# INVESTIGATION OF MORPHOLOGICAL CHANGES AND REGIONAL HAEMODYNAMICS IN PSEUDOEXFOLIATIVE GLAUCOMA

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ABSTRACT

**Objective**: A comparative study of the choroidal, retinal ganglion complex (GCC) thickness and regional hemodynamics in patients with POAG (Primary open angle glaucoma) and PEG (Pseudoexfoliative glaucoma).

**Materials and Methods**: We observed 40 patients with POAG and 36 with PEG at the same stage of glaucoma: MD was –1.52±0.27 with POAG and –2.38 ± 0.35 with PEG (p=0.069). Patients in both groups were well matched for age (ranged from 60 to 70 years: the PEG was 69.41±1.207 and POAG was 66.32 ± 0.75 (p=0,32)), and the axial length (the average axial length with PEG was 24.08±0.38 mm and with POAG was 23.48±0.27mm (p=0.208).

**Results:** a significant difference between patients with POAG and PEG was revealed according to the data of focal loss of retinal ganglion cells (FLV). PEG at this figure was 3.535±0.684, and POAG 1.875±0.399 (p=0.035). We also observed a decrease in the choroidal thickness in PEG compared to POAG: in the foveolar area it was 219.55±17.81 at PEG and 266.93±15.9 with POAG (p=0.048); and for peripapillary area it was 117.1±10.1 in PEG and 158.3±14.8 in POAG (p=0.026). We discovered a reduction in blood flow velocity in the ophthalmic artery (29.08±2.38 sm/sec), central retinal vein (6.03±0.21 sm/sec) and the superior ophthalmic vein (5.22±0.29 sm/sec) at PEG in alignment with POAG, for which the differences were for ophthalmic artery — 34.10±1.47 sm/sec (p=0.05); central retinal vein — 7.54±0.53 sm/sec (p=0.012) and superior ophthalmic vein — 6.47±0.33 sm/ sec (p = 0.007), respectively.

**Conclusion**: the study showed that at the same stage of glaucoma with PEG there is a more pronounced thinning of the choroid, the destruction of the retinal ganglion complex and reduced blood flow in large retrobulbar vessels compared to POAG .

**Keywords:** Pseudoexfoliative glaucoma, Primary open angle glaucoma, retinal ganglion complex, choroidal thickness, ophthalmic vessels blood flow velocity.

Glaucoma today remains the leading cause of visual disability in Russia [1,2] and pseudoexfoliative form of glaucoma (PEG) is most common [3].

PEG is characterized by excess production and accumulation of elastofibrills and their components in the structures of the eye, including the basal membrane of blood vessels. Alteration of ocular blood flow is an important risk factor for the development and progression of PEG [4,5]. Peripapillary choroid plays a special role in the blood supply to the optic disk. Nowadays with the advent of spectral tomographers, it has become possible to undertake a non-invasive study of the choroid [6,7,8,9]. It is also important that spectral OCT allows to measure rather precisely thickness of internal layers of retina, affected in glaucoma, in particular — complex of retinal ganglion cells [10,11,12,13,14,15,16]. However, there is no data about the choroidal thickness in PEG. There is also a lack of information on specific features of damage to the retina and optic disc in PEG.

**The aim** of this study was to compare a thickness of choroid, retinal ganglion cells complex and regional hemodynamics in patients with POAG and PEG.

MATERIALS AND METHODS

The study was approved by the ethical committee (Institutional Review Board) at the Institution of Federal Medical and Biological Agency of Russian Federation and was conducted in accordance with Good Clinical Practice within the tenets of the Helsinki agreement. Each patient/subject was required to sign an informed consent statement before being enrolled in the study and prior to any study measurements being taken.

We observed 40 patients with POAG and 36 with PEG. For the study, patients were selected from the same stage of glaucoma that rated according to the data of the automatic static perimetry. Patients in both groups were well matched for age and size of the anterior-posterior axis of the eye. In PEG 12 cases were first detected (33 %), in 5 cases (14 %) patients were treated with fixed combination brinzolamide + timolol, in 11 (30.5 %) — latanoprost, 8 (22 %) — carbonic anhydrase inhibitors . In POAG these figures were — 27(67.5 %), 7 ( 17.5 % ), 4 (10 %) and 4 (10%), respectively. The control group consisted of 30 somatically healthy persons of the same age (12 men and 18 women) who do not have ophthalmic pathology.

