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MORPHOLOGICAL STUDY OF CORNEAL ENDOTHELIUM IN PSEUDOEXFOLIATION GLAUCOMA: A SINGLE INSTITUTE STUDY IN KASHMIR

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ABSTRACT Pseudoexfoliation syndrome is a generalized disorder of the extracellular matrix associated with excessive production and progressive accumulation of abnormal fibrillar material in intraocular and extraocular tissues. Pseudoexfoliation glaucoma accounts for approximately 25% of all open angle glaucomas worldwide. Specular microscopy of the corneal endothelium has revealed a significantly lower than normal cell density in eyes with the exfoliation syndrome and changes in cell size and shape. A hospital based study was conducted to evaluate the corneal endothelial cell parameters in 128 patients of pseuexfoliative glaucoma. The endothelial cell density in PXG group was significantly lower compared to control group. There was a statistically significant difference between PXG group and controls in terms of percentage of hexagonal cells and coefficient of variation. Identifying these alterations in these patients prior to surgical procedure like cataract or trabeculectomy important to minimize intra surgical endothelial loss and avoid post surgery corneal decompensation.

KEYWORDS : Intraocular pressure (IOP), Pseudoexfoliation glaucoma (PXG), Pseudoexfoliation syndrome (PXF).

INTRODUCTION

Pseudoexfoliation syndrome (PEX) is a generalized disorder of the extracellular matrix associated with excessive production and progressive accumulation of abnormal fibrillar material in intraocular and extraocular tissues[1]. In glaucoma patients, the prevalence of pseudoexfoliation is high, and elevated intraocular pressure occurs in 15%-50% of patients of PEX, about 6-10 times the rate in eyes without it[2,3]. The characteristics of pseudoexfoliation glaucoma (PXG) are high intraocular pressure, fluctuation in diurnal curve of intraocular pressure, marked spiking and pressure peaks, pigment dispersion and trabecular pigmentation, and poor response to medical therapy. Smaller optic disc, and significant correlation between intraocular pressure level and the mean visual field defect suggest that intraocular pressure is the main factor for glaucomatous damage[4].

PXG accounts for approximately 25% of all open angle glaucomas worldwide[5]. Its prevalence as reported by population-based surveys from South India vary between 7.5 and 13%[6,7]. It has a more serious clinical course and a worse prognosis than primary open angle glucoma[8,9].

Flakes of exfoliative material and pigment accumulation may be seen on the corneal endothelium. Specular microscopy of the corneal endothelium has revealed a significantly lower than normal cell density in eyes with the exfoliation syndrome and changes in cell size and shape. These findings have also been observed in the unaffected eye of unilateral cases, leading the researchers to suggest that these corneal endothelial changes might serve as an early sign of the disorder.[10]

In eyes with marked asymmetry of mesh work pigmentation, glaucoma is more common in the more pigmented eye[11]. Ultrastructural studies indicate that there is active exfoliation production in the trabecular meshwork, schlemm canal and collector channels as well as passive deposition of exfoliative material within intertrabecular spaces[12].

Most eyes with exfoliative glaucoma have an open angle mechanism, although acute angle closure glaucoma also occurs in a small number of cases[13,14,15,16]. Mechanism of IOP elevation in exfoliative glaucoma associated open angle may include local production of exfoliative material, endothelial cell damage of the trabecular meshwork and passive deposition of exfoliative material and pigment originating from elsewhere in the anterior segment[17,18]. Corneal endothelial morphology parameters include endothelial cell density (ECD) and the coefficient of variance of cell area CV / polymagatheism. These parameters can be affected by a broad range of disorders, such as contact lens complications, glaucoma, dry eye, and diabetes mellitus[19,20,21,22]. Furthermore, it is predictable that a normal healthy endothelium will have a low CV values[30]. The conventional method to estimate ECD is by using slit-lamp biomicroscopy.[23,24]; however, a disadvantage of this technique is that it is a manual assessment that requires subjective interpretation by the observer.[25]

