Gelatinous drop-like corneal dystrophy: a review

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ABSTRACT
Gelatinous drop-like corneal dystrophy (GDLD) is a rare autosomal recessive form of corneal dystrophy characterised by subepithelial and stromal amyloid deposits. It is relatively common in Japan. It usually presents in the first two decades of life with subepithelial nodular lesions that later coalesce to form mulberry-like opacities. Although various surgical modalities have been attempted, recurrence remains a major challenge.

INTRODUCTION
Gelatinous drop-like corneal dystrophy (GDLD) is an autosomal recessive disease characterised by corneal subepithelial and stromal deposits of gelatinous amyloid material, insidious in onset and presents usually in the first two decades of life. It was first described by Nakazumi1 in 1914 and named as gelatinous drop-like dystrophy, prior to which, it was known as primary familial amyloidosis or subepithelial amyloidosis. It is bilaterally symmetric, has a low degree of penetrance and manifests commonly between 8 and 18 years of age.2-3

GDLD is a monogenic disease caused due to a homozygous biallelic loss-of-functional mutation of the tumour-associated calcium signal transducer 2 (TACSTD2) gene, located on the short-arm of chromosome 1.4 This gene encodes for TACSTD2 protein which is implicated in the disease pathogenesis.

EPIDEMIOLOGY
It is signifi cantly more common in Japan with the highest reported prevalence of 1 in 33 000 but is a rarity in other parts of the world.4-7 It is noted to occur in India and China, with a few cases scattered in Europe. It has also been found in Vietnamese, Tunisian, Turkish and Iranian families.8 Parents of affected individuals have a markedly higher frequency of consanguineous marriages than the general population.7 The autosomal recessive inheritance accounts for its rarity. In a study conducted at a tertiary eye care centre in India, Pandrowala et al8 evaluated 181 corneal buttons of 144 patients with corneal dystrophies who underwent penetrating keratoplasty (PK) and found GDLD in eight buttons only, thus accounting for about 4.4% of the total cases of corneal dystrophies seen by them. Elsewhere, Santo et al10 evaluated 80 patients with corneal dystrophies and found 15 patients with GDLD (18.8%).

DIFFERENTIAL DIAGNOSES
Spheroidal degeneration
Spheroidal degeneration of the cornea or climatic droplet keratopathy may present in a similar manner with the above-mentioned complaints and is also typically bilateral. Exposure to ultraviolet rays seems to be a risk factor. The lesions are classically elevated and golden yellow in colour.20 Simultaneous occurrences of GDLD and spheroidal degeneration has been reported in literature; however, the authors feel that it is purely an incidental observation since spheroidal degeneration is a degenerative disorder and can be associated with any other corneal disease.19 21

Clinical features
Patients’ symptoms include severe photophobia, lacrimation, foreign body sensation, blepharospasm and a relatively later onset of progressively deteriorating vision, with manifestation in the first two decades of life.11 Clinically, this disease is characterised by multiple, small subepithelial, gelatinous excrescences, which may give the corneal surface a mulberry-like appearance in typical cases (figure 1A, B). It may also be characterised by recurrent corneal epithelial erosions.4 The deposits or lesions have different appearances depending on the type of illumination used in the slit lamp-opaque with direct illumination and translucent on retro illumination, in contrast to the multiple white or grey-white elevated lesions of Salzmann’s nodular degeneration.7 12 The corneal epithelium also shows increased fluorescein permeation in GDLD. Disease progression leads to superficial and deep corneal vascularisation in the areas of the opacity with further deposition of amyloid in deeper layers causing severe visual loss.13-16 Amyloid deposit has also been reported to arise from perilimbal conjunctival stroma in patients with GDLD.19 17

In case of recurrence of GDLD after keratoplasty, it has been shown to recur along the sutures.18 An early sign of recurrence is glass-like subepithelial haze.

Ide et al13 described four clinical phenotypic varieties—band keratopathy, stromal opacity, kumquat-like and typical mulberry. Of these, the two predominant clinical forms are the mulberry type and the band keratopathy type. It is unclear if the four different phenotypes might change from one to the other in a single person. However, Akiya et al reported a case of one eye with mulberry type and the other eye with the band keratopathy type. The mulberry and the band keratopathy types tend to occur in the early to intermediate stage, while the kumquat-like type tends to occur in the very late stage.13 There are no directly associated systemic disorders associated with gelatinous drop-like dystrophy; thus, it was previously named as primary corneal amyloidosis and later classifi ed as corneal dystrophy, category-1.

