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THE INFLUENCE OF PSEUDOEXFOLIATIVE SYNDROME ON CORNEAL MORPHOLOGY BASED ON *IN VIVO* CONFOCAL MICROSCOPY

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✧ ***Background:*** Confocal microscopy is a modern examination method that enables real-time, noninvasive *in vivo* imaging of the cornea, limb, and conjunctiva. ***Aim:*** To evaluate the main morphological changes observed using confocal microscopy in patients with pseudoexfoliation (PEX) syndrome. ***Methods:*** Overall, 21 patients were examined: 12 with PEX syndrome were enrolled in the examination group and nine patients without PEX in the control group. ***Results:*** In patients with PEX, a decreased cell density in the epithelium and stroma of the cornea as well as a significant increase of hyper-reflective intercellular microdeposits and dendritic cells was observed ($p < 0.05$).

✧ ***Key words:*** confocal microscopy; pseudoexfoliation syndrome.

ВЛИЯНИЕ ПСЕВДОЭКСФОЛИАТИВНОГО СИНДРОМА НА МОРФОЛОГИЧЕСКИЕ СВОЙСТВА РОГОВИЦЫ ПО ДАННЫМ КОНФОКАЛЬНОЙ *IN VIVO* МИКРОСКОПИИ

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✧ Конфокальная микроскопия — современный метод исследования, позволяющий в режиме реального времени оценить неинвазивно *in vivo* структуру роговицы, лимба и конъюнктивы. ***Цель*** — оценить основные морфологические изменения роговицы, наблюдаемые при конфокальной микроскопии у пациентов с псевдоэксфолиативным синдромом (ПЭС). ***Материалы и методы.*** Был обследован 21 пациент. Основную группу составили 12 пациентов с ПЭС, группу контроля — 9 пациентов без ПЭС. ***Результаты.*** У пациентов с ПЭС наблюдалось снижение плотности клеток эпителия и стромы роговицы, большое количество гиперрефлективных межклеточных микровключений и дендритических клеток ($p < 0,05$).

✧ ***Ключевые слова:*** конфокальная микроскопия; псевдоэксфолиативный синдром.

BACKGROUND

Pseudoexfoliation syndrome (PEX) is a systemic age-related disease characterized by the production and accumulation of extracellular matrix similar to amyloid [3, 5–7]. PEX affects various tissues and organs, but ophthalmologic manifestations may be the most important for the diagnosis [3, 4, 6] because routine microscopic examination is sufficient to detect pseudoexfoliation material (PEM). PEM usually accumulates on the anterior capsule of the lens and on the pupillary margin of the iris. PEM clusters can also be found on the endothelium, anterior chamber

angle, surface of the iris, and zonules of Zinn [3, 6]. PEX is considered a risk factor for a wide spectrum of intraocular complications including phacodonesis, lens subluxation, angle-closure glaucoma, poor mydriasis, and keratopathy [3–7].

PEX causes the development of the so-called atypical endothelial dystrophy. PEX-associated endotheliopathy is an always bilateral asymmetric, slowly progressive disease of the corneal endothelium. It may lead to early decompensation of the corneal endothelium, which subsequently causes the development of bullous keratopathy and acute vision loss [8, 9].

According to the data from several studies, PEX is also characterized by a decreased corneal sensitivity, reduced central corneal thickness, and the tear-film instability, resulting in damage to the ocular surface tissues [1, 8, 10, 11]. The nature of morphological changes underlying these manifestations remains unclear. Cellular structures of the cornea, limbus, and conjunctiva can be assessed *in vivo* using confocal microscopy. High resolution of confocal microscopy enables tissues visualization at the cellular level, measurement of the layers thickness, and evaluation of the number, shape, and size of the cells, including those of corneal epithelium, stroma, and endothelium [12–16].

The aim of this study was to evaluate morphological features of the cornea in patients with PEX.

MATERIALS AND METHODS

Overall, 21 patients admitted to the 5th Department of Ophthalmology at the City Hospital No. 2 were the subjects of the study. Patients were divided into two groups: the main group included 12 patients with PEX (PEX group) and the control group included nine patients without PEX (non-PEX group). PEX diagnosis was based on the detection of PEM in the anterior capsule of the lens, pupillary border of the iris, or in the anterior chamber angle. Patients in both groups were matched for gender and age (Table 1).

