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Macular Corneal Dystrophy: An Updated Review

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ABSTRACT

Macular Corneal Dystrophy is an autosomal recessive form of corneal dystrophy due to a mutation in *CHST6* gene, which results in abnormal proteoglycan synthesis. There is accumulation of abnormal glycosaminoglycans in the corneal stroma and endothelium. The deposition results in progressive loss of corneal transparency and visual acuity. The histopathology shows characteristic alcian blue positive deposits. Management in the cases with visual loss requires keratoplasty either full thickness or lamellar. The decision about the ideal type of keratoplasty depends on age and pre-operative clinical features. Although prognosis after keratoplasty is good, recurrences can occur. Future research should be targeted towards gene therapy in this condition.

INTRODUCTION

Corneal dystrophies are typically defined as rare, inherited disorders of the cornea, that are bilateral, often symmetric, slowly progressive and not related to environmental and systemic factors.[1,2] Abnormal accumulation of deposits in the different layers of the cornea determine the primary characteristics.[3] However, there are deviations to the typical description of dystrophies as not all dystrophies are inherited, bilateral, symmetrically bilateral or associated with deposition of abnormal substances in the different layers of the cornea. The traditional system of classification of corneal dystrophies was based on the layer of cornea primarily affected. The newer classification of corneal dystrophies by the International Committee for Classification of Corneal Dystrophy (IC3D) are based on the clinical and genetic documentation of the dystrophies.[4,5] As per the IC3D system, macular corneal dystrophy

(MCD)[MIM#217800] falls in the Category 1, i.e., a well-defined corneal dystrophy in which the gene has been mapped and identified and the specific mutations are known.

MCD was first described by Groenouw in 1890. It is an autosomal recessive corneal stromal dystrophy, characterized by deposition of glycosaminoglycans within keratocytes and corneal endothelium with extracellular deposition of the similar material in corneal stroma and Descemet membrane.[3]Although classified under stromal dystrophies, the condition can have variable involvement of the endothelium- Descemet membrane complex.[3,6]

EPIDEMIOLOGY

The prevalence of MCD is higher in those communities where consanguinity is common. Although it has been recognised throughout the world, its prevalence is notably more common in India, Saudi Arabia and Iceland.[7-10] According to the registry maintained by Klintworth in the United states, prevalence of MCD is 0.3 individuals per 2,50,000 inhabitants.[7,11] Estimates from Claims data in US, found that the prevalence of stromal dystrophies was low (~1%), but amongst the three dystrophies namely lattice, granular and macular, MCD was commonest.[12] A report from Iceland indicated that MCD accounted for one third of corneal transplants.[8] Similarly, in the studies from Saudi Arabia, it was suggested that MCD was the most common corneal stromal dystrophy that required keratoplasty.[9,13] A recent retrospective electronic medical record based study from Southern India, reported MCD to be the second commonest corneal dystrophy after Fuchs endothelial corneal dystrophy.[14]

CLINICAL FEATURES

Patient's symptoms commonly include photophobia, tearing and gradually deteriorating vision, which commonly manifests in the second and third decade of life. The lesions of MCD are mostly symmetrical and grayish white in color. As per the classical description of

MCD, the deposits are seen in the superficial cornea as fleck like opacities in the initial stages, that later coalesce to reach the limbus, deeper stroma and the endothelium.[1-3,7] However, the diversity in the clinical presentation of MCD is increasingly recognized in the recent years.[15-17] Chaurasia et al[15] described patients of MCD who at an early age had co-existing anterior stromal lesions in the central cornea and non-contiguous deep stromal pre-Descemetic lesions in the peripheral cornea. An unusual case of a 67-year-old female with MCD who had predominantly deep stromal lesions in the peripheral cornea with sparse anterior stromal deposits is recognised.[16] Another case report of MCD with isolated peripheral Descemet membrane deposits has been reported by Zhang et al.[17] The anterior stromal and subepithelial deposits affect the visual acuity due to an altered corneal surface and irregular astigmatism. Recurrent corneal erosions can occur.[18] One of the important features characteristic of MCD is progressive corneal thinning which is because of the decreased inter-fibrillar spacing.[3,19] However, progression of deposits in the endothelial cells can eventually lead to thickening of the Descemet membrane, endothelial decompensation and increased pachymetry .[6,15,16]

