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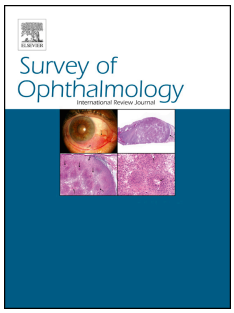

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Macular Corneal Dystrophy: A Review

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Abstract

Macular corneal dystrophy (MCD) is a corneal stromal dystrophy which leads to progressive vision loss. MCD is an autosomal recessive condition in which there is abnormality of proteoglycan synthesis. Mutations in the carbohydrate sulphotransferase gene (CHST6) prevent normal sulfation of corneal keratan. Different immunophenotypes have been described depending on the presence of keratan sulfate in cornea and or serum. The deposition of abnormal proteoglycans leads to loss of corneal transparency and decreased vision. Imaging techniques such as invivo confocal microscopy and anterior segment OCT have helped enhance our understanding of the corneal ultra-structural changes in this condition. These imaging modalities provide additional information without the need for a tissue biopsy or excision. Traditionally, full thickness penetrating keratoplasty to replace the opacified cornea has remained the standard of treatment to improve vision. However, newer surgical interventions such as deep anterior lamellar keratoplasty and phototherapeutic keratectomy have also been shown to play a role in treatment. Disease recurrence remains a challenge and the reason for poor visual prognosis. Newer techniques such as gene targeting therapies and enzyme replacement therapies are being studied for a potential permanent solution in MCD. Recent research is directed towards development of genetically modified products to integrate in host corneal DNA and block the mutant genes and hence overcome the underlying pathophysiology. Enzyme replacement therapy is another intervention with potential to treat MCD. Animal studies show clearance of accumulated keratan sulfate in the body tissues in the treatment of systemic mucopolysaccharidosis by long term enzyme replacement therapy (ERT). Future research should be directed toward elucidation of the relationship between the mutated CHST6, the mechanism of deposit formation, and the development of pharmaceutical agents based on gene therapy.

Keywords: stromal corneal dystrophies, macular corneal dystrophy, and genetic basis of corneal macular dystrophy.

I. Introduction

I a. Introduction to Corneal Dystrophies:

Corneal dystrophies are traditionally defined as rare inherited disorders of the cornea that are bilateral, and often symmetric, slowly progressive and not related to environmental or systemic factors. They are characterized by abnormal accumulations of insoluble deposits at different layers of the cornea. However, there are many exceptions to this broad definition as not all corneal dystrophies are inherited, bilateral, symmetric bilaterally or demonstrate deposition of abnormal substances into the cornea.[36, 79] Recently, the International Committee for Classification of Corneal Dystrophies (IC3D) developed a cataloging system for corneal dystrophies based on the layer of the cornea involved. The four categories are: epithelial and sub-epithelial, epithelial-stromal TGFBI, stromal and endothelial corneal dystrophies, however, many dystrophies involve more than one corneal layer.

I b. Introduction to Macular Corneal Dystrophy:

Macular corneal dystrophy (MCD) is a stromal corneal dystrophy that typically progresses to significant bilateral corneal opacities and thinning. It was first noted and detailed by German ophthalmologist Oskar Fehr in 1904.[21] Fehr was the first to differentiate between MCD, granular and lattice dystrophy and hence MCD was also known as Fehr spotted dystropy.[79] Jones and Zimmerman identified MCD as a unique entity, separate from granular and lattice stromal dystrophies using histopathology. They noted accumulations of glycosaminoglycans within stromal keratocytes in MCD. As observed by light microscopy, the

abnormal glycosaminoglycan material is primarily deposited in the stroma in an irregular fashion but also infiltrates the adjacent corneal structures including Bowman's layer, Descemet's membrane, and the endothelium. Although the majority of corneal dystrophies are autosomal dominant, MCD is an exception. It was shown to be inherited in an autosomal recessive fashion by Bücklers in 1938.[51] He studied twelve families with hereditary corneal dystrophies and determined that the granular corneal dystrophy (Groenouw type I) was Mendelian dominant while MCD (Groenouw type II) had recessive inheritance. Although, the eponymic designations of Groenouw types I and II have been time honored, they can be quite misleading because these names do not refer to different sub-types of the same pathology but to two different diseases, MCD and GCD.