In addition to the standard ophthalmological examination, all patients underwent confocal microscopic examination of the eyes. We used a confocal laser scanning microscope Rostock Cornea Module (RCM) of the Heidelberg Retina Tomograph 3 (HRT3, Heidelberg Engineering GmbH, Germany). The examination was performed under epibulbar anesthesia using sterile disposable caps. The HRT3-RCM has a helium-neon diode laser with a wavelength of 670 nm. It provides images representing an area of 400 μm × 400 μm (384 × 384 pixels in size).

Morphological features of the cornea were assessed in its central area. The average number of images per patient was 1,000. Three of the best images of each layer (surface epithelium, basal cell layer of the epithelium, the layer of sub-basal nerve fibers, anterior stroma, and posterior stroma) were chosen for the analysis. Images were evaluated by an expert who was blinded to the patients' data including the information on the ophthalmic status. To assess the morphological features of the cornea, we used a specially developed algorithm for ocular surface evaluation via *in vivo* confocal microscopy (Table 2). A scoring system was used for the assess-

Table 1

Age and gender distribution of the patients (*n* = number of patients)

Таблица 1

Распределение групп по полу и возрасту (*n* — количество пациентов)

Parameters		PEX group, $n = 12$	Non-PEX group, $n = 9$	Significance of the difference, p
Age		72.2 ± 3.8	73.3 ± 4.1	0.51
Gender	Male	3 (25%)	3 (33.3%)	0.21
	Female	9 (75%)	6 (66.6%)	

Table 2

Ocular surface assessment algorithm using the *in vivo* confocal microscopy

Таблица 2

Алгоритм оценки качественных показателей состояния роговицы при помощи конфокальной микроскопии *in vivo*

Parameter	Score
Dendritic cells (Langerhans cells)	0-3 points
Desquamation of the surface epithelium	0-3 points
Hyper-reflective intercellular microinclusions	0-3 points
Thickening of the Bowman's membrane	0-3 points
Bead-like formations in the sub-basal nerve fibers	0-3 points

ment of parameters, depending on their severity. For each group, we calculated the mean score reflecting the severity of each change.

The following parameters were quantitatively evaluated: density of epithelial cells, stroma, and nerve fibers of the sub-basal plexus along with their length and tortuosity coefficient. Analysis of cell density was performed for wing cells, cells of the basal layer, and cells of the anterior and posterior stroma. Normal density of the intermediate cells is approximately 5,000 cells/mm^2 and that of the basal cells is between 3,600 and 8,996 cells/mm^2 [12, 13, 17]. The highest density of keratocytes is observed in the anterior stroma [18, 19–21].

The condition of the sub-basal plexus was evaluated using the semi-automatic *CCMetrics Image Analysis Software v.1.1*. We estimated the density of the nerve fibers, density of their branches, and the tortuosity coefficient. Calculations were performed according to the method described by Kinard et al. The density of the fibers and their branches was evaluated both in the field of view and over an area of 1 mm2. The density of nerve fibers was calculated as follows: length of the nerve fibers × coefficient (0.00075)/scanning area. The tortuosity coefficient was calculated automatically [22].

Patients with corneal dystrophy and diabetes mellitus and those who used contact lenses were excluded. We also excluded patients on treatment with hypotensive drops or artificial tears.

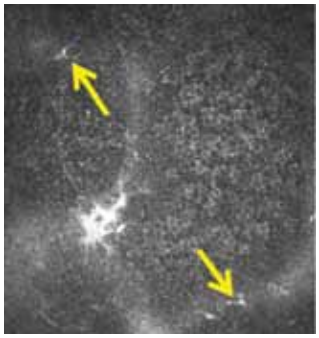
Statistical analysis was performed using SPSS Statistics v 20.0. Normality of the data was checked using the Kolgomorov–Smirnov test. Quantitative variables were compared using the Student's *t*-test. Differences were considered significant for $p < 0.05$.