PATHOGENESIS

MCD appears to be the result of a metabolic abnormality in keratan sulfate.[20] Keratan sulfate is found in the corneal epithelium, Bowman's membrane, keratocytes, Descemet membrane and endothelium. Carbohydrate sulfotransferase (*CHST6*) gene on chromosome 16(16q22) gene is explained to be important in producing sulfated keratan sulfate which is important glycosoaminoglycan in the adult cornea. *CHST6* gene encodes N-acetylglucosamine 6-0-sulfotransferase, an enzyme which transfers sulfate to the unsulfated keratin chains on lumican.[21,22] Lumican preserves the crucial size, ordered structure, impacts corneal hydration and hence the corneal transparency. This explains the stromal haze and the loss of corneal transparency due to mutation in *CHST6* gene in MCD.

Initially, it was believed that the metabolic abnormality of keratan sulfate was restricted to cornea alone. As keratan sulfate is derived from the normal turnover of cartilage, studies have looked at the keratan sulfate levels in cornea, serum and other cartilage samples of the body.[23] Klintworth et al in one their studies reported that serum assays of patients with MCD showed absence of sulphated keratan sulfate.[20] This pointed towards the defects in the synthesis of keratan sulfate in MCD. Thonar et al[24] showed that the levels of keratan sulfate were higher in children of age group 13-15 years and patients with osteoarthritis. They also showed decreased levels of keratan sulfate in serum of patients with MCD, deriving that there is a possibility of systemic manifestation in patients with MCD.

Depending on the reactivity of keratan sulfate in the serum and cornea to anti-keratan sulfate antibodies, MCD is categorised into 3 variants[5]:

1. MCD type I-Keratan sulfate is absent in both the serum and the cornea. Corneal epithelium, stroma and endothelium all of them contain unsulfated keratan
2. MCD type IA-Keratan sulfate is absent in the serum but stroma shows immunoreactivity to Keratan sulfate antibodies
3. MCD type 2-Keratan sulfate levels are decreased in serum and corneal stroma. But epithelium and endothelium show unsulfated keratan

Clinically and histopathologically, the three variants are indistinguishable.[25,26]

HISTOLOGY AND ULTRASTRUCTURAL CHARACTERSTICS

Histopathologic features of MCD is characteristic (Figure 1a-c). The stromal keratocytes, Descemet membrane and endothelial cells show intra and extracellular deposition of granular material.[3,6] Bowman's membrane can be absent, disrupted and thinned out. Epithelium invariably remains spared of the deposits. The depositions which are due to abnormally sulphated keratin sulphate appear as basophilic granular material. Granular material is

chemically acid mucopolysaccharide (glycosaminoglycans) and stains positively with periodic acid Schiff, alcian blue, metachromatic dyes and colloidal iron.[27] Electron microscopy substantiates this finding with intracellular deposition of glycosaminoglycans within the endoplasmic reticulum of stromal keratocytes especially superficial keratocytes.[28] Numerous electron- transparent lacunae are randomly distributed throughout MCD corneas.

The abnormal keratan sulphate interferes with the collagen fibrillar rearrangement. The collagen fibrils may have a normal diameter but the interfibrillar spacing of collagen fibrils in affected corneas is less than that in the normal cornea.[3] Some studies have reported that the collagen fibrils are smaller with a decrease in the interfibrillar spacing.[29] This close packing of collagen fibrils is responsible for the reduced corneal thickness in MCD.

The anterior banded portion of Descemet membrane is of normal thickness and has an unremarkable ultrastructure, whereas the posterior layer usually contains numerous corneal guttae with granular deposits within the corneal endothelium.[3,6] This indicates that the abnormal glycosaminoglycan is not produced by the fetal endothelial cells. Snip et al[6] reported that Descemet membrane acts like a physical barrier and it is unlikely for the fibrogranular material in the vacuoles of endothelium to be a phagocytosed product of granular material deposited in the stroma and suggested that the material is derived from the endothelium suggesting that the involvement of corneal endothelium may be primary feature of the disease.