In normal population with advancing age, there is a decline in the cell density, this decline was found to be on an average 0.29% per year. The rate of loss slows into the mid twenties and even lower rates of approximately 0.52% loss per year continue into older age. As cell density decreases with age individual cells enlarge and lose their hexagonal shape. Polymegathism, irregularity in the normal regular mosaic pattern may be quantified as a coefficient of variation in cell size.[26]

There is a considerable functional reserve for the endothelium. Therefore, corneal decompensation occurs only after more than 75% of the adult age cells are lost (i.e. when the endothelial cell count becomes less than 500 cells /mm^2). Aim of our study was to evaluate the various corneal endothelial cell parameters in patients with PXG presenting to our institute and comparing them with control population in similar age group.

MATERIALS AND METHODS

This study was hospital based prospective comparative observational study conducted in the Postgraduate Department of Ophthalmology, Government Medical College, Srinagar after obtaining the ethical clearance from the Institutional Ethical Committee. The study was conducted frm May 2015 to July 2018 and consequitive 128 patients of PXG who reported to our department and met the inclusion criteria were included in our study. Patients who had no previous corneal surgeries or history of contact lens wearing with untreated IOP≥21mmHg, an Open angle having ypical pseudoexfoliation material within the angle and

upon the lens and in the pupillary area and glaucomatous optic disc and visual field defects were included in our study. Non cooperative patient, those with previous intra-ocular surgery or history of ocular trauma, uveitis, corneal scars, lens induced glaucoma and other ocular pathology that could have led to secondary glaucoma were excluded from the study.

After obtaining informed consent from the patients, ocular examination in all patients was performed with slit lamp examination, gonioscopy with Goldmann two mirror indirect gonioscope and dilated fundus examination using +90D lens. The IOP was recorded with a Goldmann Applanation Tonometer.(Haag-Streit, Koniz, Switzerland) Visual Field Assessment (VFA) was performed using Humphrey Field Analyser II (Carl Zeiss, Meditec). Optical coherence tomography (OCT) for retinal nerve fibre layer (RNFL) was performed with ZEISS CIRRUS HD-OCT. (Carl Zeiss AG, Feldbach).The corneal endothelial parameters and central thickness were studied with TOPCON SP-1P Non-Contact Specular Microscope. The readings were taken by a single examiner.

The patients were seated at the instrument with the chin on the chin rest and the forehead against the forehead band. When the endothelium was in proper focus the instrument automatically took a picture of the endothelium. The parameters measured were endothelial cell density (ECD), percentage of hexagonal cells (HEX), coefficient of variation of cell area (CV).

RESULTS

A total of 128 patients with PXG were examined with equal number of control subjects with similar characteristics. The demographic characteristics of the participants are summarized in tables 1. The mean age in control group was 74.2years (SD 8.4) and in PXG group were 75.6 years (SD 9.8) with a range of 60-86 and 62-88 respectively. This difference was statistically not significant. (p= 0.416). Similarly no significant differences were found in between age and sex among the patients of two groups.

Table 1: Depicting age groups and gender distribution

		Normal		PXG		p value
		N (128)	%age	N (128)	%age	
Age Group	60-69	44	34.3	41	32.2	0.231
	70-79	43	33.5	44	34.3	
	≥80	41	32.2	43	33.5	
Gender	Male	66	51.5	68	53.1	0.734
	Female	62	48.5	60	46.8	

Statistically Non-significant Difference (P-value<0.05)

The ECD (cells/mm^2) in PXG group was significantly lower compared to control group which was statistically significant. Similarly there was a statistically significant difference between PXG group and controls in terms of percentage of hexagonal cells and coefficient of variation as is depicted in table 2.

