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Research Article

The influence of post-COVID-19 syndrome on microcirculation of the optic nerve head among patients with primary open-angle glaucoma

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ABSTRACT

BACKGROUND: Glaucoma is one of the leading causes of blindness in the world. This is a multifactorial ophthalmopathology, which also results from impaired microcirculation in the optic nerve. One of the diseases affecting ocular blood flow is acute coronavirus infection (COVID-19).

AIM: The aim of this study is the assessment of blood flow parameters of the optic nerve head in patients with primary open-angle glaucoma (POAG) against the background of post-COVID-19 syndrome using laser speckle flowgraphy.

MATERIALS AND METHODS: The study included 40 patients with advanced stage primary open-angle glaucoma who had COVID-19 within the previous 3 months. Patients were divided into 2 subgroups depending on the severity of the disease. The comparison group consisted of 20 individuals with an advanced stage of primary open-angle glaucoma who did not have COVID-19. All subjects were over 60 years old and had normal blood pressure parameters. Optic nerve head blood flow was measured using the LSFG-NAVI device (Japan) and assessed by LSFG Analyzer software. MBR parameters (MA, MV and MT), as well as pulse wave indicators (Skew, BOS, BOT, RR, FR, FAI, ATI and RI) were analyzed.

RESULTS: The most significant decrease was found for the MV and MT parameters, reflecting the blood flow in large vessels and the microvasculature of the optic disc. MV decrease by 20%, MT — by 23%, MA — by 16% were noted, as well as pulse wave parameter changes, in patients with an advanced stage of primary open-angle glaucoma, post-COVID syndrome after moderate COVID-19 compared with patients with an advanced stage of primary open-angle glaucoma who did not have COVID-19 ($p \leqslant 0.05$).

CONCLUSIONS: Laser speckle flowgraphy allows rapid and effective assessment of ocular blood flow. Parameters estimated at the examination may be considered as new biomarkers for the detection and evaluation of vascular diseases.

Keywords: post-COVID-19 syndrome; primary open-angle glaucoma; ocular blood flow; laser speckle flowgraphy; LSFG; MBR; pulse wave indicators.

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Научная статья

Влияние постковидного синдрома на микроциркуляцию диска зрительного нерва у пациентов с первичной открытоугольной глаукомой

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АННОТАЦИЯ

Актуальность. Глаукома — одна из ведущих причин слепоты в мире. Это многофакторная офтальмопатология, к которой приводит в том числе и нарушение микроциркуляции в зрительном нерве. Одним из заболеваний, влияющих на глазной кровоток, является острая коронавирусная инфекция (COVID-19).

Цель — оценка параметров кровотока диска зрительного нерва у пациентов с первичной открытоугольной глаукомой на фоне постковидного синдрома с помощью лазерной спекл-флоуграфии.

Материалы и методы. В исследование были включены 40 пациентов с развитой стадией первичной открытоугольной глаукомой, перенёсших COVID-19 в течение предшествующих 3 мес. Пациенты были разделены на 2 подгруппы в зависимости от тяжести заболевания. Группу сравнения составили 20 лиц с развитой стадией первичной открытоугольной глаукомы, не болевших COVID-19. Все обследуемые были старше 60 лет и имели нормальные параметры артериального давления. Кровоток диска зрительного нерва измеряли с помощью устройства LSFG-NAVI (Япония) и оценивали программным обеспечением LSFG Analyser, анализировали интегральный показатель кровотока — среднюю скорость размытия (MBR, в том числе MA, MV и MT), а также показатели пульсовой волны (Skew, BOS, BOT, RR, FR, FAI, ATI и RI).