Clinical characteristics of patients are presented in Table 1.

Table 1. Clinical characteristics of the examined patients with glaucoma

| Characteristic | POAG | PEG | Healthy |
|---|---|---|---|
| Sex (No, SD [%]) | female 26 (65%)<br>male 14 (35%) | female 21<br>(58,3%)<br>male 15 (41,7%) | female 18 (60%)<br>male 12 (40%) |
| Age, y (mean [SD]) | 66,32±0,75 | 70,11±1,35 | 64,27 (60-75)<br>530,03±4,4 |
| | 540,28±5,3 | | |
| Central corneal thickness (micrometers) | P=0,141 | | |
| | 18,03±0,68 | | 18,94±0,78 |
| IOP,mm Hg (mean [SD]) | P=0,38 | | |
| | 92,22±2,67** | | 95,88±1,93** |
| RNFL (micrometers) | P=0,27 | | |
| | | | |
| GCC avg. (micrometers) | 85,21±1,00* | 83,75±1,72* | 92,3±2,42<br>(87,34 — 95,32) |
| | P=0,466 | | |
| FLV (%) | 1,875±0,399** | 3,535±0,684** | |
| | P=0,035 | | 0,49±0,14 |
| GLV (%) | 11,792±0,94** | 13,741±1,629** | |
| | P=0,305 | | 4,56±2,21 |
| MD, dB (mean [SD]) | -1,52±0,27* | -2,38±0,35* | |
| | P=0,059 | | -1,36±0,22 |
| PSD, dB (mean [SD]) | 1,91±0,18* | 2,38±0,26* | |
| | P=0,147 | | 1,53±0,13 |

** Significance of differences among subgroups compared to control p <0,05, ** p<0,001*

*RNFL — retinal nerve fiber layer; GCC avg — average thickness of retinal ganglion cell complex; FLV, GLV — indicators characterizing the volume of focal and global loss of GCC; PSD — pattern standard deviation; MD — mean deviation*

The exclusion criteria were eye surgery and laser treatment. Systemic beta-blocker and calcium channel blocker therapy, chronic autoimmune diseases, diabetes mellitus and any comorbid conditions treated with steroids were also regarded as exclusion criteria. Patients with a history of ocular trauma or any known eye disease other than glaucoma were excluded. A history of ocular venous obstruction (branch or central occlusion) or systemic conditions associated with venous congestion (e.g. heart failure) was also considered to be excluded. Information regarding functional and structural damage from glaucoma patients was collected from examinations undertaken on the day of the study visit.

Careful investigation of all the patients' anamnesis was carried out, special attention was paid to the signs of the primary or secondary vascular dysregulation (migraine, vasospasm, cardiopsychoneurosis) [17], which were identified on the basis of a special questionnaire [18]. All patients were counseled by a neurologist and therapist. Diagnostic testing for glaucoma included tonometry (ORA, Reichert, USA), pachymetry (Tomey), optical coherence tomography for anterior segment of the eye (Visante, Carl Zeiss Meditec, Dublin, CA), a detection of retinal nerve fiber layer thickness and ganglion cells complex (RTVue-100 (Optovue, Inc., Fremont, CA), and standard automated perimetry (Humphrey, Carl Zeiss Meditec) for threshold program 24-2.

Ocular and retrobulbar blood flow was registered by means of color Doppler Imaging (CDI) and *impulse Doppler sonography* (multifunction diagnostic scanner «My lab 70» Esaote) using a linear sensor frequency of 10 to 16 MHz by corresponding procedure [19]. Blood flow was studied in the ophthalmic artery (OA), central retinal artery (CRA), central retinal vein (CRV), *lateral* and medial *short posterior ciliary arteries* (SPCA), vortex veins (VV), and superior ophthalmic vein (SOV). We registered the Doppler frequency shift (DFS) and obtained quantitative blood flow parameters: peak systolic blood flow velocity (*Vsyst*), diastolic *blood flow velocity* (*Vdiast*), mean blood flow velocity *(Vmean)*, and the *resistivity index*(*RI)*.

Patients were instructed to avoid caffeine intake, smoking and exercise for 5 hr prior to the study visit. The study of choroidal thickness was conducted on OCT (RTVue 100) in tracking mode. Choroidal thickness was defined as the distance between the signal line from pigment epithelium (PE) to a continuous line on the border of sclera/choroid. Choroidal measurement technique was developed by us and described previously [20].