Table 2: Comparison of Corneal endothelial parameters

Parameters		Normal (control)	PXG	p value
Endothelial Cell Density (cells/mm^2)	Mean	2564.2	2232.5	<0.001*
	SD	160.65	256.33	
	Range	2168-3191	1440-2815	
Mean Percentage of Hexagonal cells	Mean	57.3	50.4	<0.001*
	SD	4.16	2.28	
	Range	48-63	45-57	
Coefficient of variation	Mean	34.2	38.6	0.002*
	SD	2.21	2.06	
	Range	30-42	34-44	

SD: Standard deviation

* Statistically significant difference (P-value<0.05)

DISCUSSION

Pseudoexfoliative glaucoma is a disease that has a greater prevalence in older population as reported by Schlotzer-Schrehardt and Sood [27,28]. Patients enrolled in our study had mean age of 74. 2 years which is comparable to previously published reports [16,17,29].

There are conflicting reports of gender differences in pseudoexfoliative glaucoma reported by Ringvold A et al, and Mitchell P et al.[30,31] however in our study there was no significant difference in gender distribution of the disease.

There are a number of studies that describe the reduction of endothelial cells with age because these cells appear to have little or no possibility of dividing after birth. The loss of these cells involves an increase in size and a reduction of hexagonicity as described eloquently by Quiroga et al, and Niederer et al.[32,33]

However there are factors that can contribute to reducing the number of endothelial cells than normal age related reductions. One of these factors seems to be presence of pseudoexfoliative material which leads to corneal endothelial cell degeneration and alterations in their number and morphology. In addition, hypoxic changes have been described in anterior chamber as well as variations in the composition and dynamics of the aqueous humor caused by the rupture of blood aqueous barrier in eyes with PEX which could affect the function of endothelium as has been reported by Kuchle et al., in 1995 [34].These findings contribute to explain the results of this study in which it was observed that eyes with PEX lose cells in the corneal endothelium together with significant variations in the cell size and endothelial alterations observed in eyes with PEX to true keratopathy with its own entity capable of causing corneal decompensation with moderate IOP increases or after cataract surgery. However other studies by Inoue et al and Ostern et al, have not found any significant modifications in endothelial morphometric parameters in eyes with PEX.[35,36]

The mean corneal endothelial density per mm^2 in PXG eyes has been reported as 1812±297 by Knorr et al., 2052±264 by Seitz B et al. and 2234±270 by Hattori [37,38,39].In our study the mean corneal endothelial cell density per mm^2 was 2232.5±256.33 which was similar to previous reports mentioned above and showed a statistically significant difference against the normal group[2564.2±160.65].

A normal healthy endothelium will be expected to have a low coefficient of variation value while a stressed or traumatized endothelium will be more likely to have a high CV value as reported by Huan Sheng et al., in 2004).[40] The polymegathism value is a coefficient describing the variation in cell area and is determined with equation [CV = SD cell area (μm^2) / mean cell area (μm^2)]. The mean coefficient of variation in the cell area in PXG has been reported as 28.2 ±3.7 by Knorr et al, 32.3±6.6 by Hattori and 33.9±7.3 by Miyake et al.[10,37,39] .In present study the mean coefficient of variation in cell area was 38.6±2.06 which was similar to previous reports [10,39].There was a statistically significant difference between the study group and the control group in this parameter

In a healthy cornea, more than 60% of the endothelial cells are hexagonal. A decrease in six-sided cells and a corresponding increase in cells with more or fewer than six-sides is called pleomorphism. When some corneal endothelial cells die and disappear because of ageing, trauma or other stress, the remaining cells cannot divide to replace the dead cells. Instead, they enlarge and spread to cover the dead cells in order to maintain the intact monolayer mosaic. However, not all corneal endothelial cells enlarge to the same degree. Therefore some of the cells become larger than other and thus increase the variation of cell shapes and sizes (Huan Sheng et al.)[40].

The mean percentage of hexagonal cells in PXG eyes in our study was 50.4±2.28 which was in accordance to the data reported in previous studies [10,37,39] Also there was a statistically significant difference in this parameter when compared to the normal

group[57.3±4.16].

CONCLUSION

This study thus confirms the existence of significant difference in various corneal morphometric parameters in PXG patients. Identifying these alterations in these patients prior to surgical procedure like cataract or trabeculectomy must lead to consider measures to minimize intra surgical endothelial loss and avoid post surgery corneal decompensation.