CLINICAL FEATURES
Patients’ symptoms include severe photophobia, lacrimation, foreign body sensation, blepharospasm and a relatively later onset of progressively deteriorating vision, with manifestation in the first two decades of

multiple blue-white subepithelial nodules arranged circularly in the central part of the cornea. Unlike GDLD, Salzmann’s nodular degeneration presents commonly in middle to older age groups.

Lattice corneal dystrophy

Lattice corneal dystrophy, a corneal stromal dystrophy, associated with amyloid protein deposits mainly within the corneal stroma is clinically characterised by branching stromal lattice lines. In addition, there is presence of subepithelial opacities which can be band-like, thus making differentiation from GDLD difficult in some cases. Nakamura et al. have described few patients of GDLD with clinical features that may resemble lattice dystrophy type-1.

Band-shaped keratopathy

It is characterised by the appearance of a band across the central cornea. Primary band-shaped keratopathy, when bilateral, may clinically mimic GDLD. Bilateral primary band-shaped keratopathy has been reported to progress to GDLD over years; however, authors feel that this could have been primarily a case of GDLD. The primary GDLD band keratopathy shows no endothelial changes, whereas secondary band keratopathy is seen as a clinical sign in different endothelial dystrophies as a moon crater-like endothelial changes visible with retroillumination and a dilated pupil.

Secondary corneal amyloidosis—GDLD type

Secondary corneal amyloidosis is known to occur after chronic ocular irritation/inflammatory/infective disorders like trichiasis, entropion, keratoconus and so forth. It has been classified into three subtypes according to their clinical appearance. The GDLD type secondary corneal amyloidosis resembles GDLD lesions morphologically, having milky white soft masses on the corneal surface. Correlation with clinical history is of paramount importance for its differentiation from primary corneal amyloidosis. The deposits seem to be confined to the site of inflammation or chronic irritation. These patients have an earlier age at presentation as compared with the other secondary corneal amyloidosis types but were still considerably higher than patients with GDLD.

INTERNATIONAL CLASSIFICATION

According to International Committee for Classification of Corneal Dystrophies Classification of corneal dystrophies, it is classified as an epithelial and subepithelial dystrophy, category-1. It is an autosomal recessive disease and individuals may be compound heterozygotes or homozygotes for disease manifestations to occur.
GENETICS OF THE DISEASE

TACSTD2 gene (also termed as TROP-2, EGP-2, GA 733-1) is an intron-less gene, consisting of only a single exon, located in chromosome 1 (1p 32). The TACSTD2 gene encodes a human glycoprotein consisting of an additional transmembrane domain and acts as cell surface receptor. In 1998, Tsujikawa et al28 mapped the locus for GDLD at the short-arm of chromosome 1, thus excluding association of serum amyloid P gene27 and the transforming growth factor β-induced gene as the possible candidate gene/s for GDLD.28 At the same time, sequence analysis of DNA isolated from patients with GDLD also showed absence of mutations in the entire coding region of big-h3 gene.28 Further in 1999, Tsujikawa et al28 identified the TACSTD2 gene30 as the possible candidate for GDLD harbouring four deleterious mutations. The mutations identified were p.Gln118Ter (Q118X), c.632delA, p.Gln207Ter (Q207X) and p.Ser170Ter (S170X), of which p.Gln118Ter (Q118X) was found to be the most commonly observed mutation.29 Interestingly, their group also demonstrated absence of genetic variability in Japanese patients who presented with phenotypic variations and were clinically initially diagnosed as atypical bilateral amyloidosis.31 The p.Gln118Ter (Q118X) mutation consists of a C→T transition at nt352, replacing the nucleotide sequence codon encoding for glutamine at position 118 with a stop codon, which in turn truncates the protein sequence at that point. This results in abnormal functioning or loss of function of the gene. A novel compound heterozygous mutation—p.Gln118Ter (Q118X) with p.Tyr184Cys (Y184C) was found in a Chinese patient with GDLD.32 Jing et al33 reported in-frame mutation c.526→576del51 in two Chinese brothers. However, Alavi et al34 concluded that there was evidence for the existence of at least one other gene locus for GDLD as the disease in their pedigree was probably not caused by a mutation in TACSTD2 gene. This is important as it has led to an increased appreciation of previously presumed benign mutations.