Результаты. Наиболее значимое снижение выявлено для показателей MV и MT, отражающих кровоток в крупных сосудах и микроциркуляторном русле диска зрительного нерва. У лиц с развитой стадией первичной открытоугольной глаукомы, постковидным синдромом после перенесённого COVID-19 средней степени тяжести отмечалось снижение MV на 20 %, MT — на 23 %, MA — на 16 %, а также изменения параметров пульсовой волны по сравнению с лицами с развитой стадией первичной открытоугольной глаукомы, не болевших COVID-19 ($p \leqslant 0{,}05$).

Заключение. Лазерная спекл-флоуграфия позволяет быстро и эффективно оценить глазной кровоток. Параметры, определяемые при исследовании, могут расцениваться как новые биомаркеры для выявления и оценки сосудистых заболеваний.

Ключевые слова: постковидный синдром; первичная открытоугольная глаукома; глазной кровоток; лазерная спекл-флоуграфия; ЛСФГ; MBR; показатели пульсовой волны.

Как цитировать

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BACKGROUND

Glaucoma is one of the leading causes of blindness worldwide. According to the data of epidemiological studies, to 2040, the number of people suffering from this disease will reach 111.8 mln [1, 2]. Glaucoma is a neurodegenerative disease characterized by the loss of retinal ganglion cells and leading to progressive and irreversible blindness. The most common glaucoma form is the primary open angle glaucoma (POAG) [3, 4].

The POAG pathogenesis is still understudied. Glaucoma is a multifactorial ophthalmic condition, which could develop due to such causes as aging, myopia, diabetes mellitus, oxidative stress, heredity [5]. There are two main theories of glaucoma etiopathogenesis – mechanic one and vascular one [6]. The mechanic theory asserts that increased intraocular pressure (IOP) compresses the intraocular structures, including the optic nerve by deformation and displacement of lamina cribrosa layers precluding the axoplasmic flow in nerve fibers [7]. The vascular theory suggests that glaucomatous optic neuropathy may be secondary relative to insufficient ocular perfusion [8]. The decrease in ocular hemodynamics causes the impairment of vascular regulation leading to local hypoxia, oxidative stress, induces apoptosis of retinal ganglion cells, and leads to tissue remodeling as well [9]. There is increasing evidence that impairments of microcirculation in the optic nerve influence the development and the progression of glaucoma [10, 11].

Impairments of ocular hemodynamics play an important role in the pathogenesis of many ophthalmic diseases, that is why a lot of attention is paid to the investigation of ocular blood flow. Laser speckle flowgraphy (LSFG) is a method, which allows a noninvasive and highly reproducible registration of blood flow in large and small fundus vessels – in normal eyes as well as in various ophthalmic diseases, including glaucoma [12, 13]. LSFG analyzes the blood flow based on averaging of a series of pulsating blood flow waves during several cardiac cycles, obtained during 4 sec at the speed of fundus “speckle”-images fixation 30 frames per second. Based on obtained data, a main indicator of the optic disc blood flow is analyzed — mean blur rate (MBR), and pulse wave parameters. The results of examinations carried out at our Center, showed changes of MBR and pulse wave parameters depending on the age of examined patients, as well as in various conditions, including POAG [13, 14].

One of the diseases influencing both the systemic blood flow and ocular microcirculation is the acute coronavirus infection (COVID-19) [15, 16]. The severe acute respiratory syndrome caused by coronavirus (SARS-CoV-2), first observed in China in 2019, in January 2020, was declared by World Health Organization to be a Public Health Emergency. In March 2020, a planet-scale level of pandemic infection was reached, and this caused an impact on social life, economics, and health care system. COVID-19 apart from acute respiratory virus infection and/or pneumonia could lead to various complications, respiratory and polyorgan insufficiency among others. After previous acute COVID-19 disease, later on, a post-COVID syndrome may arise, which is confirmed when symptoms and signs are preserved during 4–12 weeks (and longer) after virus infection start [16, 17].