II. Epidemiology and Demographics

MCD has been recognized throughout the world.[25, 28, 29, 41, 48, 67, 72, 73, 78] While it is relatively rare in the United States, it is reported to be most prevalent in southern India,[72, 73, 78] Saudi Arabia [5, 38] and Iceland due to increased rates of mutations in genes identified to cause MCD in these areas, much of which can be attributed to consanguinity.[28, 29, 48] In a national managed-care network claims study in the United States, Musch et al[55] reviewed the records of 8 million enrollees who had eye care visits from 2001 to 2009 and found an overall corneal dystrophy prevalence rate of 897 per million covered lives. MCD has been estimated to occur at a rate of 9.7 per million. Based on a registry maintained in the United States by Klintworth,[23] the prevalence of MCD in the United States is about 0.3 individuals per 250,000 inhabitants while in Iceland this number corresponds to 19. High prevalence of MCD in Iceland is also reflected by the fact that MCD accounts for approximately one-third of all corneal grafts.[28] A study

conducted in South India evaluated 36 patients from 31 families, in which 20 of the 31 families were known to have consanguinity.[72] Al Faran et al reported that 52% of all corneal dystrophies in Saudi Arabia are MCD, with 42% of MCD cases observed in offspring of consanguineous marriages.[5]

In MCD, stromal lesions typically start in the first decade of life and patients often progress to develop severe vision loss by the third decade of life.[79] The age of onset of clinical symptoms in the study reported from South India ranged from 13 to 49 of age, with the significant majority experiencing onset in their teenage years.[72] Initially, minute gray punctate opacities deposit in the cornea in teenage years that progress over time and develop into a diffuse stromal opacity. Pain due to rare corneal erosions may develop. Consequently, depending on the rate of progression and severity of the disease, age at presentation varies. Jonasson et al[28] initially studied 19 patients in Iceland and reported that age at diagnosis ranged between 3 and 25 years, while vision started decreasing between 15 and 25, progressing to the point of affecting daily activities between the ages of 19 and 35. In the United States' database, the mean age of patients with MCD was 47.3 years, about 15 years younger than the mean age of those with endothelial dystrophy. [55] This is likely because endothelial dystrophies tend to be late onset with slow progression and become significant with loss of endothelial cells with aging. The specific subtypes of endothelial dystrophies have not been reported in the database but majority were Fuchs' endothelial corneal dystrophy.

III. Pathogenesis and Ultrastructural Changes:

Early efforts to understand the pathogenic mechanisms involved light and electron microscopic studies of the explanted corneas of patients affected by MCD. This pathology was shown to be an inherited disease of the acid mucopolysaccharide metabolism localized in the keratocyctes (corneal fibroblasts).[24, 30, 31] The cytoplasm of the keratocytes showed small and large vacuoles of acid mucopolysaccharide material staining positively with periodic acid Schiff (PAS) stain. Histochemical studies using acridine orange and other metachromatic dyes have identified that this fibrillogranular material stains positively for glycosaminoglycans (GAGs) (Figure 1.A.; 1.B.) [42, 45] Electron microscopy showed intracytoplasmic accumulations in the endoplasmic reticulum of the keratocytes throughout the corneal stroma. These regions of enlargement of the smooth endoplasmic reticulum and intracytoplasmic vacuoles corresponded to the GAGs identified on histology.[35, 25] Synchtron X-ray diffraction studies demonstrated 4.6 Aº periodic repeats seen by high reflectance in large GAG molecules.[63] Using molecular sieve chromatography, Hassel et al[26] showed that in MCD, a glycoprotein with unusually large oligosaccharides is synthesized. Also, interestingly, electron microscopy shows similar findings in MCD and systemic mucopolysaccharidosis that show corneal involvement, specifically Hurler, Hurler-Scheie and Maroteaux-Lamy. The differentiating feature is the clinical appearance of flecks in MCD compared to more diffuse opacity in systemic mucopolysaccharidosis.[79]

Cell cultures of fibroblasts from diseased corneas, lysozyme enzyme assays, biochemical analyses and kinetic studies on synthesis of GAGs have shown that the underlying defect in MCD is decreased synthesis of corneal keratan sulfate in affected eyes. Using corneal fibroblast cultures from normal and MCD explants and comparing the 35 – S sulfate labelled GAGs profile, Klintworth showed that in MCD, keratan molecules are unsulfated. [26, 5, 34, 40, 58] In

addition to a decrease in production of keratan sulfate, there is a greater percentage of chondroitin 6 sulfate.