TACSTD2 also transduces intracellular calcium signals. The gene mutation and the disturbed localisation of cell-to-cell adhesion molecules cause an abnormal increase in corneal epithelial permeability.35 In addition, the phosphatidylinositol 4,5-bisphosphonate (PIP2) binding site, presumed to be located at the C-terminal intracellular domain of TACSTD2 gene, has an ability to regulate binding to other molecules or the plasma membrane. The mutations may lead to loss of the PIP2 binding site, thereby leading to loss of the various cell adhesion functions.35 To summarise, TACSTD2 is an important component of desmosomes and zonulae occludentes and is central to disease pathogenesis in GDLD. The mutations may cause an abnormal functioning or loss of function of the gene, which leads to an increase in corneal epithelial permeability and affect cell adhesion functions.

DNA sequence analysis

For this study, blood sample was collected after obtaining approval from the Institutional Review Board and written informed consent from the patient. Genomic DNA was isolated using QIAamp DNA Mini Kit as per the manufacturer’s instructions. TACSTD2 gene was amplified by PCR as described previously.21 The entire coding region of the gene was sequenced. The obtained genomic DNA sequence showed a transversion of thymidine to guanine at nucleotide position 614 (c.614). This homozygous single base substitution predicted an amino acid change from leucine to arginine at position 205 of the protein sequence (L205R) (figure 2). TACSTD2 gene is known to harbour mutations throughout the coding sequence. L205R is in very close proximity to another key mutation Q207X that was shown to be deleterious in GDLD. Both leucine at 205 and glutamine at 207 are conserved residues across different species. Substitution of non-polar amino acid leucine by basic polar amino acid arginine is expected to change the structure and function of the protein.

PATHOGENESIS

TACSTD2 gene is explained to be responsible for proper maintenance of corneal epithelial barrier function by binding to claudin 1 and 7 tight junction-related proteins.36 The abnormal increase in the permeability of the corneal epithelium in GDLD37 has been demonstrated by diffusion of fluorescein into the corneal stroma. This supports the finding observed in GDLD that the tight junctions are disturbed due to the mutations and the disease process. The corneal epithelium in these patients shows abnormal gaps. The superficial layer of cornea showed abnormal basal epithelium with disordered desmosomes between them.38 Uhlig et al39 concluded that corneal vascularisation and mechanical stress promoted the development of gelatinous deposits in GDLD.

HISTOPATHOLOGY

Sections from corneal tissue show morphological changes, predominantly in the central cornea. Epithelium is of varying thickness, with or without intercellular oedema, and may lie separated from the stroma. There is destruction of epithelial basement membrane, with interruptions and/or absence of Bowman’s layer (figure 1C, D). Homogenous, acellular eosinophilic deposits are seen in the subepithelial, intraepithelial and anterior stromal location. The deposits may appear band-shaped, nodular and/or like small linear strands. The nodular subepithelial and/or intraepithelial deposits raise the basement membrane/epithelium, causing their destruction/interruptions, giving a mulberry-like appearance. The deposits are positive for periodic acid Schiff’s stain; however, they stain with less intensity as compared with the Descemet’s membrane. They display congophilia (brick red stain) when subjected to Congo red stain and demonstrate characteristic apple green birefringence under polarised light (figure 1E, F). Mondino et al40 reported that the
amyloid found in corneas of patients with GDLD is of serum amyloid protein type.

On immunohistochemistry, these deposits stain for lactoferrin. In addition, lactoferrin expression has been observed in the nuclei of the overlying corneal epithelium; however, the mutation associated with GDLD is not linked with lactoferrin gene.\(^4\) Amyloid typing in a single case of GDLD performed by using shotgun liquid chromatography/tandem mass spectrometry has also suggested lactoferrin as the precursor protein.\(^4\) It has been postulated that increased permeability of corneal epithelium is responsible for lactoferrin expression and thus lactoferrin-related amyloid formation, it being a component of the human tear film. Nishida et al\(^4\) has demonstrated localisation of apolipoproteins J as well as E, in patients with GDLD, which they hypothesise could be involved in the pathogenesis or may be an additional protein in these corneas with increased epithelial permeability. Yoshida et al\(^4\) reported expression of vitronectin, an extracellular matrix adhesion molecule in cornea of patients with GDLD and suggested its role in corneal neovascularisation occurring in patients with GDLD in advanced cases.