The investigations carried out in patients with post-COVID syndrome, revealed virus persistency and persistent impairment of the vasculature, Including endotheliopathy, hypercoagulation, thrombosis, neutrophil extracellular elements, chronic immune dysregulation, imbalance of the renin-angiotensin-aldosteron system, and manifestations of hyperinflammation / autoimmune disturbances. Of special interest are the autoantibodies to G-protein coupled receptors (GPCR-AAb). The functional imbalance of these receptors caused by functionally active GPCR-AAb leads to the microcirculatory impairment, and this was confirmed by a study in glaucoma patients [17].

The COVID-19 infection could cause a longstanding impairment of the cardiovascular system, this is related to the SARS-CoV-2 virus action on the receptors of angiotensin-converting enzyme 2 (rACE-2), which express in the heart (endothelium of the coronary arteries, myocytes, fibroblasts, epicardial adipocytes), vessels (vascular endothelium and smooth muscle cells), intestine (intestinal epithelial cells), lungs (tracheal and bronchial epithelial cells, type 2, pneumocytes, macrophages), kidneys (luminal surface of epithelial cells of tubules), seminal vesicles, brain [18]. In experimental study, it was shown that rACE-2 are present in the internal nuclear and the plexiform retinal layers [19]. It is anticipated that ACE-2 prevents atherosclerosis and protects endothelial cells by means of inflammation inhibition, and the rACE-2 deficit sequentially induces vascular inflammation and atherosclerosis. It is possible that SARS-CoV-2, aimed at ACE-2, has molecular characteristics of this receptor deficit [19, 20]. If the SARS-CoV-2 could imitate the rACE-2 deficit, then retinal microcirculation may be damaged, namely in the internal plexiform and nuclear layers, where the receptors to ACE-2 are located. It may be assumed that the microcirculation impairment is one of the factors favoring the development of clinical signs of the post-COVID syndrome, and in POAG patients it may lead to the ocular blood flow change with possible disease progressing.

Aim — evaluation of optic disc blood flow parameters in POAG patients on the background of the post-COVID syndrome using the laser speckle-fluography method.

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MATERIALS AND METHODS

In the study, 60 patients were included, divided into two groups: first (comparator) group — 20 patients (40 eyes, mean age 64.9 ± 4.9 years, 10 men and 10 women) with moderate POAG stage, without COVID-19 history (COVID-19 was not diagnosed before, this was confirmed by the absence of specific immunoglobulin G in the serum); second group — 40 patients (80 eyes, mean age 67.9 ± 6.9 years, 15 men and 25 women) with moderate POAG stage, with COVID-19 history within previous 3 months (minimum period after earlier coronavirus infection was 1.5 months, maximum one — 2.5 months). Recovery was confirmed by two consecutive negative results of the PCR-test in nasopharyngeal swab. An inclusion criterion for this group was also the persistence of the post-COVID syndrome, which was diagnosed according to the presence of such complaints as asthenia, fatigue, taste and/or smell perversion, arthralgia, myalgia, palpitation, anxiety, which persisted after convalescence.

All examined patients were elder than 60 years and had normal blood pressure parameters to the moment of investigation (124 ± 3.9 / 85 ± 3.5 mm Hg). As glaucoma therapy, the patients of both groups received local hypotensive treatment (44 people — 16 people — combined therapy by prostaglandin analogues, non-selective beta-blocker, and carbonic anhydrase inhibitors), IOP compensation was noted, no patient had a history of antiglaucoma surgery.

Patient selection according to glaucoma stage was performed with consideration of morphological optic disc changes, revealed by ophthalmoscopy (pathological deviation of the neural rim from normal proportions, glaucomatous optic disc excavation, peripapillary atrophy), and of changes in visual fields. Standard automated perimetry was carried out using the Octopus perimeter (Switzerland), the criteria for moderate glaucoma stage were MD between –6.03 and –11.78 dB, SLV — more than 19 points with $p < 5\%$, and more than 12 points with $p < 1\%$.

