

Epidemiological and Histopathological Assessment of Corneal Dystrophies Leading to Corneal Transplantation

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Abstract

Purpose: To carry out an epidemiological assessment of corneal dystrophies leading to corneal transplantation and to determine different subtype frequencies.

Patients and Methods: In this retrospective study, pathological records of patients who had corneal transplantations other than endothelial keratoplasty between the years 2002 and 2014 were examined. To determine different subtype frequencies when corneal dystrophies led to corneal transplantation the IC3D classification of corneal dystrophies-edition 2 was used.

Results: Of the 5867 eyes undergoing corneal transplant surgery during the study timeframe, 239 (4.07 %) belonged to patients with corneal dystrophy. The most common age group was between 20 and 29 years (n = 57 ; 23.8 %). Macular corneal dystrophy was the most frequent corneal dystrophy subtype (n = 117 ; 49 %). Patients with epithelial and sub-epithelial dystrophies were significantly younger, and patients with Fuchs endothelial corneal dystrophy and lattice corneal dystrophy were the oldest age group when undergoing corneal transplantation.

Conclusions: Based on our findings macular corneal dystrophy was the most common corneal dystrophy subtype in patients scheduled for corneal transplantations other than endothelial keratoplasty.

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Introduction

Impaired vision due to corneal pathology is a challenging issue, especially in developing countries¹. Corneal opacity can result from trauma, inflammation, infection, metabolic and genetic disorders². Corneal dystrophy (CD) has high importance as a genetic disorder causing corneal opacities resulting in corneal transplantation surgery³⁻⁶. CD is a corneal alteration which is mostly bilateral, symmetric and not associated with systemic, inflammatory and environmental factors⁷. Aside from congenital hereditary endothelial dystrophy (CHED), which is a congenital disorder, and posterior polymorphous corneal dystrophy (PPCD), which can present itself as a congenital disease, other types of CD usually appear during the first and second decades of life⁸. CD primarily involves one layer of the cornea in the central area and often progresses slowly⁹. Corneal dystrophies are categorized into epithelial, sub-epithelial, epithelial-stromal, stromal and endothelial types based on the affected cellular layer^{8,10}. Previously, clinical and histopathological characteristics of CD were the only tools available for distinguishing the different types and classifying this disease¹¹. Using these two features alone, without putting to use the genetic attributes of the disease, causes some limitations in classification. Nowadays molecular genetics techniques have made it possible to reach a more precise classification and have significantly helped us in diagnosing the atypical forms of the disease^{12,13}. The diagnosis of CD is based on clinical signs and symptoms and confirming the diagnosis is via genetic and histopathological studies⁷. Determining CD's pathological attributions paves the way for health planners to assess the health needs of these patients and guide ophthalmologists about the types of CD which

should be considered in their geographic region.

Patients and Methods

The present study was approved by the ethics committee of Tehran University of Medical Sciences, Tehran, Iran.

In this retrospective study, histopathologic findings of patients who underwent any form of corneal transplantation other than endothelial keratoplasty between March 2002 and March 2014 at Farabi Eye Hospital (a referral eye center in Tehran the capital city of Iran) were reviewed and pertinent samples with a confirmed diagnosis of CD were selected. These specimens were previously fixed with formalin and embedded into paraffin. All tissue blocks were cut at 5 micron sections and stained with hematoxylin and eosin (H&E). Specific stains were applied including Masson's trichrome to diagnose hyaline depositions in granular corneal dystrophy (GCD), Alcian Blue, mucicarmine and Periodic Acid Schiff (PAS) to diagnose mucopolysaccharide accumulations in macular corneal dystrophy (MCD) and Congo Red to diagnose amyloid precipitations in lattice corneal dystrophy (LCD). The diagnoses were corroborated and classified based on the IC3D classification of corneal dystrophies edition 2. Patients' demographics were extracted from their pathology records. Data were analyzed using SPSS software version 20 (Armonk, NY: IBM Corp.). In this assessment, p values less than 0.05 were regarded as statistically significant.

