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Changes in corneal endothelium and risk factors for surgical treatment of cataracts in the presence of pseudoexfoliation syndrome

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Characteristic of pseudoexfoliative syndrome (PEX) corneal changes in the form of keratopathy which affects all layers of the cornea as the process progresses is a risk factor in cataract surgery especially in countries with a large elderly population. In cataract surgery, the corneal endothelium deserves increased attention because cells do not recover from their damage (Schlotzer-Schrehardt et al., 1993; Zheng, 2013). We studied corneal endothelial changes in 58 patients (58 eyes) with PEX from the perspective of the progression of the syndrome, risk factors of cataract surgery. From the standpoint of the risk of potential complications of cataract surgery dystrophic symptoms complex of eye structures, the degree of development of PEX (3 stages) analyses of indicators of morphological changes in the corneal endothelium revealed significant differences in indicators depending on the degree of PEX progression. From the standpoint of cataract surgery in the eyes with PEX, there is a tendency for changes in the morphological parameters of the corneal endothelium with progressing syndrome.

Keywords: *Pseudoexfoliation syndrome (PEX), corneal endothelium, cataract surgery, risk factors, stage of PEX, open-angle glaucoma (OAG), pseudoexfoliative material (PEM)*

INTRODUCTION

Currently, there is a steady trend toward increasing life expectancy and aging of the population. While in many countries people over 60 years old (or 841 million) account for 20% of the population, by 2050 according to the UN, this figure will increase 2.5-3 times (up to 2 billion people or more) (Chan, 2015; http://www.who.int). According to the WHO, the majority of the 1.3 billion global population with visual impairment are over 60 years of age, whereas cataracts and glaucoma are the main causes of blindness (http:// www.who.int/ru/news-room/fact-sheets/detail/blindness-and-visual-impairment; Zhao et al., 2015).

Pseudoexfoliation syndrome (PEX) is among the age-related changes and leads to a high incidence of cataracts and glaucoma worldwide. As a systemic dystrophic process, PEX is differed by characteristic deposits of pseudoexfoliative material (PEM) not just inside the eye but orbit, skin, internal organs and has a close link to cardiovascular pathology (Schlötzer-Schrehardt and Naumann, 2006; Wirostko et al., 2018; Yildrim et al., 2017; Chung et al., 2018; Siordia et al., 2016; Zikou et al., 2018).

PEX remains a mystery in the field of ophthalmology which is confirmed by the numerous publications of scientists from different countries on various aspects of the problem (Detorakis et al., 2021).

Nevertheless, cataract surgery is one of the most common procedures worldwide, surgery in patients with PEX is still very challenging and possesses an increased risk of complications, such as corneal decompensation, contractile capsular syndrome, dislocation of the capsular-bag

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complex which are known to be based on the ligamentous failure and reduced tolerance to mechanical (surgical) trauma (Namazova et al., 2016; Baig et al., 2021; Shingleton et al., 2017; Tekin et al., 2019; Vanags et al., 2020).

Among the structures that are subject to the most careful care and increased attention during cataract surgery is corneal endothelium, since these cells do not recover after their damage. The corneal changes in the form of keratopathyare characteristic of PEX. While PEX progresses, it affects all the layers of the cornea causing an increased incidence of bullous keratopathy, especially in countries with a large elderly population, such as Japan (Schlotzer-Schrehardt et al., 1993; Zheng, 2013).

Some studies emphasize the relationship between changes in the corneal endothelium and the severity of changes in PEX (Aoki et al., 2020; Palko et al., 2017; Yüksel, 2016; Demircan et al., 2015). At the same time the assessment of the degree (stage) of PEX from the standpoint of the surgical risk for potential complications remains ambiguous (Naumannand Schlotzer-Schrehardt, 2000; Inazumi et al., 2002; Takhchidi et al., 2010).

Thus, it is extremely important in eyes with signs of a potential danger of corneal endotheliumdecompensation, to prevent possible changes by choosing the optimal surgical technique. At the same time, the results of many studies of corneal endothelium have found a statistically significant lower density of corneal endothelium in the eyes of patients with PEX compared with healthy subjects, although the cornea guttata not found in patients with PEX. Available data on the presence of changes in open-angle glaucoma (OAG) and PEX are mixed (Bozkurt et al., 2015; Palko et al., 2017; Yüksel et al., 2016; Demircan et al., 2015).

