Prevalence and Histopathological Characteristics of Corneal Stromal Dystrophies in Saudi Arabia

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ABSTRACT

Purpose: The aim was to determine the frequency and describe the main histopathologic features of corneal stromal dystrophy in Saudi Arabia.

Methods: A single-center, retrospective analysis of 193 corneal specimens diagnosed with stromal dystrophy. All samples were retrieved from the Histopathology Department at King Khaled Eye Specialist Hospital over a 10-year period (2002 to December 31, 2011). Cases of stromal dystrophy undergoing keratoplasty were included in the study. Routine histopathologic stains and specific stains were used to determine a diagnosis. The corresponding demographic data and basic clinical/surgical information were collected via chart review.

Results: The study sample was comprised of 193 eyes. The final diagnoses were macular corneal dystrophy (MCD) in 180 (93.26%) eyes, granular corneal dystrophy (GCD) in 9 (4.66%) and lattice corneal dystrophy (LCD) in 4 (2.07%) eyes. The mean age at presentation was 27.03 years for MCD, 26.33 years for GCD and 53.75 years for LCD. The interval between diagnosis and surgical intervention was not statistically different between the macular and granular groups (P = 0.141). There was a positive family history for the MCD (37.22%) and GCD (44.44%) groups. All eyes underwent penetrating keratoplasty (PKP) except 10 MCD cases that underwent lamellar keratoplasty. Diffuse stromal deposits were present in 87.2% of MCD corneas and 66.67% of GCD corneas. Seventeen eyes with MCD were misdiagnosed as GCD. None of the LCD cases were clinically identified since all of these cases were diagnosed as corneal scarring. In eyes with MCD that underwent PKP, there was diffuse stromal involvement (in 87.22% eyes) and changes in Descemet’s membrane (in 53.5% eyes).

Conclusion: This pathological study suggested that MCD was the most common corneal stromal dystrophy that required keratoplasty in Saudi Arabia. Patient with MCD and GCD presented at a significantly younger age than LCD. The clinical diagnosis of MCD is not achieved in all cases likely due to a more severe phenotype in the Saudi population or the presence of corneal scarring that is associated with previous trachoma, which obscures the classical appearance of LCD. We believe that PKP is first-line surgical treatment, especially for MCD because it involves all corneal layers. However, deep stromal involvement and changes in Descemet’s membrane in MCD should be considered when selecting the surgical procedure.

Key words: Corneal Stromal Dystrophy, Histopathology, Keratoplasty, Saudi Arabia
INTRODUCTION

Corneal dystrophies are inherited disorders characterized by bilateral, symmetrical, or asymmetrical corneal opacity. The corneal opacities are caused by progressive accumulation of deposits affecting transparency or the refractive power of the cornea. They are primary corneal lesions which are not associated with prior inflammation or trauma. The usual onset is around the first decade of life, and the condition slowly progresses throughout life.1,2

The latest classification of corneal dystrophies by the international committee for classification of corneal dystrophies is based on organizing dystrophies according to the anatomic level of involvement. Dystrophies with a known documented genetic basis are grouped together.3

According to this classification, stromal dystrophies include the following:
- TGFBI dystrophies:
  - Lattice corneal dystrophy (LCD 1 and 2)
  - Granular corneal dystrophy (GCD 1 and 2) in addition to Reis-Bucklers.
- Macular corneal dystrophy (MCD)
- Schnyder’s corneal dystrophy (SCD)
- Congenital stromal corneal dystrophy
- Fleck corneal dystrophy
- Posterior amorphous corneal dystrophy
- Central cloudy dystrophy of Francois
- PreDescemet’s corneal dystrophy (PDCD).

The diagnosis of these disorders is based on the correlation between history and clinical findings then confirmation by histopathological analysis, tissue diagnosis and identification of the genes responsible for these diseases.4,4

The management of these conditions depends on the severity, progression and the effect on vision. Treatment with different modalities is based on the type of dystrophy and depth of the deposits. Treatments for corneal dystrophies include conservative management, superficial keratectomy, phototherapeutic keratectomy (PTK), and keratoplasty.