Keratan sulfate is found in the corneal epithelium, Bowman's layer, stroma, keratocytes, Descemet's membrane and endothelium of normal corneas.[46] It is the major component of lumican and keratocan, which are important in collagen fibril organization, thus maintaining corneal transparency. Due to abnormal sulfation, the keratan molecules cannot be metabolized;[57] and they precipitate in the extracellular matrix. Also, the collagen fibrils have been shown to be smaller, with a decrease in the inter-fibrillar spacing.[3, 53, 63] These factors cause loss of corneal transparency in MCD. It is unclear whether the ultrastructural changes are seen uniformly across the stroma or are more prevalent at certain stromal depths. Per IC3D, unlike GCD, in MCD, deposits are seen to involve the limbus and deep stroma down to Descemet's membrane.[79] A study using microbeam synchrotron X-ray fiber diffraction patterns suggested that posterior stroma is affected the most,[59] while a different study found that there were no changes in inter-fibrillar packing in the anterior and posterior stroma.[3]

IV. Immunophenotypes of MCD:

Initially, it was believed that this anomalous metabolism of keratan sulfate was restricted to the cornea alone. However, ELISA assays using monoclonal antibodies against keratan sulfate detected that the quantity of keratan sulfate was reduced in the serum of patients with histopathologically confirmed MCD.[37] Since keratan sulfate is derived from the normal turnover of cartilage,[74] studies looked at the levels of keratan sulfate in cornea and other cartilage samples from the body.[17, 62] Karcioglu et al analyzed ear cartilages in patients with MCD and demonstrated reduced concentrations of keratan sulfate chains in corneas and cartilage tissue

from same patients. [32] This confirmed that MCD is only one manifestation of a systemic disorder of keratan sulfate metabolism.

Based on the distribution and reactivity of the keratan sulfate in serum and cornea, immunophenotyping studies have identified that there are 3 variants of MCD – type I, I A, and II which are clinically indistinguishable (40). This terminology should not be confused with Groenouw types I and II.

In MCD-I, keratan sulfate is absent in both serum and cornea. The epithelium, stroma and endothelium all contain unsulfated keratan. In MCD-II, keratan sulfate is present in serum and corneal stroma in decreased levels.[18, 83] The corneal epithelium and endothelium show unsulfated keratan. A third immunophenotype, MCD I A, was identified initially in Saudi Arabia. These patients had no detectable levels of keratan sulfate in the serum, as in MCD-I, however the keratocytes in the stroma showed immunoreactivity to the keratan sulfate antibodies.[38] More recently, MCD I A has been described outside of Saudi Arabia as well.[13]

V. Genetic Basis:

Increased understanding of the genetic basis is important for earlier accurate diagnosis and development of potential targets for genetic therapy. MCD has been shown to be an autosomal recessive disorder. Molecular genetic studies have helped to identify the genetic basis of MCD. A locus on chromosome 16, 16q22 D16S518 was found to be associated with MCD in a study on Icelandic and American families.[77] Akama et al[2] identified that mutations of carbohydrate sulphotransferase gene (CHST6), encoding an enzyme designated corneal N-acetylglucosamine-6-sulphotransferase (C-GlcNAc6ST) are responsible for development of

MCD. This enzyme is responsible for normal sulfation of the keratan molecules. It has 4 exons, and mutations in exon 3 have been associated with MCD, as it contains the coding portion of the gene. [56] MCD-I has been shown to occur due to missense mutations while in MCD-II, deletions and/or rearrangements in the region between CHST6 and CHST5 have been reported.[1, 2]

Genomic studies have described types of mutations in CHST6 in different ethnicities. A study of 70 patients with MCD in Southern India showed that the majority had homozygous missense mutations, although other homozygous mutations including deletion and replacement were also identified in the coding region of CHST6 gene.[78] Similar mutations were found in a large study on American families. However, in some of the patients, mutations were not identified in the coding region itself, rather there were deletions identified upstream.[41] Studies in Chinese populations have found homozygous mutations in 6 of 19 families tested, while other families showed allelic heterogeneity. Missense, nonsense and frameshift mutations were identified and a Q298X mutation was believed to be the founder mutation in the Chinese population.[14, 49] Other molecular analyses done in different study populations in Britain,[20] South Korea[60], South Africa[8], and Czech Republic[47] have also identified novel mutations in the CHST6 gene; thus expanding the mutational spectrum of MCD.