Electron microscopy study of a case of GDLD showed abnormally thickened epithelium with increased intercellular spaces and intact desmosomes. Similar observations have also been reported by Kinoshita et al.\(^5\) They explained presence of amyloid deposits in the stromal collagen fibrils, which led to some stromal disorganisation. The amyloid deposits were non-branching, irregularly arranged fibrils, often in the form of spheres and ranged from tens of nanometres to several microns in diameter.\(^6\) Ohnishi et al reported intact basal lamina and Bowman’s layer in early cases. However, in severe cases, the basal lamina of the basal cells was discontinuous and there were numerous long processes protruding into the amyloid substance.\(^7\)

OTHER INVESTIGATIONS

Anterior segment optical coherence tomography

Fourier-domain optical coherence tomography (OCT) shows high reflectivity in the area of amyloid deposition. A recent study done by Magalhães et al\(^8\) on anterior segment OCT (ASOCT) in GDLD showed that the treatment modality could have been changed if the ASOCT had been done earlier as their patient showed involvement of superficial corneal layers only. Thus, it may be important in early diagnosis and in establishing the best possible treatment option in them.

Confocal microscopy

Laser scanning confocal microscopy has revealed that the epithelial cells were irregular in shape and often elongated in contrast to polygonal shape of normal epithelium. Mild disorganisation of epithelial cells and large accumulation of brightly reflective amyloid materials were noted beneath the epithelium and anterior stroma.\(^9\)

MANAGEMENT

Medical management

Medical treatment is usually inadequate for this disorder. But in the initial stages of the disease, it can be started with lubricating eye drops and bandage contact lenses for symptomatic relief to the patient.

Surgical management

The various surgical treatment options include superficial keratectomy, penetrating keratoplasty, lamellar keratoplasty, limbal stem cell transplant (LSCT) (either a living-related allogenic transplant or a cadaveric allogenic transplant) and keratoprosthesis (K-Pro) (Table 1).

Superficial keratectomy

Superficial keratectomy can be done to debulk a lesion initially, improving the vision to some extent. The effects of this are short-lived, as the deposits are invariably known to recur. A phototherapeutic keratectomy (PTK) may be performed to smoothen the corneal surface and to provide symptomatic relief. In one of the latest articles published, Alex et al\(^10\) have performed amniotic membrane graft (AMG) overlay to promote corneal cell migration and proliferation in addition to PTK. They have hypothesised that the additional anti-fibrotic and anti-inflammatory properties present in an AMG reduces postoperative fibrosis. Although it reoccurred earlier, the patient remained comfortable for a much longer duration (up to 22 months). Thus, this could be a promising modality of treatment in patients where the primary aim of surgery is not visual rehabilitation.

Penetrating keratoplasty

PK is an option commonly used to treat GDLD; however, the surgery may be complicated because of fragility of corneal tissues. Recurrence even after keratoplasty is a problem, with reported recurrence rates as high as 50%–70%.\(^1\) Therefore, repeat keratoplasty is almost always needed. This leaves room for possible secondary complications such as glaucoma, cataract and infections. An early sign of recurrence is the development of a subepithelial glass-like haziness, which usually occurs 8–12 months after a PK.\(^1\) According to few studies, subepithelial haze has been seen to develop as early as 1 month

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Modality of treatment for GDLD with outcome</th>
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<tbody>
<tr>
<td>Authors</td>
<td>No. of eyes/cases</td>
</tr>
<tr>
<td>Shimazaki et al(^6)</td>
<td>9 eyes (7 cases)</td>
</tr>
<tr>
<td>Shimazaki et al(^6)</td>
<td>35 keratoplasties in 7 patients in the study</td>
</tr>
<tr>
<td>Alex et al(^11)</td>
<td>1 case</td>
</tr>
<tr>
<td>Movahedan et al(^12)</td>
<td>3 eyes</td>
</tr>
<tr>
<td>Omoto et al(^13)</td>
<td>2 cases</td>
</tr>
<tr>
<td>Fadlallah et al(^14)</td>
<td>1 case</td>
</tr>
<tr>
<td>Cortina et al(^15)</td>
<td>1 case</td>
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</tbody>
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AMG, amniotic membrane graft; BCVA, best-corrected visual acuity; DALK, deep anterior lamellar keratoplasty; GDLD, gelatinous drop-like corneal dystrophy; K-Pro, keratoprosthesis; LSCT, limbal stem cell transplant; PTK, phototherapeutic keratectomy.
postoperatively around suture materials. Post-keratoplasty recurrence may be reduced by the use of bandage soft contact lens wear, which acts by decreasing the epithelial turnover.49

Lamellar keratoplasty
Lamellar keratoplasty may be done for a good effect considering the inevitable recurrence with a PK as the inner corneal layers are essentially normal. This can reduce the risk of endothelial rejection reported in a few cases.18 Deep anterior lamellar keratoplasty (DALK) can be tried before attempting a PK in these cases. Femtosecond-assisted anterior lamellar keratoplasty is also an option where the involvement is limited to anterior corneal stroma. Femtosecond-assisted surgery has the advantage of a more precise and a regular incision through the anterior stroma.