**Statistical analysis**

Analysis was performed with «SPSS11.0 for Windows» software. The statistical analysis included the calculation of means, standard deviation, standard error as well as Pearson's correlation coefficient. The threshold P value for statistical significance was 0.05.

RESULTS

Results showed a significant difference between patients with POAG vs PEG according to the data of focal loss of retinal ganglion cells complex.

The study revealed a significant thinning of choroid in foveolar and peripapillary areas in patients with PEG compared to POAG. These results are shown in Table 2.

Table 2. Choroidal thickness in patients with POAG and PEG

| | PEG | POAG | Healthy |
|---|---|---|---|
| Foveal choroidal thickness (μm) | 219,55±17,81** | 266,93±15,9* | 312,9±25,3 |
| | P=0,04 | | |
| Choroidal thickness Peripapillary (μm) | 117,1±10,1** | 158,3±14,8 | 144,9±17,3 |
| | P=0,026 | | |
| Axial length, mm(mean [SD]) | 23,84±3,1 | 24,25±3,5 | 24,67±2,1 |
| | P=0,208 | | |

** Significance of differences among subgroups compared to control p <0,05, ** p<0,001*

We discovered a reduction of blood flow velocity in the ophthalmic artery, central retinal vein and the supraorbital vein at PEG in alignment with POAG. The results are shown in Table 3.

Table 3. CDI variables of the retrobulbar vessels in the studied groups

| Variables | PEG (cm/s) | POAG (cm/s) | Healthy | Pairwise PEG versus POAG p-value |
|---|---|---|---|---|
| OA V syst | 29,08±2,38* | 34,10±1,4 | 39.29±6.18 | **P=0,05** |
| OA V diast | 8,7±0,77* | 9,36±0,59 | 9.27±3.72 | P=0,5 |
| OAV mean | 16,28±1,34* | 17,87±0,89 | 17.21±4.48 | P=0,331 |
| OA RI | 0,95±0,29** | 0,91±0,19* | 0.77±0.06 | P=0,906 |

| | | | | |
|---|---|---|---|---|
| OA PI | 1,19±0,08 | 1,43±0,07 | 1.77±0.37 | **P=0,045** |
| CRA V syst | 13,92±1,98* | 12,48±0,83** | 14.13±1.8 | P=0,506 |
| CRA V diast | 5,03±0,78 | 3,95±0,36 | 3.68±0.86 | P=0,22 |
| CRA V mean | 8,75±1,33 | 6,86±0,49 | 7.04±1.25 | P=0,194 |
| CRA RI | 0,82±0,1** | 0,7±0,01 | 0.74±0.04 | P=0,225 |
| CRA P1 | 1,64±0,24 | 1,28±0,03 | 1,04±0,05 | P=0,135 |
| sPCA lat. V syst | 12,24±0,53* | 12,37±0,42* | 14.38±1.82 | P=0,851 |
| sPCA lat. V diast | 4,17±0,36* | 4,53±0,26* | 5.17±1.15 | P=0,427 |
| sPCA lat. V mean | 6,92±0,42** | 7,37±0,27* | 8.45±1.32 | P=0,37 |
| sPCA lat. R1 | 0,68±0,03 | 0,82±0,16 | 0.63±0.07 | P=0,426 |
| sPCA lat. P1 | 1,3±0,1 | 1,11±0,04 | 1.09±0.2 | P=0,101 |
| sPCA med V syst | 11,22±0,43** | 11,36±0,4 | 13.83±2.23 | P=0,816 |
| sPCA med V diast | 3,81±0,27* | 4,14±0,19 | 4.69±0.95 | P=0,32 |