RESULTS

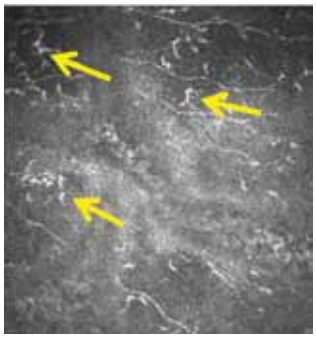
The mean number of dendritic cells was higher in patients in the PEX group than that in the control group. One-third of the participants in the non-PEX group had no dendritic cells in the optical center (Table 3, Figure 1). Patients in both groups were found to have desquamation of the surface epithelium of varying severity. Individuals in the PEX group mostly had moderate desquamation, whereas the control group had slight desquamation (Table 3, Figure 2).

Hyper-reflective intercellular microinclusions were detected in both groups; however, this was significantly higher in patients with PEX (Table 3, Figure 3). Thickening of the Bowman's membrane was observed in all patients in the PEX group; 58.4% had medium degree of thickening and 33.3% had heavy degree of thickening. In the control group, these values were 33.3% and 12.8%, respectively (Table 3, Figure 4). Patients with PEX demonstrated severe tortuosity of the sub-basal nerve fibers (Table 3, Figure 5). Bead-like formations in the sub-basal nerve fibers were observed in all patients of the PEX group and only in two patients of the control group (Table 3, Figure 6). Therefore, patients with PEX had more significant morphological changes in the anterior corneal surface than control patients ($p = 0.0004$).

The rest of the parameters describing the condition of the sub-basal nerve fibers (except for the number of their branches) did not differ significantly between the two groups. The number of branches of sub-basal nerve fibers was significantly higher in patients with PEX (Table 4). The density of cells in all tested layers was significantly lower in the PEX group than in the control group. The biggest difference was observed in the basal cells and the smallest difference in the keratocytes of the posterior stroma ($p < 0.012$



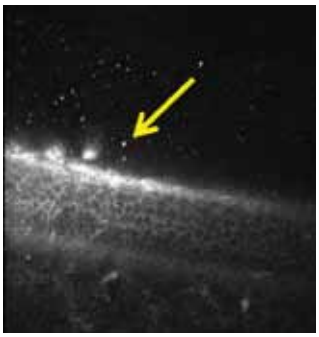
a



b

Fig. 1. Dendritic cells: *a* – in control group, *b* – in PEX group

Рис. 1. Дендритические клетки (Лангерганса): *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативым синдромом



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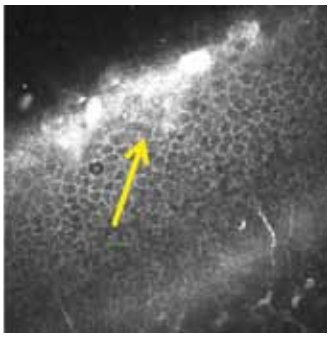


b

Fig. 2. Desquamation of superficial epithelium: *a* – in control group, *b* – in PEX group

Рис. 2. Очаги десквамации поверхностного эпителия: *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативным синдромом

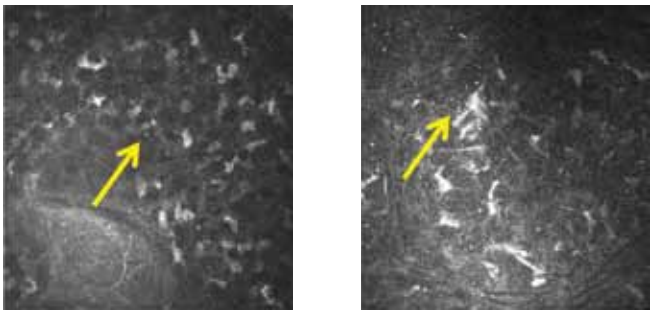
Table 3

Corneal morphological changes in the groups (*n* = number of patients)

Таблица 3

Результаты качественной оценки морфологических свойств роговицы в исследуемых группах (*n* — количество пациентов)