VI. Clinical Manifestations

Affected patients develop severe progressive visual impairment that occurs between 10 and 30 years of age. Decreased vision is the most common presenting symptom. Vision at presentation can range from 20/40 to 20/100 or worse depending on location and density of corneal deposition. A study looking at 130 eyes with MCD reported average visual acuity

ranging from log MAR of 1.1 to 1.3.[65] In addition to decreased vision, symptoms of pain, irritation, photophobia and reduction of corneal sensitivity are noted although these are not as common as decreased vision and are thought to develop as a result of recurrent corneal erosions.[72] On slit lamp bio-microscopic examination, early diffuse stromal haze followed by accumulation of irregular whitish deposits is noted in the corneal stroma. (Figure 2.A.) These areas are commonly noted in both the anterior and posterior layers of the stroma. Anterior stromal deposition and occasionally sub epithelial deposition can lead to marked refractive error by altering the contour of the corneal surface, causing irregular astigmatism. The non-vascularized, poorly demarcated, grayish-white irregular opacities extend from limbus to limbus and do not have intervening areas of clear cornea, unlike granular corneal dystrophy.[2, 38, 67, 80] Thinning of the central cornea is seen as the disease progresses.[15, 19, 64] (Figure 1.B.) With progression, Descemet's membrane and endothelium are involved with deposits as well. The involvement of Descemet's membrane with excrescences may eventually lead to endothelial decompensation. It is at this point, if not sooner, that patients exhibit significant functional impairment and require surgical intervention.[22, 37, 38]

Corneal Imaging in MCD:

Recent advances in corneal imaging have helped to visualize the corneal ultrastructure non-invasively. In vivo confocal microscopy (IVCM) is a sophisticated modality that uses infra-red laser and provides high resolution corneal images. IVCM of two patients with MCD showed deposits of hyper reflective material with ill-defined borders in the subepithelium and anterior stroma with loss of normal keratocytes. In middle stroma homogenous deposits with dark striae were seen. Normal endothelium was reported in this study.[43] However a more recent study described hyper-reflective cells with bright cytoplasm in basal epithelium and bright granular

keratocytes in the stroma. This study reported changes in the endothelium as well. A change in the shape of cells with bright granular deposits in endothelial cells were seen.[54] In contrast to MCD, in GCD, irregular highly reflective deposits are seen in deeper stroma with normal surrounding keratocytes. In lattice corneal dystrophies, finer, sharp linear threadlike deposits are observed in anterior stroma.[68] Corneal topography has also been used to diagnose MCD. Kocluk et al[44] analyzed the Pentacam Scheimpflug imaging of 28 eyes of MCD patients and compared corneal densitometer findings to other forms of stromal dystrophies. They found that corneal density at the corneal apex was higher in the MCD group compared to lattice corneal dystrophy and GCD. They also found that the central corneal thickness and corneal thickness at the thinnest point of the cornea in MCD was lower than the other two groups. Other studies have also shown that MCD leads of thinning of central cornea. In addition, smaller corneal volume and higher Kmax and front elevations of the cornea have been reported.[15, 64] Dudakova etal[16] demonstrated increased sagittal curvature. However these patients do not show posterior corneal elevation and focal ectasia that is seen is true keratoconus. (Figure 3). There have been a few cases of bilateral coexistence of keratoconus and MCD.[6, 27] In these cases, corneal thinning paves the way to infero-temporal bulging and corneal ectasia. The thinning leads to additional irregular astigmatism. Computerized video-keratography further helped confirm the apparent corneal ectasia.[27] Ultrasound biomicroscopy can demonstrate posterior corneal changes including deep opacities and focal protrusions of the posterior cornea and thus help in choosing the appropriate surgery (i.e. PKP vs. DALK).[66] Anterior segment OCT shows abnormal hyperreflective areas throughout the corneal stroma with hyper-reflective deposits disrupting the lamellar arrangement of collagen fibrils.[69] Using wavefront analysis, Yagi-Yaguchi et al[82] have shown increased higher order aberrations in MCD that correlate with decreased visual acuity.