The main inclusion criterion for the present study was history of COVID-19, confirmed by polymerase chain reaction to SARS-CoV-2 antigens in the smear from pharynx or nose, no longer than 3 months. Based on the 15th version of the clinical guidelines on prophylactics, diagnosis, and treatment of the new coronavirus infection (COVID-19), the main group was divided into subgroups according to the severity of the disease course: mild (1st subgroup) and moderate severity (2nd subgroup) course. It is to be mentioned that 2nd subgroup patients were in-patients as well as out-patients and receive combined therapy, which included glucocorticosteroids, anticoagulants, and anti-virus medications.

Both groups were comparable in age, sex, overall health, systemic diseases and history of ophthalmic conditions. Arterial hypertension was present in 16 patients of the 1st subgroup and 32 patients from the 2nd subgroup, but blood pressure was compensated at hypotensive therapy regimen.

Exclusion criteria: smoking, mature cataract, retinal or optic nerve diseases, all but POAG, high myopia (refractive error more than –6.00 D), systemic diseases, which could influence the ocular blood flow, such as systemic hypertension with uncompensated blood pressure, hypotony, diabetes mellitus.

The blood flow of the optic nerve head was measured using the LSFG-NAVI (Nidek, Japan) and estimated using the software of the LSFG Analyzer. Analyzed were the main integral blood flow indicator MBR, including the MA (total MBR), MV (MBR of large vessels) and MT (MBR of the microcirculatory bed) of the studied area, as well as pulse wave indicators expressed in conditional units. LSFG images were obtained after 10-minutes rest in a dark room, without the use of mydriatics. 24 hours before, patients were not allowed to take coffee and alcohol. The LSFG method used for blood flow measuring was described in detail in previous publications [12–14]. On the obtained composed blood flow chart, using a “double circle” pattern, the examined area of the optic nerve head was marked, the pattern parameters were set automatically. At following computer processing, the software, based on the MBR analysis, generates the pulse wave parameters: index of distribution asymmetry (Skew), blowout score (BOS), blowout time (BOT), rising rate (RR), falling rate (FR), flow acceleration index (FAI), acceleration time index (ATI) and resistivity index (RI).

Statistical processing of the study results was performed using the Microsoft Excel 2016 application. Samples corresponded to the allocation of patients to groups. Analyzing the data of 60 patients, we calculated mean values of parameters *M*) and their standard errors of mean (*m*). All samples complied with the normal law of distribution. To explore the significance of differences between sample means the parametric Student’s paired two-tailed t-test was used. The differences were considered as significant ones at the significance level $p \leqslant 0.05$.

RESULTS

Maximal indices of blood flow velocity in the optic nerve head are found in patients with moderate POAG stage without a history of coronavirus infection (the comparator group). A significant ($p \leqslant 0.05$) progredient change of blood flow velocity indices in the optic nerve head area in POAG patients against the background of the post-COVID syndrome, after prior COVID-19 of moderate severity (2nd subgroup).

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It is worth noticing, that by comparative analysis of results obtained in the present study, with the results of the previous investigation performed in our Center, in which age-related blood flow changes in healthy volunteers were analyzed [14], a significant decrease both in MBR indices characteristic for the whole examined area, for large vessels, and for the microcirculatory bed, and the change of various pulse wave parameters in glaucoma patients.

Most significant decrease was revealed for MV and MT indices reflecting the blood flow in large vessels and in the microcirculatory bed of the optic nerve head. MV reduction was 20%, MT — 23%, MA — 13% in patients with moderate glaucoma stage and the post-COVID syndrome after prior COVID-19 of moderate severity compared to patients with moderate glaucoma stage and without prior COVID-19 history ($p \leqslant 0.05$).

It should be noted that MA, MV and MT indices in the group of POAG patients on the post-COVID syndrome background after prior mild COVID-19 (1st subgroup) demonstrated non-significant changes; and this suggests that one of the factors influencing the microcirculation is the severity degree of the course of the prior acute period of coronavirus infection (Table 1).