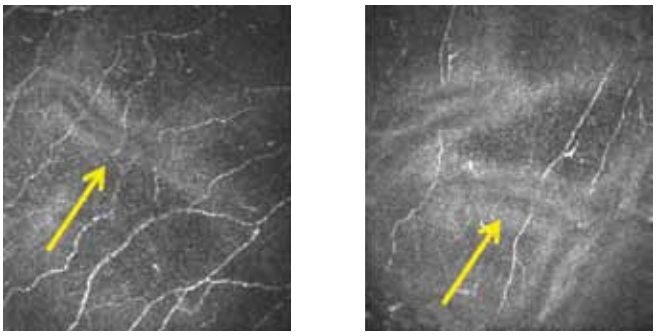
Parameter	Mean score. PEX group, (*n* = 12)	Mean score. Non-PEX group, (*n* = 9)	Significance of the difference, *p*
Dendritic cells (Langerhans cells)	1.75	1.3	0.0004
Desquamation of the surface epithelium	1.75	1	
Hyper-reflective intercellular microinclusions	1.75	0.2	
Thickening of the Bowman's membrane	2.4	1.3	
Bead-like formations in the sub-basal nerve fibers	2.1	1.1	



a *b*

Fig. 3. Hyperreflective intercellular micro-inclusions: *a* — in control group, *b* — in PEX group

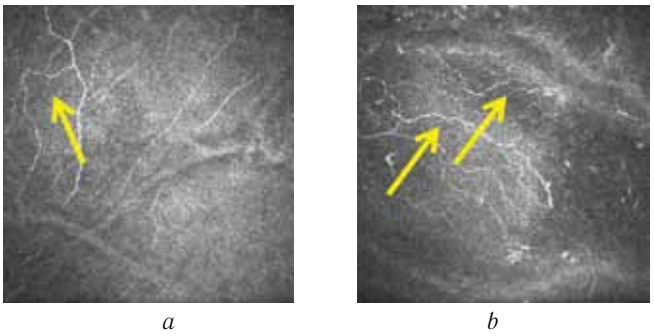
Рис. 3. Гиперрефлективные межклеточные микровключения: *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативным синдромом



a *b*

Fig. 4. Bowman membrane stiffening: *a* — in control group, *b* — in PEX group

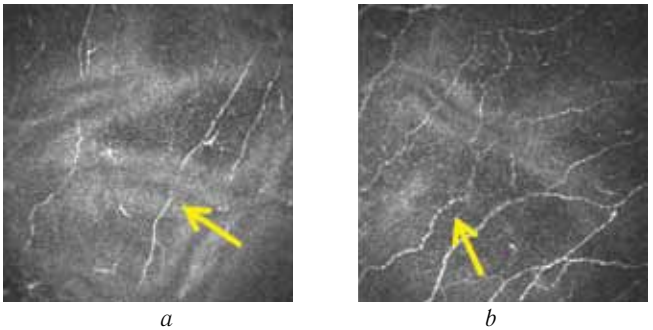
Рис. 4. Уплотнение боуменовой мембраны: *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативным синдромом



a *b*

Fig. 5. Tortuosity of subbasal nerve plexus: *a* — in control group, *b* — in PEX group

Рис. 5. Извитость суббазальных нервных волокон: *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативным синдромом



a *b*

Fig. 6. Structure of subbasal nerve plexus like granules: *a* — in control group, *b* — in PEX group

Рис. 6. Гранулоподобные структуры суббазальных нервных волокон: *a* — у пациентов без псевдоэксфолиативного синдрома, *b* — у пациентов с псевдоэксфолиативным синдромом

Table 4

The condition of the sub-basal nerve plexus in the groups (*n* = number of patients)

Таблица 4

Показатели состояния суббазальных нервных сплетений в исследуемых группах (*n* — количество пациентов)

Parameter	PEX group, *n* = 12	Non-PEX group, *n* = 9	Significance of the difference, *p*
Number of nerve fibers in the field	3.25 ± 1.08	3.89 ± 1.22	0.35
Number of nerve fibers per 1 mm^2	20.3 ± 6.77	24.3 ± 7.64	0.35
Number of nerve branches in the field	7.67 ± 1.2	2.56 ± 0.8	0.045
Number of nerve branches per 1 mm^2	47.9 ± 13.5	16.0 ± 4.94	0.045
Total length of all nerve fibers in the field	1390 ± 294	1310 ± 280	0.81
Density of nerve fibers, mm/mm^2	6.49 ± 1.3	6.13 ± 1.1	0.81
Tortuosity coefficient	0.067 ± 0.002	0.052 ± 0.002	0.48

and $p < 0.036$, respectively). Our data suggested that PEX mainly affects the density of corneal epithelium (Table 5).