Perhaps this is due to the characteristics of the instruments used, the size, the ethnicity, age and other factors that can contribute (Palko et al., 2017; Yüksel et al., 2016).

All these factors to a certain extent create difficulties in assessing the process, predicting and choosing optimal treatment tactics. Thus, given that the problem remains within the discussions, assumptions, the purpose of this study was chosen to elaborate on optimal tactics to approach those kinds of pathologies.

The purpose of the current work was to study changes in the corneal endothelium in the eyes of patients with pseudoexfoliation syndrome from the point of view of the syndrome progression and risk factors for cataract surgery.

MATERIALS AND METHODS

The results of the examination of 58 patients aged from 56 to 86 years (mean age 72.2±0.9), 26 men (44.8%), 32 women (55.2%) hospitalized for cataract surgery. Criteria for inclusion in the study: patients with cataracts and concomitant PEX confirmed by two-stage biomicroscopy and ultrasonic biomicroscopy (UBM). Among them, 46(79.3%) patients with PEX had intraocular pressure (IOP) within the normal range, 12 (20.7%) had open-angle pseudoexfoliative glaucoma (OPXG). The groups were equal in gender and age. All patients underwent all necessary ophthalmological examinations.

The ophthalmic examination consisted ofvisual acuity check (uncorrected, corrected), 2-stage biomicroscopy (undilated, tonometry and dilated) gonioscopy, ultrasound biomicroscopy (UBM-plus, Accutome, USA), biometry (IOL - Master, Zeiss, FRG), specular microscopy (Tomey EM-3000, Japan).

Results of anterior segment biomicroscopy in patients with PEX were analyzed according to the criteria of the potential risk of cataract surgery complications (including inflammatory ones). Evaluation criteria in UBM were usual landmarks: relief of surface profile, the reflectivity of the investigated structure, spatial and quantitative parameters of the interrelation of anatomical structures. Axial longitudinal, tangential slices (scanning variants), color reproduction were used (Pavlin et al., 1998; Inazumi et al., 2002).

The corneal endothelium studies by specular microscopy before surgery in patients with varying degrees of surgical risk, varying degrees of structural changes total in 58 eyes of patients with PEX.

Statistical processing: one-dimensional statistics methods with calculations of the Kruskal-Wallis and Mann-Whitney tests.

The research protocol has been approved by

the ethical committee of the National Opthalmology Centre named after acad. Zarifa Aliyeva. Informed consent was obtained from all patients.

RESULTS AND DISCUSSION

Based on the risk factors significant for cataract surgery3 types of different criteria were identified. The aforementioned criteria were based on the severity of dystrophic changes in the eye structures and deposits of the PEM within them.

In the first variant, it was established in 11 (18.97%) eyes with a distinctive feature as the preservation of the pupil's reaction to light and mydriatics; I stage PEX). At the same time, the destruction of the pigmented border of the pupillary edge (partial) in the control group was present only in 14 (35%) eyes. In 20 (43.48%) eyes dystrophic component of PEX was more pronounced: smoothness of the iris pattern, moderate pigmentation of the surface was accompanied by changes in the pigmented border of the pupillary edge manifesting as partial disappearance and more often as a complete destruction indicating a more significant change (II stage of PEX). Deposits of PEM along the edge of the pupil were more pronounced, dystrophic changes in the stroma were especially evident in the trabecular and mixed type of iris structure, rather than spongy. Pseudoexfoliative deposits were present on the corneal endothelium of 10 (50%) eyes. There was a decrease in pupil response to mydriatics but no significant changes were observed in the zonules of crystalline fibers. A decrease in pupillary reactions was more often caused by the development of iridocapsular synechia. At the same time, the presence of iridocapsular planar synechia was explained by increased extravasation from the vessels of the iris, appearance of proteins unusual for it in the anterior chamber (Podgornaya et al., 1988).

