grafts at mean age of 44 years. The opacities recur within 15 months in the graft periphery, but the central graft can remain clear for many years.

Subepithelial Mucinous Corneal Dystrophy (SMCD)
Inheritance: Autosomal dominant. Genetic locus and gene remain unknown.19

Signs
Bilateral, homogenous subepithelial haze, most dense centrally, fading towards the periphery

Symptoms
The onset is characterized by frequent, recurrent corneal erosions in the first decade. These subside during adolescence with the formation of subepithelial opacities, causing progressive decreased vision.19

Histopathology
Light microscopy reveals a subepithelial band of eosinophilic, periodic acid–Schiff–positive, Alcian blue–positive, Masson trichrome-positive hyaluronidase-sensitive material anterior to the Bowman layer. The overlying epithelium is thinned out. Immunohistochemistry staining is positive for combination of chondroitin-4-sulfate and dermatan sulphate.19

Management
Initial treatment includes management of recurrent corneal erosions. The superficial location of the pathology makes PTK a potential treatment modality.

Meesmann Corneal Dystrophy (MECD)
Alternate name: Juvenile hereditary epithelial dystrophy.

This bilateral, diffuse corneal dystrophy involves the accumulation of intracytoplasmic debris in the corneal epithelium, manifesting clinically with the formation of epithelial cysts.

Historical perspective
First described clinically by Pameijer (1935).19

Histopathological description was given by Meesmann (1938).21

Inheritance Autosomal dominant with incomplete penetrance and variable expressibility.

Recessive form has been reported by Stocker and Holt.22
Genetics: Locus 12q13 (KRT3); gene Keratin K3 (KRT3).
Locus 17q12 (KRT12); gene Keratin K12 (KRT12): Stocker–Holt variant.
These genes encode cytoskeletal proteins.

Onset and course
Clinical signs may be visible as early as 12 months of age and increase throughout life.
The dystrophy follows a slowly progressive course and majority of the patients may remain asymptomatic till the fourth or fifth decade of life. Patients with the Stocker-Holt variant demonstrate more severe signs and symptoms with earlier onset compared with classic Meesmann corneal dystrophy.

Signs
Corneal involvement is usually bilateral. Multiple, tiny epithelial vesicles extend to the limbus and are most numerous in the interpalpebral area with clear surrounding epithelium. These appear as white spots on focal illumination and are seen as refractile cysts of retroillumination. Cysts may coalesce to form refractile linear opacities with intervening areas of clear cornea.

Stocker–Holt variant encompasses the entire cornea. Fine, grayish punctuate epithelial opacities that take up fluorescein and fine linear opacities in whorl-like pattern are visible.

Symptoms
Patients are usually asymptomatic till the fourth or fifth decade of life. Photophobia, redness and pain may occur due to recurrent corneal erosions with the rupture of the epithelial cysts. Most patients retain good functional vision, few may complain of blurred vision secondary to corneal irregularity and scarring.

Histopathology
Light microscopy documents diffuse cytoplasmic vacuolization of all cells in the affected area. Transmission Electron Microscopy reveals intracytoplasmic “peculiar substance” representing a focal collection of fibrogranular material surrounded by tangles of cytoplasmic filaments. Tuft et al reported hyporeflective areas in the basal epithelium ranging from 40 to 150 mm in diameter, with potential reflective spots inside visible on confocal microscopy.

Associations
Cremona et al reported a rare case of bilateral and symmetric Meesmann corneal dystrophy concurrent with bilateral epithelial basement membrane dystrophy and bilateral but asymmetric posterior polymorphous corneal dystrophy in a patient of Armenian origin.

Management
Most patients remain asymptomatic and may not require any treatment. Palliative treatment includes ocular lubricants, cycloplegia, and therapeutic contact lenses. In severe cases, management with epithelial debridement, phototherapeutic keratectomy, and lamellar keratoplasty has been advocated. Yeung et al have suggested keratectomy with mitomycin C application in recurrent cases of Meesman’s dystrophy.