DISCUSSION

In vivo confocal microscopy allows rapid, non-invasive, and microstructural imaging of the cornea and generates high resolution images. There are very few studies that have assessed the cornea of patients with PEX using confocal microscopy. None of them have evaluated parameters such as the number of dendritic cells, hyper-reflective intercellular microinclusions, severity of desquamation of surface epithelium, and thickening of the Bowman's membrane. Martone et al. reported a case of PEX in which dendritic cells and hyper-reflective intercellular microinclusions were detected [23]. Several authors have demonstrated the possibility of PEM visualization using confocal microscopy [12, 24, 25].

Our study was aimed at comprehensive assessment of corneal morphological features using *in vivo* confocal microscopy. Patients with PEX had more significant desquamation of the surface epithelium, which supported our hypothesis that PEX can result in damage to the ocular surface tissues.

A substantial number of dendritic cells observed near the sub-basal nerve plexus in patients with PEX points toward the presence of local inflammation. We assumed that clusters of hyper-reflective intercellular microinclusions detected in the deep epithelial cell layers and anterior stroma are the PEM clusters that trigger local inflammatory changes. Excess amounts of PEM along with dendritic cell infiltration may contribute to neuropathy development that affects the sub-basal nerve plexus. Several studies have reported reduced density and increased tortuosity of the sub-basal nerve fibers in patients with PEX [8, 24, 25]. Our study failed to demonstrate a significant decrease in their density in patients with PEX. However, PEX was found to be associated with a significantly larger number of the nerves branches and bead-like formations in the sub-basal plexus, which may indicate either damage or an increased metabolic activity. Thickening of the Bowman's membrane was observed in both groups; however, in patients with PEX, it was more pronounced. We believe that thickening of the Bowman's membrane should be considered as a sign of involutional changes, and PEX further aggravates them.

Individuals with PEX were shown to have a significantly decreased density of the wing epithelial cells, basal cells, and cells of the anterior and posterior stroma. The pathogenetic mechanisms underlying these changes are still unclear. In our opinion, it may be induced by oxidative stress and PEM accumulation. Oxidative stress is one of the most important mechanisms of cell damage.

Table 5

Evaluation of the cell densities in the groups (*n* = number of patients)

Таблица 5

Оценка плотности клеток эпителия и стромы роговицы в исследуемых группах (*n* — количество пациентов

Cell density	PEX group, *n* = 12	Non-PEX group, *n* = 9	Significance of the difference, *p*
Wing cells	5465 ± 600	6355 ± 614	0.019
Basal cells	8315 ± 705	9430 ± 754	0.012
Cells of the anterior stroma	614 ± 51	736 ± 121	0.026
Cells of the posterior stroma	397 ± 73	478 ± 59	0.036

The number of keratocytes may decrease with age in response to increased oxidative damage and reduced antioxidant protection. All ROS oxidize cellular components; high concentrations of ROS may cause irreversible cell damage. The defense against ROS is achieved through the antioxidant system [26]. Demirdögen et al. showed that patients with PEX or pseudoexfoliation glaucoma have a lower antioxidant defense than control patients. Besides, they have shown that the lack of antioxidants may contribute to the development of these pathological conditions [27]. The second possible reason for decreased cell density is PEM accumulation. Some authors suggest that hyper-reflective inclusions are PEM clusters that cause local inflammation and activate apoptosis of keratocytes [26, 27].

We conclude that PEX induces significant morphological changes in the cornea; confocal microscopy is a unique method that enables detailed evaluation of these changes.

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