One of the close differential diagnosis of MCD is mucopolysaccharidoses (MPS).[30] Unlike the sparing of the epithelium that is seen in MCD, systemic mucopolysaccharidoses shows pan-corneal involvement with glycosaminoglycans. Another differentiating feature is that the site of deposition in MCD is rough endoplasmic reticulum whereas in MPS, it is in Golgi apparatus.

GENETICS

Genetics of a dystrophy is important in understanding the underlying basis of the disease and may also help in the development of gene therapy or other targeted therapies for the disease. The involvement of keratan sulphate in the pathology of MCD was evident from biochemical studies of MCD corneas using organ culture of corneas of patients affected with MCD and those of unaffected controls.[31] The defect in MCD appeared due to two disturbances. There is an absence of sulfate residues in the carbohydrate side chains from keratan sulfate proteoglycan and secondly the oligosaccharide side chains are much smaller in MCD-affected corneas than keratan sulfate side chains present in normal corneas.

MCD was linked to human chromosome number 16 in families of American and Icelandic origin.[32] Akama et al[33,34] identified mutations in the gene for *CHST6* among patients with both the types of MCD. MCD type I is the predominant type and involves mutations of the coding regions of *CHST6* whereas in MCD type II, deletions and rearrangements have been found in the upstream region of the gene. Various studies show that MCD patients from different regions of the world have mutations in the same gene.[22,35-37] There are many mutant alleles identified so far indicating allelic heterogeneity in MCD. Data from about 200 families from across the world analysed for mutations in *CHST6* show that approximately half of all MCD patients reported so far are from India. There is a predominance of missense mutations, detected in about 50% or more of patients with MCD from different populations while nonsense mutations, deletions, insertions or indels are found in about one-third of cases.[38] Being an autosomal recessive disorder, MCD is mostly seen in consanguineous and inbred families, in which the majority of patients are homozygous for the mutations, and rest are compound heterozygotes for two different alleles.[39] There are no obvious correlations

between genotypes and phenotypes of patients with MCD, either the immunophenotypes or clinical features.[40,41]

INVESTIGATIONS

Anterior segment optical coherence tomography (OCT)

High Resolution OCT shows hyperreflectivity at the site of deposits associated with thinning of the epithelium over the deposits.[42] Line scans passing through the peripheral cornea characterise the pre-Descemetic nature of the peripheral deposits.[15] In some patients, thickening of the Descemet membrane may be noted. In advanced stages of the dystrophy, the dense stromal deposits cause an optical shadow in the posterior part of cornea.

In vivo confocal microscopy

In vivo confocal microscopy showed altered reflectivity of basal epithelial cells, hyperreflectivity in the anterior stroma, granular appearance of keratocytes and extracellular matrix, and dark striae in the middle and posterior stroma. The endothelial cells showed bright granules and polymegathism.[43] In one study, normal endothelium was reported.[44]

Scheimpflug imaging

There are few reports of coexistence of keratoconus and MCD.[45] Several studies have shown thinning of the central cornea in MCD. Dudakova et al[46] used pentacam scheimpflug imaging system in patients with MCD and concluded that all eyes showed diffuse corneal thinning with paracentral steepening of the anterior corneal surface that was graded as keratoconus by the integrated software, but without associated ectasia of the posterior corneal surface or regional thinning.

Ultrasound bio microscopy (UBM)

Rubinstein et al[42] used UBM in the evaluation of patients with MCD that could help to examine important posterior lamellar changes that could help to decide the choice of keratoplasty- full thickness versus lamellar keratoplasty. UBM helped to characterise posterior corneal surface interruptions, loss of continuity and focal protrusions. Penetrating keratoplasty (PK) could be the surgery of choice compared to deep anterior lamellar keratoplasty (DALK) in patients with involvement of the posterior corneal layers.