METHODS

This was a retrospective study of 193 corneas from 145 patients with a histopathological diagnosis of corneal stromal dystrophy who underwent either penetrating keratoplasty (PKP) or lamellar keratoplasty (LKP). The study was approved by research/Institute for Human Rights and Business committee at King Khaled Eye Specialist Hospital (KKESH).

A review was performed by a single pathologist of the histologic sections prepared for tissue examination in the Histopathology Department at KKESH over a 10-year period (2002–2011). The corresponding medical records of these cases were reviewed.

A data collection sheet was used to collect age at presentation, (to determine how early dystrophy could manifest), gender, nationality, clinical diagnosis (for comparison to the final histopathological diagnosis), family history of corneal dystrophy, and surgical procedure.

The visual impairment was evaluated using a grading system from 1 to 4 in which, Grade 1 indicated vision better than 20/100; Grade 2 indicated vision from 20/100 to <20/200; Grade 3, indicated vision from 20/200 to < counting finger (CF) and; Grade 4 indicated CF vision or worse.

A component of the study includes histopathologic analysis to identify the type of dystrophy and compared to the clinical diagnosis. The choice of the surgical procedure (PKP or LKP) determined the type of specimen and availability of comments on stromal thinning and changes in Descemet’s membrane. The depth of deposits was evaluated in order to comment on the appropriate surgical procedure for the various dystrophies. Routine processing and histopathologic staining by hematoxylin and eosin in addition to periodic acid schiff was performed on all corneal specimens. Special staining for each type of dystrophy was used to confirm the diagnosis. Hyaline deposits stain bright red with Masson Trichome in GCD and amyloid deposits stain with congo red in LCD. As with all amyloid, they demonstrate apple-green birefringence under polarized light and accumulation of glycosaminoglysans in the cornea that stain with colloidal iron or Alcian blue in MCD. Additional significant histopathologic findings include corneal epithelial changes, associated Bowman’s layer interruption, stromal scarring and/or stromal thinning where applicable. Descemet membrane changes (guttata) were assessed in full thickness corneal tissues obtained during PKP. Descriptive analysis of the results with comparison between some variables was performed with SPSS version 19 software (IBM Corp., New York, NY, USA). P < 0.05 was considered as statistically significant.

RESULTS

The study sample included 193 eyes from 145 patients. There were 97 (50.25%) males and 96 (49.75%) females. There were 89.7% Saudi patients and 10.3% of patients were of non-Saudi nationalities.

The mean age at presentation was 27.03 years (range, 12–72 years) in the MCD group, and 26.33 years (range, 11–45 years) in the GCD group (P = 0.359). The mean age at presentation in the LCD group was 53.75 years (range, 45–62 years). The difference in mean age at presentation was statistically significant between the MCD and LCD groups (P = 0.001), and between the GCD and LCD groups (P = 0.011).
The mean interval between presentation and surgical intervention (histopathologic diagnosis) was 36.28 months in the MCD group and 22.22 months in the GCD group \( (P = 0.141) \). In the LCD group, the mean was 75.75 months that were relatively longer.

One hundred and sixty-five (85.5%) eyes were clinically diagnosed with MCD. The remaining preoperative diagnoses included, 21 eyes (10.9%) with GCD, four eyes (2.1%) with an unspecified corneal dystrophy and 3 (1.5%) eyes with corneal scarring. The postoperative histopathological diagnosis using special stains confirmed the diagnosis of MCD in a higher number in 180 eyes (93.26%) compared with the clinical diagnoses above. Histopathology indicated GCD in 9 (4.66%) eyes. LCD was confirmed by histopathology in 4 (2.07%) eyes. An example of each is presented in Figures 1-3.

Based on the difference in the clinical and histopathologic diagnoses, 17 eyes in the MCD group were incorrectly diagnosed clinically as GCD and two eyes were diagnosed as unspecified corneal dystrophy. Three cases were misdiagnosed as MCD, but were GCD based on histopathology. Two cases of unspecified corneal dystrophy were GCD based on histopathology. Only one case on LCD was clinically identified as MCD whereas the remaining three cases were diagnosed as corneal scarring. This might be partially related to a presumed variation in the clinical appearance of the deposits or coexisting stromal scarring, which obscures the classic presentation.