Limbal stem cell transplant
Shimazaki et al48 50 reported that LSCT when done along with a PK decreases the chances for recurrence. Simultaneous keratoplasty with allogenic LSCT has been shown to maintain corneal clarity and useful vision for up to 2 years after surgery in patients with GDL D.13 In a study by Omoto et al,51 LSCT done with DALK had no recurrence up to 2 years postoperatively. Donor-derived epithelial cells found on the central graft several years after LSCT suggests that stem cells on the allograft continue to supply corneal epithelial cells preventing abnormal amyloid deposition, thus, helping in maintaining stable visual acuity for a longer period.

A well-documented serious complication of LSCT is ocular hypertension.52 Hence, a regular check on the intraocular pressure (IOP) and, if possible, early diagnosis and treatment of the same are needed to maintain visual potential. Inability to examine IOP and disc status preoperatively and removal of episcleral venous tissue, which drains the aqueous intraoperatively, are the causes of raised IOP, which is further compounded by the use of steroid eye drops postoperatively. The limbal area contains numerous Langerhans cells making the risk of immunological reactions more likely than seen with lamellar or PK.53 These risks suggest that intensive postoperative management is equally important after any treatment procedure and is responsible for long-term success. In cases undergoing LSCT, treatment with oral ciclosporin A, mycophenolate mofetil and prednisolone has been used for a duration of up to 18 months, with regular blood cell count monitoring.15 LSCT overall has been shown to suppress recurrence and maintain corneal clarity for a longer duration.

In spite of achieving acceptable vision after LSCT for various indications, a progressive decline in vision and graft survival occurs with time. PK done simultaneously with LSCT may not have the best outcome. A second LSCT has been shown to have better long-term survival than the first one in patients with total limbal stem cell deficiency.54 Thus, Movahedan et al15 have suggested repeat allogenic LSCT as a good option to treat initially failed cases of LSCT in GDL D.

Keratoprosthesis
Boston type 1 K-Pro has been used as an alternative option to treat this disorder and has been shown to be more effective in preserving vision for a longer duration of time than a keratoplasty. Cortina et al15 reported the first case of Boston type 1 K-Pro as a primary penetrating procedure in a patient with GDL D in their study. K-Pro done as a primary procedure reduces the long-term visual rehabilitation needed for a highly recurring dystrophy like GDL D.

In case of a recurrence in an eye which has undergone a previous PK, K-Pro may be done to avoid another recurrence and/or speed up the rehabilitation process of the involved eye.56 Currently, Boston K-Pro is considered to be better if not the best modality of treatment, in cases of recurrent graft failure. However, it is important to understand that Boston K-Pro is associated with severe complications in a few which may lead to permanent blindness. These include formation of a retroprosthetic membrane, persistent epithelial defect, elevated IOP, corneal stromal necrosis to name a few.57 A complication that needs mention in K-Pro is recurrent epithelial defect(s) around the optical cylinder, which can be the entry way for keratitis with further spread of infection. GDL D being primarily an epithelial disease, it is very important to keep these patients on a close watch to make sure the epithelium stays intact. The use of bandage contact lens in K-Pro has been shown to decrease complications.

CONCLUSION
GDL D, an uncommon autosomal recessive disease, is characterised by bilateral corneal amyloidosis. It can manifest in different phenotypical forms. The TACSTD2 gene is implicated in GDL D. Newer treatment options like limbal stem cell treatment and K-Pro are practiced currently to decrease the risk of recurrence and also to offer better visual outcomes for patients.

METHOD OF LITERATURE SEARCH
PubMed was queried with combinations not limited to the following search terms: gelatinous drop-like corneal dystrophy, genetics, histopathology, investigation and treatment. We included references that we considered to have major contributions to the understanding of GDL D. The abstracts of the non-English articles were also included. Case reports without additional value over another report of the same condition were not included.

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