Statistically significant ($p \leqslant 0.05$) changes if most of the studied pulse wave parameters are elicited in the 2nd subgroup patients, after prior COVID-19 of moderate severity. BOT and BOS indices showed a 12 and 7% decrease, and Skew and RI increased by 8 and 7%, respectively. Detected Rr increase and Fr decrease were statistically not significant. Most actively in the 2nd subgroup ATI indicator increased — by 16%, and for the FAI indicator, a decrease by 18% was revealed, and this is a maximal value among all the pulse wave parameters. The changes in pulse wave parameters in the 1st subgroup showed the same tendency, but were non-significant (Table 2).

DISCUSSION

In 2020, the COVID-19 infection became a pandemic healthcare problem. Apart from pulmonary complications, at human organism damage by SARS-CoV-2 virus, hemodynamic disturbances appear leading to cardiovascular lesion. Characteristic features of the coronavirus damage are microvascular damage, endothelial dysfunction and thromboses related to intensive systemic inflammatory and immune reactions.

Table 1. MBR indicators in the optic disc area in study groups, *M* ± *m*

Таблица 1. Показатели средней скорости размытия (MBR) в области диска зрительного нерва в исследуемых группах, *M* ± *m*

Blood flow parameters	Blood flow parameters, c.u.		
	comparator group	1st subgroup	2nd subgroup
MV	31.74 ± 3.38	30.19 ± 1.15	25.39 ± 1.02*
MT	9.96 ± 1.29	10.48 ± 1.09	7.67 ± 1.31*
MA	17.32 ± 1.63	16.01 ± 1.59	14.64 ± 1.47*

Note. MV — MBR of large vessels; MT — MBR of the microcirculatory bed; MA — total MBR. *$p \leqslant 0.05$, the difference with the comparator group is statistically significant.

Table 2. Parameters of the pulse wave of the optic disc area in study groups, *M* ± *m*

Таблица 2. Показатели пульсовой волны области диска зрительного нерва в исследуемых группах, *M* ± *m*

Blood flow parameters	Blood flow parameters, c.u.		
	comparator group	1st subgroup	2nd subgroup
BOT	41.8 ± 0.72	40.1 ± 1.15	36.7 ± 0.89*
BOS	70.4 ± 0.51	69.6 ± 0.39	65.4 ± 0.46*
Skew	11.3 ± 0.47	11.01 ± 0.59	12.2 ± 0.48*
ATI	32.7 ± 1.45	33.2 ± 1.52	37.9 ± 1.25*
Rising rate	12.3 ± 0.38	12.1 ± 0.45	12.9 ± 0.35
Falling rate	14.5 ± 0.42	13.8 ± 0.37	13.6 ± 0.37
FAI	1.8 ± 0.25	1.7 ± 0.23	1.5 ± 0.21*
RI	0.44 ± 0.30	0.4 ± 0.36	0.47 ± 0.32*

Note. BOT — blowout time; BOS — blowout score; Skew — index of distribution asymmetry; ATI — acceleration time index; FAI — flow acceleration index; RI — resistivity index. *$p \leqslant 0.05$, the difference with the comparator group is statistically significant.

Most patients, infected by SARS-CoV-2, do not completely recover during several months after the discharge from the hospital and continue to suffer from such symptoms, as fatigue, dyspnea, chest pain, palpitation, myalgia, anxiety, depression leading to the quality-of-life impairment. Recent data showed that more than 13% infected people present symptoms of the post-acute COVID-19 disease, preserving during 4 weeks after convalescence, 4.5% — during 8 weeks, and 2.3% of people present symptoms during 12 weeks [21].

Ocular lesions in COVID-19 are not that common, but are described. Of relatively frequent occurrence is the anterior segment involvement. Complaints of patients vary from blurred vision to progressive visual loss with concomitant discharge and/or itching, and clinical picture of follicular, pseudomembranous and hemorrhagic conjunctivitis and keratoconjunctivitis [22]. At ophthalmoscopic examination, focal hemorrhages, cotton-wool spots may be found, being evidence of the impairment of retinal microcirculation [23].