REFERENCES

1. Altintas O, Yuksel N, Karabas VL, Qaglar Y. Diurnal intraocular pressure elevation in pseudoexfoliation syndrome. Eur J Ophthalmol 2004; 14: 495-500.
2. Konstas AG, Hollo G, Astakhov YS, Teus MA, Akopov EL, Jenkins J, Steward WC. Presentatioin and long term follow up of exfoliation glaucoma. Eur] Ophthalmol 2006; 16: 60-5.
3. Ho SL, Dogar GF, Wang J et al. Elevated aqueous humour tissue inhibitor of matrix metalloproteinase -1 and connective tissue growth factor in pseudoexfoliation glaucoma. Br J Ophthalmol 2005; 89: 169-73.
4. Koliakos GG, Konstas AG, Schlotzer-Schrehardt U, Hollo G, Mitova D, Kovatchev D, Maloutas S, Georgiadis N. Endothelin-1 concentration is increased in aqueous humour of patients with exfoliation syndrome. Br.I Ophthalmol 2004; 88: 523-7.
5. Ritch R. Exfoliation syndrome-the most common identifiable cause of open-angle glaucoma. J Glaucoma 1994; 3: 176-7.
6. Arvind H, Raju P, Paul PG, Baskaran M, Ramesh SV, George RJ, et al. Pseudoexfoliation in South India. Br] Ophthalmol 2003; 87: 1321-3.
7. Krishnadas R, Nirmalan PK, Ramakrishnan R, Thulasiraj RD, Katz J, Tielsch JM,et al. Pseudoexfoliation in a rural population of southern India: the Aravind Comprehensive Eye Survey. Am J Ophthalmol 2003; 135: 830-7.
8. Ritch R. Exfoliation syndrome. Curr Opin Ophthalmol 2001; 12: 124-30.
9. Konstas AG, Stewart WC, Stroman GA, Sine CS. Clinical presentation and initial treatment patterns in patients with exfoliation glaucoma versus primary open-angle glaucoma. Ophthalmic Surg Lasers 1997; 28: 111-7.
10. Miyake K, Matsuda M, Inaba M. Corneal endothelial changes in exfoliation syndrome. Am J. Ophthalmol 1989;108(1):49-52.
11. Ritch R. Exfoliation syndrome and occludable angles Trans. Am Opthalmol Soc. 1994;92: 845-944.
12. Schlotzer – Schrehordt U, Naumann GOH. Trabecular mesh work in exfoliation syndrome with and without open angle glaucoma. A Morphometric, ultrastructural study. Invest Opthalmol Vis. Sci 1995; 36(9): 1750 – 1764.
13. Roth M, Epstein DL. Exfoliation syndrome. Am J Ophthalmol 1980; 89(4): 477-481.
14. Layden WE, Shaffer RN. Exfoliation syndrome. Am. J Ophthalmol 1974; 78(5):835-841.
15. Brooks AM, Gillies WE. The presentation and prognosis of glaucoma in exfoliation of the lens capsule ophthalmollgy 1988; 95(2): 271-276.
16. Gillies WE, Brooks AM. The presentation of acute glaucoma in exfoliation of the lens capsule. Aust NZJ Ophthalmol 1988; 16(2): 101-106.
17. Undblom B, Thorburn W. Functional damage at diagnosis of primary open angle glaucoma. Acta Ophthalmol. 1984; 62(2) 223 – 229.
18. Futa R, Shimizu T, Furuyoshi N et al. Clinical features of capsular glaucoma in comparision wth primary open angle glaucoma in Japan. Acta Ophthalmol 1992; 70(2): 214-219.
19. Solomon OD. Corneal stress test for extended wear. CLAO J 1996; 22:75-78.
20. Sihota R,Lakshmaiah NC,Titiyal JS,Dada T,Agarwal HC.Corneal endothelial status in the subtypes of primary angle closure glaucoma.Clin Exp Ophthalmol.2003;31:492-5.
21. Liu Z, Pflugfelder SC. Corneal thickness is reduced in dry eye. Cornea 1999; 18: 403—407.