Results

During the time interval of this retrospective analysis, between 2002 and 2014, 5867 corneal samples were sent to the pathology department with diagnosis of CD made in

239 (4.07 %) of samples. Among the samples diagnosed as CD, stromal dystrophies were the leading cause with 120 (50.2 %) samples, followed by endothelial dystrophies with 61 (25.5 %) samples, epithelial and subepithelial dystrophies with 30 (12.6 %) samples and finally epithelial-stromal TGFB1 lattice dystrophies with 28 (11.7 %) samples. Regarding the frequency of different types of CD, MCD with 117 (49 %) cases, was the most common type followed by Fuchs endothelial corneal dystrophy (FECD) with 39 (16.3 %) cases, gelatinous drop-like corneal dystrophy (GDL) with 30 (12.6 %) cases, CHED with 21 (8.8 %) cases, GCD type 1 (GCD1) with 13 (5.4 %) cases, LCD with 9 (3.8 %) cases, GCD type 2 with 3 (1.3 %) cases and congenital

stromal corneal dystrophy (CSCD) and PPCD with 1 (0.4 %) case each. In two samples, the clinical and pathologic evidence of Schnyder corneal dystrophy (SCD) existed as globular empty spaces in the superficial stroma that were probably tracks of lipid depositions previously dissolved during tissue processing. Ultimately, we reported these two slides as cases of SCD (Table 1). When we examined the frequency of CDs based on the patients' gender, we observed that 119 (49.8 %) CD positive samples were female, and 120 (50.2 %) were male. In our study, the prevalence of GDL was two times higher in females than in males ($P = 0.048$). There was no other significant relationship between sex and the type of dystrophy in our analysis. Regarding the patients' age,

Table 1: The prevalence of corneal dystrophies among patients entering the study

Type of CD		Gender		Total Number	Mean age (years)
		Male	Female		
Epithelial and subepithelial	Gelatinous drop - like	10 (33 %)	20 (66 %)	30 (12.6 %)	25.8
	Total epithelial and subepithelial	10 (33 %)	20 (66 %)	30 (12.6 %)	25.8
Epithelial - stromal TGFB1	Reis - Buckler	1 (33 %)	2 (66 %)	3 (1.3 %)	43.3
	Lattice	7 (77.7 %)	2 (22.3 %)	9 (3.7 %)	56.1
	Granular type 1	6 (46.15 %)	7 (53.85 %)	13 (5.5 %)	44.3
	Granular type 2	2 (66 %)	1 (33 %)	3 (1.3 %)	50.6
	Total epithelial - stromal TGFB1	16 (57.1 %)	12 (42.9 %)	28 (11.7 %)	48.6
Stromal	Schnyder	0 (0 %)	2 (100 %)	2 (0.9 %)	59
	CSCD	1 (100 %)	0 (0 %)	1 (0.4 %)	17
	Macular	65 (55.55 %)	52 (44.45 %)	117 (49 %)	36
	Total stromal	66 (55 %)	54 (45 %)	120 (50.2 %)	36.2
Endothelial	CHED	9 (42.86 %)	12 (57.14 %)	21 (8.8 %)	16.1
	PPCD	1 (100 %)	0 (0 %)	1 (0.4 %)	31.4
	Fuch's	18 (46.15 %)	21 (53.85 %)	39 (16.3 %)	58
	Total endothelial	28 (45.9 %)	33 (54.1 %)	61 (25.5 %)	43.1
Total		120 (50.2 %)	119 (49.8 %)	239	38.1

CSCD: congenital

stromal corneal dystrophy; CHED: congenital hereditary endothelial dystrophy; PPCD: posterior polymorphous corneal dystrophy

Table 2: Age Distribution of patients with corneal dystrophy undergoing corneal transplant

Age groups (years)	Epithelial and subepithelial	Epithelial–stromal TGFB1	Stromal	Endothelial	Total number
0 - 9	4	1	0	6	13 (5.4 %)
10 - 19	3	1	10	8	26 (10.9 %)
20 - 29	12	3	31	11	59 (24.7 %)
30 - 39	7	3	30	4	41 (17.2 %)
40 - 49	4	7	26	2	40 (16.7 %)
50 - 59	0	4	19	6	25 (10.5 %)
60 - 69	0	6	3	10	19 (7.9 %)
70 - 79	0	2	0	13	13 (5.4 %)
80 - 89	0	1	1	1	3 (1.3 %)
Total number	30	28	120	61	239

the highest number of corneal dystrophies was seen in 20 to 29 year age group, with 59 (23.8 %) cases (Table 2). The youngest and the oldest patients in our study were 2 and 85 years old, respectively, and both were suffering from endothelial dystrophies. Considering the affected layer, patients with epithelial and sub-epithelial dystrophies were significantly younger than patients affected by CDs involving other layers, with a mean age of 25.8 years ($P < 0.001$). Also patients diagnosed with FECD had a mean age of 58 years, and this number was significantly higher than other groups ($P < 0.001$). After patients with FECD, patients with LCD were older than other groups ($P < 0.001$). Also, the mean age of MCD patients (36 years), was significantly higher than that of CHED patients (16 years ; $P < 0.001$).