VII. Treatment and Prognosis of MCD:

The small and superficial corneal opacities seen in the first decade of life almost invariably involve the full thickness of the cornea by the fourth decade of life; causing vision to deteriorate to the point that corneal transplant is indicated. A study reported that the mean age when decreased vision was first noticed by patients was 28 ± 3 years and mean age of first PKP was 41 ± 4 years.[4]

Penetrating keratoplasty (PKP) has historically been the most common surgical treatment to restore visual acuity. However, recurrence after PKP and complications such as endothelial rejection and endothelial cell loss following transplantation have been documented.[52] (Figure 2.B.) Klintworth et al[39] reported that of the 198 patients who had undergone penetrating keratoplasty for macular corneal dystrophy in the United States, 5 (2.5%) required repeat keratoplasty. However, this is likely an underestimate as long-term follow up for these patients has been inconsistent. In a longitudinal study, 6 of 41 (15%) eyes required repeat penetrating keratoplasty and mean interval between keratoplasty and recurrence was 182 months (15.2 years).[4] The time from keratoplasty to MCD recurrence ranges from 20 months to 30 years in the literature.[42, 50, 52] The considerable time between surgery and potential recurrence warrants following these patients long-term.

Recently, use of newer partial thickness corneal transplants such as deep anterior lamellar keratoplasty (DALK) have been employed in MCD, specifically in cases when the endothelium is not involved. [70] Unal et al reported a final visual acuity of 20/60 or better in 75% of patients treated with DALK for MCD.[76] One case report found no significant difference in endothelial cell count or visual acuity in the two eyes of a patient with MCD who was treated with DALK in one eye and PKP in the fellow eye.[61] However, a different study showed that DALK had higher

progression of endothelial cell loss following surgery compared to PKP in MCD.[33] A recent study also found that patients who underwent PKP attained better best-corrected visual acuities than those in the DALK group, however complications were fewer with DALK.[10]

The largest study to date comparing PKP and DALK, including 104 patients, showed no significant difference in visual and refractive outcomes between the two groups. 67% of the patients undergoing DALK and 60% of the patients undergoing PKP attained BCVA of 20/40 or better. PK had endothelial graft rejection in 25% of the patients, with 55% in the first year. Higher graft survival was seen in the PK group compared to DALK, with estimated graft survival rate of 93% vs 80% at 1 year; and 78% vs 70% at 4 years.[65] Given these results, patients can be advised that surgical intervention offers a good chance of restoring visual acuity in MCD, despite the small but significant risk of recurrence.

Newer, less invasive techniques have also been described for MCD. Femtosecond laser-assisted lamellar keratectomy has shown recurrence in all of the cases reported, but it appears to be an effective means of delaying PKP or DALK by at least two years.[71] Excimer laser phototherapeutic keratectomy (PTK) is a technique used for treating anterior corneal dystrophies. In MCD, as full thickness cornea is affected, PTK is not a definite treatment but it has a role in patients with repeated corneal erosions. As PTK is minimally invasive and is capable of delaying the need for surgical intervention in patients with MCD. Recently, it was observed that use of mitomycin C immediately after PTK significantly delays the recurrence of disease. Recurrence was seen only in 1 out of 9 patients, occurring 22 months post-operatively. [84] In contrast, a study looked at 4 eyes with MCD that underwent PTK without mitomycin C and reported recurrence in all 4 eyes at an average of 13.5 months (range of 5-8 months). The recurrence was mostly noted in the laser ablative zone and reached deep stroma. [9]