In the article by V.A. Turgel, et al. [24], using the associated with the coronavirus infection ischemic optic neuropathy as an example, possible pathogenic correlations of COVID-19 with vascular and inflammatory conditions of the optic nerve and the retina are considered. The authors make a suggestion that the mechanism of vascular wall lesion during the post-infection period is related to its secondary autoimmune inflammation [24].

V.E. Korelina, et al. [25] remark that the new coronavirus infection has a great impact on all links of the POAG pathogenesis. The disease provokes the development of retinal ischemia and hypoxia, enhancing the ganglion cell apoptosis. The oxidative stress developing on the background of COVID-19 could promote the glaucomatous optic neuropathy progressing.

In several works, features of the blood flow in patients after COVID-19 were studied using the optical coherence tomography-angiography method. Thus, B. Hohberger, et al. [19] state, that ocular microcirculation is altered even in patients after convalescence from COVID-19. The decrease in density of superficial and deep vascular plexuses was described, and it was pointed out that the more severe the course of coronavirus infection was, the more pronounced was the decrease in microcirculation parameters. In the article by V.A. Turgel and S.N. Tultseva [26], the evaluation of retinal microcirculatory changes was carried out in patients after COVID-19 of different severity degree. There were no significant microcirculation impairments in patients with mild COVID-19 course, but in patients with moderately severe and severe degree, a significant decrease in density of superficial and deep vascular plexuses, as well as of peripapillary capillaries. Based on obtained data, it was concluded that microcirculatory retinal changes may play a role of the new biomarker reflecting the severity of human vascular system impairment arising in COVID-19 [26]. To the contrary, D. Szkodny, et al. [27], investigating the density of the superficial capillary plexus, did not find any significant impairments of retinal microcirculation after COVID-19 in all explored quadrants. Taking into consideration the inconsistency of obtained results, it is possible to draw a conclusion on the necessity of further study of the influence of the coronavirus infection SARS-CoV-2 on the microcirculatory bed, including other methods of blood flow assessment, for example, LSFG.

We did not find in the literature any publication dedicated to the investigation of ocular hemodynamics n patients on the background of the post-COVID syndrome using the LSFG; and this served as a precipitation for the present study, dedicated to quantitative and qualitative investigation of blood flow using the LSFG method, to understand the potential of use of this method in diagnosis and follow-up of the changes of the optic disc microcirculation. In our work, significant changes of the optic nerve head blood flow parameters were revealed in POAG on the background of the post-COVID syndrome. The obtained results evidence the high informational value of this method and confirm the efficacy of its use for investigating vascular impairments on ophthalmology.

CONCLUSIONS

Ocular microcirculation may be considered as a marker of the systemic hemodynamics status, and there is reason to believe that examination of the optic nerve head blood flow using the LSFG method gives a diagnostic option for the follow-up of vascular impairments not only on the ophthalmic level, but also on the systemic one.

The laser speckle flowgraphy, on the basis of the pulse wave analysis, allows to carry up a rapid assessment of ocular hemodynamics, and some pulse wave parameters may serve as new biomarkers for detection and evaluation of vascular diseases.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published, and agree to be accountable for all aspects of the study. Personal contribution of each author: Yu.S. Petrov, T.D. Okhotsimskaya — experimental design, collecting and preparation of samples, data analysis, writing the main part of the text, literature review; O.M. Filippova — experimental design, collecting and preparation of samples, data analysis, writing the main part of the text, literature review; O.I. Markelova — experimental design, collecting and preparation of samples, data analysis, writing the main part of the text, literature review.

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Consent for publication. Written consent was obtained from the patient for publication of relevant medical information and all of accompanying images within the manuscript.

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