| | | | | |
|---|---|---|---|---|
| sPCA med V mean | 6,36±0,33* | 6,94±0,22* | 8.17±1.58 | P=0,145 |
| sPCA med R1 | 0,67±0,03 | 0,78±0,14* | 0.65±0.06 | P=0,459 |
| sPCA med P1 | 1,25±0,09 | 1,29±0,2 | 1,01±0,08 | P=0,87 |
| CRV V syst | 6,03±0,21 | 7,54±0,53 | 6.92±1.14 | **P=0,012** |
| CRV V diast | 3,89±0,26* | 3,81±0,17** | 5.22±0.96 | P=0,792 |
| CRV V mean | 4,8±0,3 | 4,37±0,13 | 5.58±0.92 | P=0,198 |
| CRV R1 | 0,53±0,05** | 0,35±0,02* | 0.28±0.11 | **P=0,003** |
| CRV P1 | 0,98±0,18** | 0,49±0,04 | 0.39±0.18 | **P=0,014** |
| VV V syst | 5,58±0,16* | 5,57±0,17* | 7.1±1.09 | P=0,957 |
| VV V diast | 3,01±0,32* | 3,14±0,22* | 4.33±1.43 | P=0,75 |
| VV V mean | 4,02±0,2* | 3,8±0,17* | 5.24±1.29 | P=0,418 |
| VV R1 | 0,49±0,05 | 0,54±0,05* | 0.39±0.16 | P=0,441 |
| VV P1 | 0,75±0,1** | 0,87±0,1* | 1.07±1.44 | P=0,398 |
| SOV Vsyst | 8,28±0,3* | 9,23±0,35 | 10.41±1.82 | P=0,047 |
| SOV Vdiast | 4,76±0,42* | 5,08±0,42* | 6.44±2.77 | P=0,601 |

| | | | | |
|---|---|---|---|---|
| SOV Vmean | 5,22±0,29** | 6,47±0,33* | 7.99±2.28 | **P=0,007** |
| SOV RI | 0,45±0,04 | 0,46±0,04 | 0.41±0.23 | P=0,887 |
| SOV PI | 0,82±0,13 | 0,71±0,08 | 0.72±0.49 | P=0,479 |

***Discussion:*** *OA — ophthalmic artery, CRA — central retinal artery, CRV — central retinal vein, SPCA — lateral and medial short posterior ciliary arteries, SOV — superior ophthalmic vein, VV — vortex veins; Vsyst — peak systolic blood flow velocity, Vdiast — diastolic blood flow velocity, Vmean — mean blood flow velocity, RI, PI — resistive index and pulsativity index. Significance of differences among subgroups compared to control p <0,05, ** p<0,001. A statistically significant p-value (a difference between subgroups) is given in bold.*

PEX syndrome is a genetically caused stress — induced elastozis, which is a consequence of excessive production and accumulation of elastin fibrils and their components. The recently discovered gene modification LOXL1 (lysyl oxidase-like 1), is currently being considered as a major factor in the development of PEX syndrome and pseudoexfoliative glaucoma. LOX1 (lysyl oxidase) is an enzyme responsible for the formation of extracellular material, including elastin and collagen of connective tissues. Pseudoexfoliation material damages tissues, which contain elastic fibers. There has been speculated that a damage to the lamina cribrosa plays a key role in the origin and progression of PEG. A considerable damage of elastin fibrils in the lamina cribrosa, as well as in the wall of vortex veins, the ophthalmic artery (Schlotzer-Schrehardt, 2009) and the aorta (Schlotzer-Schrehardt, 2001) has been found in PEX syndrome. The vascular disorders are quite often observed in this form of glaucoma. For example, it was noticed that after instillation of mydriatics in patients with PEG systolic and diastolic blood flow velocity reduced in the central retinal artery and posterior ciliary arteries. A decrease in blood flow velocity in the lamina cribrosa, as well as in the carotid artery was described in PEG (Schlotzer-Schrehardt, 2009). It is believed that PEX syndrome is a risk factor for the development of optic disc hemorrhages and retinal vein thrombosis and it happens in 6-7 % of cases (Schlotzer-Schrehardt, 2001, 2009) [21,22] .

The results of this study revealed a significant decrease in blood flow velocity in the ophthalmic artery, the central retinal vein and the supraorbital vein. These are the largest vessels involved in the blood supply of the eye. Apparently, a change in their basal membranes with pseudoexfoliative material leads to narrowing of their lumen, that has been demonstrated in studies Schlotzer-Schrehardt U [21]. Nevertheless we have

not found any significant difference in blood flow velocity in the short posterior ciliary arteries (main vessels supplying the optic nerve) between the groups of patients with glaucoma. It should be emphasized, however, that the choroidal blood flow is also very important as blood supply to the optic disk and retina. The present study showed a significant decrease of choroidal thickness in foveal and peripapillary areas in patients with PEG compared to POAG.