VIII. Gene Therapy and Other New Treatment Strategies:

As many corneal dystrophies are caused due to an identifiable genetic mutation, it is theoretically possible to apply gene therapy to treat corneal dystrophies. However this can be very challenging. There are several pre-requisites in developing gene therapy for treatment of any condition. The most critical factor is identification of the exact gene responsible for disease. Modern microarray technology has been developed to use single nucleotide polymorphisms (SNP) to map genomes. After identification of the gene, genomic sequencing using PCR amplification is done. Next step is to develop the gene product and deliver to the target cell. Several vectors including both viral and non-viral vectors are being developed to deliver the gene products. Cell specific targeted gene delivery and integration are critical to success of gene therapy.[81] In an attempt to develop gene therapy for corneal dystrophies, the National Eye Institute (NEI) had started a genomic medicine network called the National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE) in 2006 This project offered DNA analysis to patients suffering from inherited eye diseases including corneal dystrophies and hence supports clinical and molecular diagnosis. It also created a data repository and a biorepository and offers controlled access to the collected information for research. The enrollment was paused in 2015. This allows creation of a database of the genotypic and phenotypic information of the various corneal dystrophies.[7]

One challenge in developing effective genetic interventions to treat corneal dystrophies is that there are no animal models available that resemble human corneal dystrophies which make in vivo testing of treatment difficult. Recently, studies on Meesman's corneal dystrophy have

shown potential use of a virus vector delivered SiRNA to block mutant gene expression in limbal epithelial cells.[11] SiRNA based treatments are also being developed for TGFB1 associated dystrophies such as corneal lattice dystrophy 1.[12] However, gene therapy in MCD is not straightforward. The most challenging part in the development of gene therapy for MCD is that is that although the gene CHST6 at chromosome 16 has been identified to cause MCD, there are 140 different genetic mutations. This makes it difficult to develop asingle target for gene therapy.

Enzyme replacement therapy is another potential therapeutic strategy. There have been studies investigating role of recombinant enzyme therapy for other metabolic disorders involving keratan sulfate. Recently, there have been studies on the treatment of mucopolysaccharidosis IVA in mice by long term enzyme replacement therapy (ERT) Recombinant human N-acetylgalactosamine-6-sulfate sulfatase (GALNS) showed clearance of accumulated keratan sulfate in the body tissue and partial remission of bone pathology.[75] These studies show potential role of enzyme replacement therapy in the treatment of MCD in the future.

IX. Conclusion:

Macular corneal dystrophy is an autosomal recessive stromal dystrophy in which there is abnormality of proteoglycan synthesis. Molecular genomic studies have identified that mutations in the CHST6 gene prevent normal sulfation of keratan in the cornea. This leads to loss of corneal transparency and decreased vision. Keratoplasty is the standard of treatment to improve vision. However, recurrence remains a challenge and reason for poor visual prognosis. Gene

targeting therapies can potentially be a permanent solution. Future research should be directed toward elucidation of the relationship between the mutated CHST6, the mechanism of deposit formation, and the development of pharmaceutical agents based on gene therapy.

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Literature Search:

A systematic search on Pubmed, Medline and Scopus was done using the following keywords: corneal dystrophies, stromal corneal dystrophies, corneal macular dystrophy, genetic basis of corneal macular dystrophy. Relevant abstracts and manuscripts were studied. There was no exclusion criteria based on year of publication. Papers of historical interest and early description of the entity from 1890 were included. Original research, case series and review papers were included. All English papers and English abstracts of non-English papers were used. Articles cited in the reference lists of other articles were also used. Bibliographies from major textbooks were also consulted.

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Figure Legends:

Figure 1. Histopathology findings in macular corneal dystrophy

A. Histopathological appearance of light cerulean colored glycosaminoglycan deposits in all layers of cornea including epithelium, stroma and Descemet's membrane. The thinning of the stroma towards the center is apparent. (Original magnification 40X, Alcian-blue stain).
B. High power detail of fibrillogranular material staining positively for glycosaminoglycans within stroma layers (Original magnification 400X, Alcian-blue stain)

Figure 2. Slit lamp bio- microscopy photograph of a patient with macular corneal dystrophy

A. Stromal opacities of varying sizes with somewhat unclear borders and intervening haze are depicted primarily in central cornea of the right eye of a MCD patient.
B. Recurrent opacities in the right eye of the same patient 5 years after PKP (white arrows). Note: Recurrence initially occurs at the periphery as diseased cells migrate from the edge of the graft.

Figure 3. Scheimpflug imaging of Macular Corneal Dystrophy.

Anterior sagittal curvature, pachymetry, and posterior elevation maps of the right cornea showing increased anterior sagittal curvature, thinning on pachymetry and lack of posterior elevation in a case of MCD