Discussion

In the present study, approximately 4.07 % of corneal transplantation procedures were carried out due to CD which is comparable with some previous studies conducted in China

(3.6 %) ⁶ and Iran (6.44 %) ¹⁴. In other studies, carried out in different parts of the world, the frequency of CD in tissue samples obtained from corneal transplant surgery candidates ranges from 3.4 % to 13.9 %. In regions such as Saudi Arabia, Taiwan, Northern parts of China and the Shandong province of China CD has been reported to be responsible for 4 %, 6.4 %, 4 %, and 3.4 % of corneal transplants, respectively and these frequencies are similar to those reported from Iran but are lower than those reported from European countries, the USA and Japan ^{3,6,15-21}.

Considering the relative frequency of MCD in corneal transplant cases, a comparable pattern between Iran, Saudi Arabia, and India exists ^{2, 2}. MCD is a genetic entity that has an autosomal recessive inheritance pattern ²²; therefore, the comparable frequencies between the three mentioned countries may be explained by the common act of consanguineous marriage in these regions, and this shows the importance of genetic counseling before and after marriage. In our assessment, FECD comprised 16.3 % of all CD cases documented. FECD displays an

autosomal dominant inheritance pattern and different genes associated with the disease have been identified. Considering the heterogeneous and complex genetic nature of FECD and existence of sporadic cases of the disease, explaining for the difference in prevalence of the disease between different societies requires more studies and knowledge about the novel genetic aspects of FECD and its risk factors. The Eye Bank Association of America reported in 2014 that FECD is the cause for 21 % of all corneal transplantations in America and it is estimated that this dystrophy has a prevalence of 4 % in the total American population²³. In another study performed by Ghosheh et al.,⁵ in the US, FECD was the underlying cause for 10.8 % to 16.3 % of penetrating keratoplasty cases, and other dystrophy types were linked to 1 % to 1.8 % of corneal transplantations. Santo et al.,¹⁶ in a study conducted in Japan on 159 corneal samples belonging to CD patients; reported only one confirmed case of FECD, which indicates the very low frequency of this dystrophy in Japan. Such a significant difference between FECD frequencies among corneas undergoing corneal transplant surgery in distinct populations could stem from the disparity between possibilities of the disease progressing towards a clinically significant state in populations with different genetic compositions. A study carried out in order to compare the endothelial cell density (ECD) of individuals between Japanese and Americans has indicated that ECD is significantly higher Japanese population²⁴. Given the fact that a decreased ECD has a role in the pathogenesis of FECD, this finding might give a justification for the lower prevalence of this disease in Japan. Studies in western countries

show that the prevalence of FECD is 2.5 to 3 times higher in women than in men, but this proportion was 1.16 in our study which indicates approximately even sex distribution of FECD in our study.

Based on scientific literature, GCD is the most common CD²⁵ but the opacities caused by GCD have a small effect on patients' vision, and therefore, a lower percentage of patients will need corneal transplantation compared to other dystrophies and those who do, will have the procedure at older ages. In the current study, two corneal samples suspicious of SCD existed, but the chance of reconfirming the diagnosis of this disease faded due to tissue processing and dissolution of fat deposits. To the best of our knowledge, the higher prevalence of GDL in females undergoing corneal transplant observed in our study has not been mentioned in previous studies. It may necessitate deeper genetic studies on this special dystrophy to find if females have a more severe disease necessitating corneal transplant or the disease is more common in females in some areas with a distinct genetic pattern other than the known autosomal recessive pattern.

Conclusions


Based on our findings Macular corneal dystrophy was the most common corneal dystrophy subtype in patients scheduled for corneal transplantations other than endothelial keratoplasty.

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Footnotes and Financial Disclosures

Conflicts of Interest:

The authors have no conflict of interest with the subject matter of the present study.