The correlation between the clinical and the final histopathological diagnosis among different types of dystrophy is presented in Table 1. Table 2 shows the positive family history of a similar problem in 67 out of 180 (37.22%) eyes in the MCD group, and in 4 out of 9 (44.44%) eyes in the GCD group. Family history was negative in the LCD group [Table 2]. In the MCD group, 52.22% of eyes presented with Grade 1 vision, 37.7% of eyes with Grade 2, 9.44% of eyes with Grade 3, and 0.5% eyes with Grade 4.

Penetrating keratoplasty was performed in 183 eyes (94.8%) and the remaining ten eyes underwent LKP. The final diagnosis in these ten corneas was MCD.

In the MCD group, deep corneal deposits (as part of diffuse deposits at all stromal levels) were evident in 87.22% eyes compared with the group with anterior and mid-stromal deposits, without significant deep stromal involvement.

Recurrence of MCD was evident in four of ten eyes that underwent LKP and in only one case that underwent PKP. Two cases with GCD had a recurrence after PKP.

Table 1: Correlation between the clinical and histopathological diagnosis in different stromal dystrophies

| Clinical diagnosis (%) | Total |
|------------------------|-------|
| Macular dystrophy      |       |
| Granular dystrophy     |       |
| Corneal scar           |       |
| Others                 |       |
| **Histopathological diagnosis** | **Total** |
| Macular                | 161 (89.4) |
| Granular               | 3 (33.3) |
| Lattice                | 1 (25) |
| **Total**              | 165 | 21 | 3 | 4 | 193 |

Table 2: The frequency of a positive family history among the 3 diagnosed types of stromal dystrophies

| Histopathological diagnosis (%) | Total |
|---------------------------------|-------|
| Macular                         |       |
| Granular                        |       |
| Lattice                         |       |
| **Positive family history**     | **Total** |
| Yes                              | 67 (37.2) |
| No                               | 133 (62.8) |
| **Total**                        | 180 | 9 | 4 | 4 | 193 |
Epithelial changes described as irregularity or variable thickness were noted in 164 (91.1%) eyes with MCD, 7 (77.8%) eyes with GCD and three eyes with LCD.

Bowmans layer was interrupted in 100/180 cases with MCD, totally absent in 78/180 eyes and intact in two eyes only. In GCD, Bowmans layer was absent in 5/9 eyes, interrupted in 2/9 eyes and intact in the remaining two eyes.

Stromal thinning was found in 113 eyes (66.4%) with MCD and two corneas with LCD [Figure 4]. None of the eyes with GCD had stromal thinning.

Stromal scarring was present in 106 eyes (58.8%) with MCD, in 3 (33.3%) eyes with GCD and in all eyes with LCD. This finding may explain the clinical misdiagnosis of these cases as corneal scarring.

Descemet’s membrane involvement with the formation of secondary guttae was found in 91/170 corneas with MCD where full-thickness corneal tissue was examined histopathologically accounting for 53.5% of eyes [Figure 5]. These changes were completely absent in other dystrophies.

Various significant histopathological changes are presented for each of the three main types of dystrophies in Graph 1-3. Associated spheroidal degeneration was found in two eyes with MCD and in one eye with LCD.

**DISCUSSION**

This pathology based study found that MCD was the most common corneal stromal dystrophy that required keratoplasty in Saudi Arabia. Almost all the patients were Saudis (approximately 90%); therefore our outcomes are a good representation of the Saudi population. The majority of the cases with stromal dystrophy undergoing keratoplasty at KKESH had MCD (93.26%). This outcome concurs with a previous study from Saudi Arabia in 1991 with a predominant proportion of MCD (62%). However, alFaran and Tabbara’s study included endothelial dystrophies. Therefore it did not reflect the actual distribution of various stromal dystrophies undergoing PKP.

The pattern of stromal dystrophies is similar to the pattern observed in South India with a similar frequency of MCD being the most common stromal dystrophy. The South Indian study included all the corneal dystrophies. Hence, congenital hereditary endothelial dystrophy was the most common corneal dystrophy.

A study from Erlangen that enrolled European patients classified dystrophies into Fuchs’ and Non-Fuchs’ dystrophies. Their results have shown Fuchs’ to be the most common...
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10 A similar observation was noted in group of patients from Baltimore (United States) where Fuchs’ dystrophy was the most common of all dystrophies but LCD was the most common stromal dystrophy in the non-Fuchs’ dystrophy group.