Choroidal artery branches are involved in the blood supply of the preliminary part of optic nerve. This region presents the bloodstream, mainly with large capillaries, it is significantly worse susceptible to autoregulation than the retinal blood flow, but better than choroidal [23]. Preliminary part of optic nerve in fact, is the only segment of the central nervous system, which does not have adequate blood-brain barrier. This is explained by the predominance of fenestrated capillaries here [24] and is directly related to the pathogenesis of glaucomatous optical neuropathy.

Reduction of choroidal vascularization and, as a consequence, reduction of blood supply to the peripapillary part of optic nerve in glaucoma were detected by A. Elshnig early last century, and were named as a key cause of glaucomatous optical neuropathy [25]. Reduced vascularization of the choroid in glaucoma later confirmed by J.Francois [26] and Z.Yin [27]. H.Kaiser and colleagues [28] found in the doppler sonography an increase of resistance index in these vessels , and D.Marangoni discovered the speed reduction of subfoveal choroidal blood flow even at the initial stage of glaucoma [29].

Application of OCT opened up new possibilities in the study of the choroid, but the results of these studies in glaucoma are controversial: some studies revealed thinning of the choroid in patients with glaucoma [15,30], some of them , on the contrary, revealed a thickening of choroid [31], while most researchers have found no change of the choroid in glaucoma [ 7,8,9,32 ] .

Our previous studies showed a significant reduction of choroidal thickness in advanced stage of glaucoma, compared to preperimetric stage. It concerned both foveolar and peripapillary zones. Wherein a significant difference compared to the control was observed only in advanced glaucoma. These differences concerned mainly choroid in the foveolar area, while the thickness of the choroid in the peripapillary area did not statistically differ from normal controls in either preperimetric or in an advanced glaucoma [Kurysheva N.I., 2013] .

It is noteworthy that in the present study we observed choroidal thinning in patients with PEG not only in foveolar area, but in the peripapillary too. These findings are novel and

allow to suggest that in PEG choroid plays an important role in the development of the disease, especially the peripapillary parts of choroid.

The literature has repeatedly emphasized the role of peripapillary choroidal blood supply to the optic disk in glaucoma. Comparing the patients with normal tension glaucoma to healthy individuals, Hirooka K. found no significant reduction in choroidal thickness in foveolar and temporal areas, however, described a significant thinning of the choroid in the peripapillary area [6]. The same results were obtained by the other authors [20,33].

We can assume that the thinning of the choroid with PEG is related to insufficient blood supply to the optic nerve disc and peripapillary retina. This may explain some special characteristics of the optic disc in pseudoexfoliation syndrome which have been described in literature: a widespread area of the optic disc blanching compared to the norm and to POAG. More pronounced size of disc excavation especially in the lower- and upper-temporal sectors has been noticed in PEG (Schlotzer-Schrehardt U.) [21]. Our previous studies have shown that at the same stages of glaucoma, the volume of excavation of the optic disk and area of excavation with PEG were 1.5 times larger than in POAG [34]. This may lead to more pronounced mechanical effects of increased intraocular pressure on the lamina cribrosa in patients with PEG, which in combination with weakness of the connective tissue in this disease leads to the formation of deep excavation of the optic disk [Kurysheva N.I, 2006].

The present study showed that PEG patients differ from patients with POAG by more pronounced volume of focal loss of retinal ganglion cells (FLV). Value of the specified parameter in the early diagnosis of glaucoma, and in determining of the rate of its progression has been emphasized by various authors and agrees with the results of our studies that emphasize the higher specificity of this index in glaucoma [10,11,12]. The present study revealed another feature of FLV: the specified parameter, according to our data, characterizes morphometric differences of PEG from POAG.
It is noteworthy that in this case, we didn’t find any significant differences between the two compared groups in any other parameters characterizing the optic nerve head and RNFL. Taking into account the more severe course of PEG, we can assume that the retinal ganglion complex is the most susceptible to higher pressure and to its fluctuations, typical to this form of glaucoma. Choroidal thickness reduction in PEG may indicate deterioration of the retina and optic nerve head perfusion, which also leads to loss of the retinal ganglion complex.

Thus, this study showed that at the same stage of glaucoma, PEG is characterized by a more pronounced thinning of the choroid, loss of the retinal ganglion complex and reduction of blood flow in large retrobulbar vessels compared to POAG. The obtained

data provides additional information in understanding the pathogenesis of PEG and in future methods for its treatment.

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