In 15 (32.61%) eyes with PEX the dystrophic component was the most significant (stage III PEX). Leaching of the pigmented border up to its absence was combined with changes in the pigment layer of the iris in a number of cases - up to translucence and exposure of the stromal vessels. Significance was acquired by changes in the Zinn ligament. If during biomicroscopy there was a deepening of the anterior chamber or tremulation of the lens or its subluxation, then UBM revealed changes in the fibers of Zinn's ligament.

The study results of the anterior segment of patients from the point of view of surgical risk for potential complications of cataract surgery the severity of the dystrophic symptom complex, where three degrees of development of PEX identified were analyzed with indicators of morphological changes in the cornea during mirror microscopy.

Results of corneal endothelium studies by specular microscopy before cataract surgery in patients with varying degrees of surgical risk, varying degrees of structural changes total in 58 eyes of patients with PEX were reflected in Table 1.

When comparing and evaluating the arithmetic mean values of the morphological parameters of the corneal endothelium a number of significant differences in indicators were established between grades I and II of PEX, grades II and III of PEX, grades I and III of PEX, including changes in the eyes with concomitant glaucoma.

The average density of corneal endothelium with variations in values (min 2743 cells/mm², max 3460 cells/mm²) in patients with PEX in the 1 degree was 2871.6 ± 57.3 cells/mm², II degree - 2388.6 ± 55.0 cells/mm² (min 188.5 ± 11.5 cell/mm², max 687.0 ± 53.6 cell/mm²); PEX III degree - 1867.1 ± 95.6 cells/mm² (min 474.0 ± 51.5 cells/mm², max 1228.1± 120.7 cells / mm²).

Comparison of morphological changes at different degrees of development of PEX, namely, with PEX of the 1 PEX of the II degree PEX, revealed that the cell density (CD) in PEX of the I degree in comparison with PEX of the II degree was 1.2 times greater value ($p<0.05$); cell polymorphism index (AVG) in PEX grade 1 was significantly lower by 1.2 times compared to PEX grade II ($p<0.05$) degree had a 1.3 times significantly lower value in comparison with the II degree PEX ($p<0.05$).

Table 1. The results of corneal endothelium studies by specular microscopy before surgery with varying degrees in patients with PEX

The degree (stage) of PEX	N	Corneal thickness	Min	Max	AVG	CD	SD	CV	HEX
PEX 1 stage	11	0.526±0.046	177.9±11.5	687.0±53.6	349.5±7.0	2871.6±57.3	105.0±11.4	30.0±2.8	59.9±5.6
PEX II stage	20	0.521±0.010	188.5±11.5	836.8±34.4	423.2±10.5	2388.6±55.0	134.5±7.4	32.0±1.7	54.8±4.2
PEX III stage	15	0.525 ±0.014	474.0±51.5	1836.5±158.9	943.6±85.9	1181.2±97.7	315.5±39.6	35.2±4.5	40.3±9.4
PEX+glaucoma	12	0.522±0.006	202.3 ±30.1	1228.1±120.7	563.6±51.0	1867.1±95.6	214.4±28.2	37.3±2.8	84.1±13.9
Total	58	0.523 ±0.006	263.2±22.3	1147.9±76.7	572.8±38.9	2060.0±89.0	192.2±16.1	33.5 ±1.5	58.1±4.5

Among non-significant differences, the coefficient of variation (CV) in PEX of the 1st degree in comparison with the indicator of PEX of the II degree had a 1.1-fold lower value ($p>0.05$), during the recovery of the corneal endothelium its value is less than 33 and it is considered normal. An increased coefficient of variation is often considered an early sign of disease as it is a marker of corneal endothelium cell remodeling.

The percentages of hexagonal cells (HEX) did not have significant differences. However, with the first degree PEX it was 1.1 times more than in the II PEX ($p> 0.05$), degree of PEX was greater than 1.0 in comparison with the II degree of PEX ($p>0.05$). Differences between the II and III stages of PEX led to significant differences in indicators: CD at stage II PEX was 2 times more ($p<0.05$); AVG at grade II PEX was 2.2 times less ($p<0.05$), SD at grade II PEX was 2.3 times lower ($p<0.05$).