MANAGEMENT

Phototherapeutic keratectomy (PTK)

Excimer laser has been used for removal of superficial opacities. Corneal dystrophies are the common indications of PTK. PTK helps to improve vision as well as those who suffer from recurrent erosion. Hafner et al[47] had described long-term result of PTK in 10 eyes of six patients with MCD. They concluded that PTK can improve visual acuity moderately for limited period. They noticed high recurrence rate (90%) during follow-up. Mitomycin (0.02%) has been used for 30 seconds on stromal bed after PTK for granular and macular dystrophies.[48]There was no difference in recurrence rate and recurrence free interval between both. Many patients need keratoplasty despite PTK due to recurrence leading to reduction of vision. Preceding PTK does not impair outcome of subsequent keratoplasties.[49] PTK can be performed in recurrence of primary pathology in graft.[50] The advantages of PTK are repeatability of the procedure and precise ablation. However, it induces hyperopic shift and stromal haze.

Femtosecond assisted lamellar keratectomy

Femtosecond LASER has been successfully used for anterior lamellar keratectomy to remove corneal opacities secondary to anterior corneal dystrophies. [51,52]It may delay more invasive surgery like keratoplasty. Corneal flap of 9.5 mm diameter was created. Corneal flap

thickness was around 110 to 140 microns.[52] Best-spectacle-corrected-visual acuity improved after the procedure. There was no hyperopic shift.

Keratoplasty

MCD constitutes a major portion of transplants performed in many places.[8,10,53] Penetrating keratoplasty was standard of care in the earlier days. Al-Swailemet al have described penetrating keratoplasty in 229 eyes of 141 patients.[54] Probability of graft survival was 98.1% at 1 year, 89.8% at 5 years, 82.1% at 10 years and 74.1% at 15 years. They found the risk of graft failure is more if patient was < 40 years during surgery. There was clinically significant recurrence in 5.2% cases after a mean interval of 84± 48.2 months. Karimian et al have described visually insignificant recurrence in one out of 62 eyes.[55] Though 19.4% eyes had immunological rejection, none of them failed.

Few studies compare outcome of DALK with PK in MCD (**Table-1**). In a prospective randomised controlled trial by Sari et al[56], there was no significant difference in final visual outcome between both groups. There is significant more endothelial cell loss in PK compared to DALK. Cheng et al had reported better visual outcome in PK group compared to DALK group.[57] However, endothelial cell loss was more in PK group. Reddy et al compared clinical outcome and risk factors of graft failure in both groups in a retrospective analysis.[58] There was no significant difference in visual outcome, astigmatism and spherical equivalent. Graft rejection was the main cause of graft failure in PK group. Intraoperative micro perforation and double anterior chamber was common complications of DALK. While most complications of DALK happened intraoperatively and early postoperative period, late phase complications such as rejection and secondary glaucoma are more in PK group.[59] Late endothelial decompensation after DALK was reported in 2 patients in the same study.[59]

Endothelial cell loss and recurrence in MCD after DALK has been more compared to Lattice dystrophy who had undergone DALK.[59,60] Kawashima et al[5] reported increased endothelial cell loss after DALK in macular corneal dystrophy in comparison to lattice corneal dystrophy. Recurrence of primary pathology is less compared to lattice and granular dystrophy after DALK.[60] Primary graft failure has been reported after DALK.[61] Descemet stripping endothelial keratoplasty is described for an atypical case of MCD, wherein glycosaminoglycans deposits were predominantly at the endothelial level.[16]

FUTURE PROSPECTS

Over last several years, there is some evidence of successful gene transfer to the cornea in experimental models and in human corneas ex vivo.[62-64] MCD has an identified and mapped genetic defect and hence, fulfils the important prerequisites that are required to attempt a clinical gene therapy. The conventional gene therapy involves transfer of a new/ replacement gene to the cells to drive its expression or to silence the expression of the abnormal gene.[65] Genome editing is a therapy where the defective gene is repaired or deleted, i.e. the host genome is 'edited'.