Lisch Epithelial Corneal Dystrophy (LECD)
Alternative Names
Band-shaped and whorled microcystic dystrophy of the corneal epithelium.

Onset in childhood with a slowly progressive course.

Signs
Direct illumination reveals localized gray opacities of varying patterns: whorl-like, radial, band shaped, flame or feathery shaped, or club shaped. Indirect illumination reveals intraepithelial multiple, densely crowded microcysts. The surrounding epithelium appears clinically normal. Similar degrees of opacities are noted in both men and women.

Symptoms
Usually asymptomatic. Patients may report blurred vision if the pupillary zone is involved.

Histopathology
Light microscopy documents diffuse cytoplasmic vacuolization of all cells in the affected area.

Management
The corneal abnormalities have been reported to recur after corneal scrapping. Lisch et al reported that wearing contact lenses for a longer duration causes a significant regression of corneal opacities in LECD (two cases reported). The etiology of this phenomenon was interpreted as a contact lens induced thinning of corneal epithelium and reduction of epithelial layers. Gelatinous Drop-Like Corneal Dystrophy (GDLD)

Alternative Names: Subepithelial amyloidosis; Primary familial amyloidosis

Inheritance: Autosomal recessive. Genetic Locus 1p32; gene: Tumor-associated calcium signal transducer 2 (TACSTD2, previously M1S1).

Signs
Onset of the disease is by the first to the second decade of life. Initial subepithelial lesions appear similar to band-shaped keratopathy. As they progress to form groups of small multiple nodules, they acquire a mulberry configuration. These lesions show late staining with fluorescein, implying hyperpermeability of the corneal epithelium.
Superficial vascularisation may be noted. As the disease progresses, patients may develop stromal opacification or develop larger nodular kumquat-like lesions. This dystrophy is usually found in Japanese people, but has been reported in other regions of the world as well.41

**Symptoms**

Significant decrease in vision, photophobia, irritation, redness, and lacrimation.

**Histopathology**

Light microscopy demonstrates subepithelial and stromal amyloid deposits. Disruption of epithelial tight junctions in the superficial epithelium and the presence of amyloid in the basal epithelial layer is visible on transmission electron microscopy.

**Management**

Corneal transplantation is required for visual rehabilitation.42,43 Deep lamellar keratoplasty has been reported to successfully treat gelatinous drop-like corneal dystrophy.44 Recurrence is common after keratoplasty, the disease may recur in nearly half the grafts. Lasram et al reported that the five cases of GDLD treated by them required multiple keratoplasties at a mean interval of five years because of recurrence of the disease on the corneal graft.45 Ito et al reported that PTK may be a safe and useful modality to remove corneal opacities that recur after lamellar grafts.46

Section III. Bowman Layer dystrophies

**Reis–Bucklers Corneal Dystrophy (RBCD)**

This dystrophy primarily involves the Bowman’s layer with secondary alterations in the epithelium and the stroma. Alternative Names: Corneal Dystrophy of Bowman layer, type I; Geographic corneal dystrophy (Weidle); Superficial granular corneal dystrophy; Atypical granular corneal dystrophy; Granular corneal dystrophy, type 3; Anterior limiting membrane dystrophy, type I.

Historical perspective: First reported by Reis in 1917.47 Detailed description was given by Buckler in 1949.48

Inheritance: Autosomal dominant with variable expressibility. Genetic locus 5q31; gene TGB1. 49,50,51

**Signs**

Irregular and coarse geographic-like opacities are seen in the Bowman’s layer and superficial stroma, secondary to generalized replacement of the Bowman’s layer by irregular collagen fibres.52 Opacities may be linear, geographical, honeycomb or ring like and are best seen with broad oblique illumination. Peripheral cornea is usually spared, although a diffuse haze extending up to the limbus may be seen in advanced cases. Corneal sensations are decreased and prominent corneal nerves may be noted.52

**Symptoms**

Recurrent corneal erosions manifest as pain, redness and tearing in the first decade of life. These attacks become less severe after the second decade with progressive deterioration of vision. The visual loss is attributable to the diffuse opaque irregular surface.