Santos et al. studied a Canadian cohort of patients that specifically included corneal stromal dystrophies and found LCD was the most common (17 of 26 eyes) followed by Avellino dystrophy (five eyes) then GCD in three eyes and MCD in one eye.

A Japanese study reported a completely different pattern of stromal dystrophy where the gelatinous drop-like dystrophy was the most common, followed by granular and lattice corneal dystrophies both of which had an almost equal distribution.

The varying results from different regions of the world may indicate that the common occurrence of MCD in our study and a study from South India could due to the higher frequency of consanguineous marriages in these two countries. This is also evident through the associated positive family history observed among MCD cases (37.22% cases), and in four eyes out of nine eyes with GCD. A previous study from Saudi Arabia has reported a positive family history in 60% of the cases with MCD. A summary of the frequency of stromal dystrophies in these studies and our study is presented in Table 3.

The mean age of presentation for MCD and GCD (27 and 26 years respectively), was not statistically significant different ($P = 0.359$). However, all cases of LCD presented after 40 years of age (mean 53.75 years) which was statistically significantly different from MCD ($P = 0.001$), and GCD ($P = 0.011$). This observation confirms that patients with LCD usually present later than other types of stromal dystrophies. The later presentation could be because LCD can be asymptomatic or presents with mild symptoms that do not affect vision. This outcome is similar to a previous report that concluded patients with MCD presented at a significantly younger age than those with LCD.

There was no gender-related differences in our study (50.25% of the cases were male). This observation concurs with the majority
dystrophy while GCD was the most common non-Fuchs’ dystrophy.

Table 3: A summary of the frequency of filtered stromal dystrophies in other regions of the world and in the current study*

| USA | Canada | Europe | Japan | South India | Saudi Arabia 1991 | Saudi Arabia (Current) |
|-----|--------|--------|-------|-------------|---------------------|------------------------|
|     | Dystrophy |    | Dystrophy |   | Dystrophy |   | Dystrophy |   | Dystrophy |   | Dystrophy |   |
| Lattice | 46 | Lattice | 65 | Granular | 43 | Granular | 37 | Macular | 71 | Macular | 84 | Macular | 93 |
| Macular | 43 | Avellino | 19 | Macular | 34 | Lattice | 20 | Lattice | 20 | Lattice | 8 | Granular | 4.7 |
| Granular | 5.5 | Granular | 12 | Lattice | 21 | Macular | 5.3 | Granular | 4.7 | Lattice | 2.1 |
| Reis-Bucklers | 5.5 | Macular | 3.9 | Reis-Bucklers | 2.1 | Avellino | 4.7 | Reis-Bucklers | 4 | Reis-Bucklers | 3.2 |
| Total | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

*The percentages are recalculated after excluding other nonstromal dystrophy cases
of studies on corneal dystrophies did not show any gender variation. However, a study from the United States reported that all corneal dystrophies were more common in females.12

The time for surgical intervention usually depends on the degree of corneal haze and the decrease in vision. The patient’s occupational needs might also be an additional factor in determining the timing of surgery. A common misconception is that MCD cases undergo earlier intervention than GCD cases. However, there were no statistically significant differences between the groups in the current study (P = 0.141). However, LCD cases were offered surgical treatment relatively late in the course of the disease. Hence, LCD cases were not included in the comparison. As previously stated, these cases were managed as cases of stromal scarring rather than stromal dystrophy. In addition, one patient was lost to follow-up for 23 years before undergoing surgery.

Although the clinical diagnosis of corneal dystrophy is usually clear, misdiagnosis can occur because due to associated corneal scar, other ocular diseases, atypical presentation or early mild forms of the disease. In our study, 17 eyes with the histopathologically proven diagnosis of MCD were initially misdiagnosed by clinical examination as GCD. This was likely related to the early presentation when the typical picture of MCD is not yet apparent. Alternately, the misdiagnosis could be due to a variable phenotype of this dystrophy in our population that might warrant further genetic studies. Alternately, severe forms of GCD can clinically simulate MCD, which was noted in three cases of histopathologically proven GCD. The clinical diagnosis of LCD in our four cases was difficult because of associated corneal scar in these cases and spheroidal degeneration in one case. Santos et al14 have correlated the clinical diagnosis with the histopathological diagnosis. The clinical diagnosis was correct in all cases, except in four out of five cases of Avellino dystrophy, which were misdiagnosed as lattice because of late progression of granular lesions.11