Among the non-significant differences there were: corneal thickness 1.0 time greater at the II stage ($p>0.05$), the CV variation coefficient at the II degree of PEX was 1.1 times less ($p>0$ 05), the percentage of HEX at grade II PEX 1.4 times higher ($p>0.05$). Differences between the 1st and the 3rd stages of PEX were studied and they showed: the cell density (CD) in PEX of the 1st degree was 2.4 times higher ($p<0.05$); the index of cell polymorphism was 2.7 times lower in PEX grade 1 compared with PEX grade 3 ($p<0.05$). The standard deviation (SD) of the mean cell area in PEX grade 1 was 3 times less ($p<0.05$).

Among the non-significant differences: the corneal thickness index was 1.0 time greater in PEX grade 1 ($p>0.05$), CV in grade 1 PEX was 1.2 times lower ($p>0.05$), hexagonal cells percentage HEX in PEX grade 1 was 1.5 times higher ($p>0.05$).

Differences in corneal endothelium were assessed in eyes with normal ophthalmotonus at grade I PEX with eyes where glaucoma also occurred. Significant differences included: CD was 1.5 times higher ($p<0.05$); AVG was 1.6 times less ($p<0.05$); SD was 2 times less ($p<0.05$). Among the non-significant differences was the index of corneal thickness, which at grade 1 was 1.0 times greater ($p>0.05$); CV was 1.2 times less ($p>0.05$), the percentage of HEX was 1.4 times less ($p>0.05$).

Differences in indicators were assessed in the II degree of PEX with eyes with glaucoma, cataracts against the background of patients with PEX. Among the significant differences in grade II PEX without glaucoma compared to eyes with glaucoma, CD was 1.3 times higher ($p<0.05$); AVG was 1.3 times less ($p<0.05$); SD is 1.6 times less ($p<0.05$).

Among the non-significant differences the AVG index at grade II compared with the eyes with glaucoma the HEX index was 1.5 times lower ($p>0.05$); CV 1.2 times less ($p>0.05$); corneal thickness was 1.0 times less ($p>0.05$).

Differences in indicators were evaluated for grade III PEX in eyes with glaucoma. Among the significant differences CD was 1.6 times less ($p<0.05$); SD was greater than 1.5 times ($p<0.05$); CV is 1.1 times less ($p>0.05$); AVG was 1.7 times greater ($p<0.05$).

Among non-significant differences, the percentage of HEX was 2.1 times higher ($p>0.05$); corneal thickness was 1.0 times higher ($p>0.05$). In terms of corneal thickness, it was not possible to identify significant correlations with any indicators.

The CD indicator for PEX for the 1st grade was 1.2 times greater than for the 2nd grade, and 2 times greater than for the 3rd grade, respectively ($p<0.05$); and the difference between the 1st and the 3rd CD was greater by 2.4 times ($p <0.05$).

Comparing the CD in patients with glaucomatous changes in PEX the 1st grade was

greater by 1.5 times ($p<0.05$) and by 1.3 times greater ($p<0.05$) compared with the 3rd grade PEX.

Comparing polymorphism of the endothelial cells (AVG) in PEX, the 1st grade was 1.2 times less than in PEX the II grade and 2.2 times less than in PEX the III grade and between the 1st and the 3rd grade - 2.7 times less. In all cases the p-value was less than 0.05.

Standard deviation (SD) was for PEX 1 in 1.3 times less than in PEX II, PEX II and PEX III 2.3 times less and PEX 1 and PEX III 3 times less. In all cases, the p-value was less than 0.05.

Results for the difference in patients with PEX the II grade in glaucomatous eyes and cataracts compared without glaucoma demonstrated CD 1.3 times greater ($p<0.05$) and for AVG parameters 1.3 times less ($p<0.05$) in patients with glaucoma. When it comes to SD values, PEX 1 to PEX II grade was 1.5 times greater ($p<0.05$), PEX II to PEX III gradewas 1.1 greater ($p<0.05$) and PEX 1 to PEX III was1.7 times greater ($p<0.05$).

It is known that PEX affects almost all layers of the cornea, causing the development of specific slowly progressive keratopathy and also causes concomitant disorders of the tear film and ocular surface in its uneven thickening as well as the capture of melanin by endotheliocytes (Naumann, and Schlötzer-Schrehardt, 2000; Zheng et al., 2011; Potemkin et al., 2017).