**Histopathology**

The Bowman’s layer is replaced by a mass of irregularly placed collagen fibres, which in advanced cases can extend to the subepithelial stroma. Epithelial cells and anterior stromal keratocytes show degenerative changes such as swelling of the endoplasmic reticulum and vacuole formation. The posterior epithelial layer shows a saw-tooth configuration.

Subepithelial electron-dense, rod-shaped bodies are noted on electron microscopy. These rod-shaped bodies are immunopositive for transforming growth factor beta–induced protein (keratoepithelin). Electron microscopy is necessary to distinguish RBCD from the Thiel–Behnke Corneal Dystrophy where curly fibres are present.53 Laser confocal scanning may also enable differentiation of Theil Benke and Reis Buckler dystrophy in vivo.54 In Thiel-Behnke corneal dystrophy, the deposits in the epithelial basal cell layer show homogeneous reflectivity with round edges accompanying dark shadows. In contrast, deposits in Reis-Bücklers corneal dystrophy in the same cell layer show extremely high reflectivity from small granular materials without any shadows. In each dystrophy, Bowman’s layer is replaced totally with pathological materials; the reflectivity of those materials is reported to be much higher in Reis-Bücklers corneal dystrophy than in Thiel-Behnke corneal dystrophy.

**Management**

Recurrent corneal erosions are treated in the initial stages. PTK has been reported to be an effective modality for the treatment of this dystrophy. Recurrence is common after this procedure. Dinh et al reported that 47% of the eyes with Reis-Bücklers dystrophy developed clinically significant recurrence an average of 21.6 months after PTK.55 Adjunctive application of topical Mitomycin-C 0.02% may be
helpful in reducing the recurrence of the disease after PTK.56 Corneal electrolysis has been reported to effectively treat subepithelial opacities in RBCD11. Keratoplasty may be required in severe cases.57 Thiel–Behnke Corneal Dystrophy (TBCD) Alternative Names: Corneal dystrophy of Bowman layer, type II (CDB2); Honeycomb-shaped corneal dystrophy; Anterior limiting membrane dystrophy type II; Curly fibers corneal dystrophy; Waardenburg–Jonkers corneal dystrophy. Inheritance: Autosomal dominant. Genetic Loci:10q24; gene: unknown.58

Signs
Symmetrical subepithelial reticular honeycomb like opacities are noted, sparing the peripheral cornea.59 Corneal sensations are normal. In advanced cases, opacities can progress to deep stromal layers and corneal periphery. It may be impossible to distinguish it clinically from Reis Buckler corneal dystrophy.

Symptoms
Progressive erosions begin in childhood. Slowly progressive deterioration of vision occurs with increasing corneal opacification. The erosions are less frequent, and the onset of visual impairment is later than in RBCD.

Histopathology
A fibrillogranular material is deposited under the epithelium and projects into the overlying cells in a “saw tooth” configuration. The epithelial basement membrane is thickened.

Electron microscopy demonstrates pathognomonic curly collagen fibers with a diameter of 9–15 nm and distinguishes this dystrophy from RBCD. These curly fibers are immunopositive for transforming growth factor beta–induced protein (keratoepithelin).53 The confocal images may also enable differentiation from RBCD.54


Signs
Bowman layer demonstrates diffuse gray-white moundlike opacities extending anteriorly into the epithelium. The intervening cornea is clear, and the peripheral cornea is spared. The corneal sensations are preserved, unlike in RBCD. 60,61

Symptoms
The onset of the disease occurs at 10 to 12 years, later than RBCD. Corneal erosions are less severe and less frequent than in RBCD and TBCD. Visual acuity is usually preserved.

Histopathology
Accumulation of abnormal material (PAS positive) in the basement membrane, with disruptions in the Bowman’s membrane are noted.

References
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