The cornea is a suitable organ for attempting gene replacement or correction of affected cells, since it is easily accessible, its immune privilege and limited size. Correction of specific mutations in the *CHST6* gene may be potentially developed by means of patient-specific gene editing approaches. An alternative that may be applicable to MCD, is that since it is an autosomal recessive disease, it is amenable to replacement of the entire gene by gene therapy with suitable viral vectors such as adeno-associated virus (AAV) that have been tried and tested in other gene therapy trials in humans. Several methods of gene editing exist such as using zinc finger nucleases (ZFNs) or artificial restriction enzymes [(transcription activator- like effector nucleases (TALENS)]. Currently, Clustered regularly interspaced

short palindromic DNA repeat (or CRISPR) and CRISPR- associated genes (cas) system of gene editing have seen increased interest and these may emerge as future therapies as it is capable of correcting gene effects in the somatic cells of a whole organism.[66] Such an approach was employed in an experimental model for correction of the keratin 12 gene defect in a mouse model of Meesmann corneal dystrophy and also in limbal epithelial cells of patients. [67]

CONCLUSION

MCD is an autosomal recessive disorder which affects young individuals. The deposition of abnormal protein lead to corneal opacification. Imaging techniques help to understand ultrastructural changes in cornea. Various modalities of treatment such as PK and DALK have been described for visual rehabilitation. The success of DALK depends upon the endothelial health. Recurrence can occur after keratoplasty. Newer therapies like gene transfer and gene editing may be a potential treatment in the future.

METHOD OF LITERATURE SEARCH

PubMed search was performed using search terms: macular corneal dystrophy, genetics, histopathology, investigations, and management of MCD. All articles published in English language and relevant to the topic were reviewed and included in this review.

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Table -1: Modality of treatment in MCD

Study	Number of eyes (patients)	Intervention	Mean follow up	Recurrence	Recurrence free period
Hafner A et al[47]	10	PTK	4.5±3.1 years	90%	3.4± 0.4 years
Yuksel et al[48]	9	PTK+MMC	-----	55.5%	5.6± 1.4months
Al Swalim et al[54]	229(141)	PK	5.9± 3.8years	5.2%	84± 48.2 months
Karimian et al[55]	62(39)	PK	52 ± 47.3months	1 case (visually insignificant)	-------
Sari SE et al [56]	82 (54)	PK vs. DALK	-----	4.8% PK 5.7% DALK	-----
Cheng et al[57]	78(51)	PK vs. DALK	5.1±4.1 years	17.5%PK 42.9%DALK	6.3± 3.1 years in PK 2.3±2.1 years in DALK

Figure 1(a-c): a.) Fleck like deposits seen in macular dystrophy. b.) Histology of MCD showing thickened Descemet membrane and excrescences (guttae). c.) Alcian blue positive glycosaminoglycan deposits in the stroma.

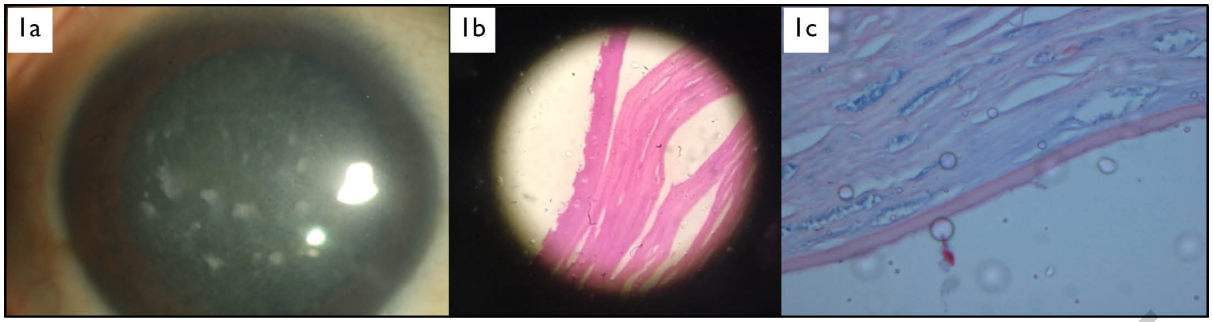

Fig 1