In addition, patients with PEX showed a decrease in density as well as an increase in the level of polymegethism and polymorphism of the corneal endothelium (Zheng et al., 2011, 2013; Aoki, 2020). According to the results of a number of studies, patients with pseudoexfoliative glaucoma have an even more pronounced degree of morphological changes in the endothelial layer of the cornea than patients with PEX (Yüksel et al., 2016; Sarowa et al., 2016).

The CD indicator in patients with PEX of the 1st degree in comparison with PEX of the II degree had a 1.2 times higher value ($p<0.05$); at grade II PEX was 2 times greater than grade III PEX ($p<0.05$). The difference between the I and the III stages of PEX showed that the cell density in PEX of the I degree was 2.4 times more than the III stage ($p<0.05$).

In comparison with glaucoma, the CD indicator in eyes with PEX grade I PEX was 1.5 times higher ($p<0.05$); at the 2nd degree PEX was 1.3 times higher ($p<0.05$).

The indicator of cell polymorphism (AVG) in PEX of the I degree had a significantly lower value by 1.2 times in comparison with PEX of the II degree ($p<0.05$); at the II degree PEX was 2.2 times less than the III ($p<0.05$) and with PEX of the 1st degree in comparison with PEX of the III degree, it was 2.7 times less ($p<0.05$).

The standard deviation of the mean cell area (SD) within the framework of the study in PEX of the 1st degree was 1.3 times lower than in the II degree of PEX ($p<0.05$); in the II degree of PEX it was 2.3 times less than the 3-rd ($p<0.05$) and with PEX of the 1st degree it was 3 times less than the III grade PEX ($p<0.05$).

Differences in indicators were assessed in the II degree of PEX with eyes with glaucoma, cataracts in patients with PEX. Among the significant differences in grade II PEX without glaucoma compared to eyes with glaucoma CD was 1.3 times higher ($p<0.05$); AVG was 1.3 times less ($p<0.05$). Among the significant differences, SD is greater than 1.5 times ($p<0.05$); CV is 1.1 times less ($p>0.05$); AVG was 1.7 times greater ($p<0.05$).

In our study, there was a progressive decrease in the density of the corneal endothelium at different degrees of the progression of PEX.

Previous studies confirm the hypothesis that a decrease in corneal endothelium can be associated with both the progression of PEX manifestations and the development of the glaucoma process and these factors can act independently of each other (Beletskaya et al., 2018; Yüksel, 2016; Sarowa et al., 2016).

Polymegethism reflects the presence of cells of different sizes among the studied cell population. With age, there is a physiological slight increase in the coefficient of variation of cells. At the same time the level of polymegethism in the norm should not exceed 30 % (Galgauskas et al., 2013; Duman et al., 2016).

A number of authors note the relationship between changes in the corneal endothelium and the severity of changes in PEX. Results showed a significant decrease in the densities of the corneal endothelial cells in PEX eyes and their fellow eyes. In addition, the clear confocal images

allowed us to detect pleomorphisms and polymegethisms of the endothelial cells. These results have shed light on the pathogenesis of decreased corneal sensitivity in eyes with PEX syndrome (Zheng, 2011, 2013; Inoue et al., 2003; Naumannand Schlötzer-Schrehardt, 2000; Aoki et al., 2020). At the same time, it is important to emphasize the lack of a unified approach in assessing the degree (stage) of PEX development. Thus, classifications reflecting the severity differ both in the number of stages of the development of the syndrome (two to five stages) and in the choice of evaluation criteria, approaches (morphostructural changes, changes with UBM scores, etc.) (Nizankowska, 2001; Naumann and Schlötzer-Schrehardt, 2000; Inazumi et al., 2002; Takhchidi et al., 2010; Aoki et al., 2020).

We have to agree with the opinion that changes in the density of endothelial cells of the cornea before cataract surgery in eyes with PEX can definitely be considered as prognostic indicators (criteria) of increased risk of corneal endothelium decompensation after surgery (Quiroga et al., 2010).

In summary, thus the progress of PEX is accompanied by the corneal changes by the increase of the corneal decompensation risk during cataract surgery.

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