22. Larsson L-I, Bourne WM, Pach JM, Brubaker RF. Structure and function of the corneal endothelium in diabetes mellitus type I and type II. Arch Ophthalmol 1996; 114: 9—14.
23. Doughty MJ, Aakre BM. Further analysis of assessments of the coefficient of variation of corneal endothelial cell areas from specular microscopic images. Clin Exp Optom 2008; 5: 438-446.
24. Rose GE. Clinical assessment of corneal endothelial cell density: an original system of grading using a slit-lamp bio-microscope. Br J Ophthalmol 1986; 70: 510-515.
25. Kim T, Sorenson AL, Krishnasamy S, Carlson AN, Edelhauser HF. Acute corneal endothelial changes after laser in situ keratomileusis. Cornea 2001; 20: 597-602.
26. McLaren JW, Bourne WM, Patel SV. Automated assessment of keratocyte density in stromal images from the confoscan 4 confocal microscope. Invest Ophthalmol Vis Sci 2010; 51: 1918— 1926.
27. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol. 2006;141:921–37.
28. Sood NN. Prevalence of pseudoexfoliation of the lens capsule in India. Acta Ophthalmol (Copenh) 1968;46:211–4.
29. Ritch R, Schlötzer-Schrehardt . Exfoliation Glaucoma. In: Weinber RN, Kitazawa Y, editors. Glaucoma in the 21st century. London: Harcourt Health Communications: Mosby International; 2000. pp. 171–9.
30. Ringvold A, Blika S, Elsås T, Guldahl J, Brevik T, Hesstvedt P, et al. The Middle-Norway eye-screening study. I. Epidemiology of the pseudo-exfoliation syndrome. Acta Ophthalmol (Copenh) 1988;66:652–8.
31. Mitchell P, Wang JJ, Hourihan F. The relationship between glaucoma and pseudoexfoliation: The Blue Mountains Eye Study. Arch Ophthalmol. 1999;117:1319–24.
32. Quiroga L, Lansingh VC, Samudio M, Peña FY, Carter MJ. Characteristics of the corneal endothelium and pseudoexfoliation syndrome in patients with senile cataract. Clin Exp Ophthalmol. 2010; 38:449-55.
33. Niederer RL, Perumal D, Sherwin T, McGhee CN. Age-related differences in the normal human cornea: a laser scanning in vivo confocal microscopy study. Br J Ophthalmol. 2007; 91:1165-9.
34. Küchle M, Nguyen NX, Hannappel E, Naumann GO. The blood–aqueous barrier in eyes with pseudoexfoliation syndrome. Ophthalmic Res. 1995; 27:136-42.
35. Inoue K, Okugawa K, Oshika T, Amano S. Morphological study of corneal endothelium and corneal thickness in pseudo-exfoliation syndrome. Jpn J Ophthalmol. 2003; 47:235-9.
36. Ostern AE, Drolsum L. Corneal endothelial cells 6–7 years following cataract surgery in patients with pseudoexfoliation syndrome. Acta Ophthalmol. 2012; 90:408-11.
37. Knorr HL, Ju¨nemann A, Ha¨ndel A, Naumann GOH. Morphometric and qualitative changes in corneal endothelium in pseudoexfoliation syndrome. Fortschr Ophthalmol 1991;88:786–789.
38. Seitz B, Mu¨ller EE, Langenbucher A, Kus MM, Naumann GO.Endothelial keratopathy in pseudoexfoliation syndrome: quantitative and qualitative morphometry using automated video image analysis. Klin Monatsbl Augenheilkd 1995;207:167–175.
39. Hattori Y. Corneal endothelial examination of pseudoexfoliation syndrome. Nippon Ganka Gakkai Zasshi (Acta Soc OphthalmolJpn) 1990;94:957–963.
40. Huan Sheng, Carol A. Bottjer, Mark A. Bullimore. Ocular component measurement using the Zeiss IOL. Master/ Optometry and Vision Science 2004; Vol. 81(1(: 27-34.