Determining the location of deposits is important for selection of the appropriate surgical intervention. In our study, all cases underwent PKP except ten eyes with MCD that underwent LKP. Upon review of the location of the deposits histopathologically in cases with MCD, it has been observed that diffuse stromal involvement was evident in 87.22% of the cases. This would support the recommendation for PKP instead of LKP as a preferred surgical procedure to avoid leaving any deposits. This significant finding might explain the recurrence in cases that underwent LKP (4 out of 10).15 Another significant finding is the changes in Descemet’s membrane such as secondary guttata (due to endothelial cell involvement) in 53.5% of the MCD group. None of these cases had corneal edema or signs of corneal decompensation at presentation as a result of these changes. However, relatively early surgical intervention may have mitigated observation of any relevant changes or sequelae that develop over time. Seitz et al14 state that the central deposits in GCD are mostly superficial and are associated with abnormalities in Bowman’s layer and the corneal epithelium. Conversely, LCD deposits were located deeper within the corneal stroma. Thus PTK was considered more effective for the treatment of GCD than LCD.15

 Interruption of Bowman’s layer, or complete absence was a prominent histopathologic feature found in all cases of MCD except two with an intact Bowman’s layer. Stromal scarring was variable and observed in 59% of the MCD cases with the associated sub-epithelial fibrosis in the areas with interrupted Bowman’s layer. This observation explains the irregularity and variability of the thickness in the epithelial layer, which was evident in almost 91% of the corneas with MCD.

Associated spheroidal degeneration was found in two eyes with MCD and in one eye with LCD. These cases underwent surgical intervention later in life; therefore, these changes could be considered a degenerative response to the long-standing nature of their pathology. Such an association has been also reported by Pandrowala et al.4

Alternately, scarring was noted in only 3 GCD cases with no other associated secondary changes and intact Descemet’s membrane. However, 6 of the 9 GCD cases had deep stromal involvement which would lead to the conclusion that LKP was an unfavorable surgical treatment even for GCD.

Cases of LCD had epithelial changes with associated Bowman’s layer interruption and stromal scarring. The clinical diagnosis of LCD in this region of the world might be difficult, due to the high prevalence of trachomatous stromal scarring and the associated amyloid deposits occurring in chronically diseased corneas.

Stromal thinning was present in 66.4% of corneas with MCD, and four cases had topographic features consistent with keratoconus. However, the histopathological appearance of these cases did not support keratoconus as an associated diagnosis based on stromal thinning alone. We also question three previously reported cases in other studies.15-17 This co-morbidity needs further study and possible genetic analysis for confirmation.

Our study suggests that MCD is the most common stromal dystrophy in Saudi Arabia that requires keratoplasty. The second most common is GCD followed by LCD. This distribution is similar to South India and likely due to the higher frequency of consanguineous marriage in these two countries. However, other parts of the world show a different distribution with the most common stromal dystrophy being either granular (in Europe and Japan) or lattice (in North America). This geographic variation implies the need for further genetic studies of stromal dystrophy cases in Saudi Arabia.
The outcomes of our study confirm that patients with MCD and GCD tend to present earlier than those with LCD. There is an overlap in the presentation between scarred corneas with secondary amyloid deposits and primary amyloid in LCD. This is likely due to the high prevalence of trachomatous scarring with made LCD harder to diagnose. Atypical or late presentation and co-morbidity are other factors that may make the correct clinical diagnosis of stromal dystrophies tenuous in general.

A limitation of our study is the lack of molecular testing to differentiate the type of dystrophy accurately. However, pathological evidence with stromal deposit was available to confirm the diagnosis that remains better than clinical diagnosis alone.

We believe that PKP is superior for stromal dystrophies due to the deep stromal deposits in all types of stromal dystrophies. PKP should be the surgery of choice for MCD that presents with deep stromal deposits in addition to the endothelial involvement and Descemet’s membrane changes in many cases.

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