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Features of the level of matrix metalloproteinase-2, -3, -9 and tissue inhibitors of metalloproteinases-1, -2, -3, -4 in the aqueous humor of patients with primary open-angle glaucoma

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ABSTRACT

Aim. To study the content of matrix metalloproteinase (MMP)-2, -3, -9 and tissue inhibitors of metalloproteinases (TIMPs) -1, -2, -3, -4 in the aqueous humor of patients with moderate primary open-angle glaucoma (POAG).

Materials and methods. The experimental group included 47 patients with verified moderate primary open-angle glaucoma. The control group consisted of 26 patients with uncomplicated cataract. The levels of MMP-2, -3, -9 were determined with Luminex Performance Human MMP Magnetic Panel 3-plex kit (R&D Systems, USA), the concentration of TIMPs-1, -2, -3, - 4 was determined with the Human TIMP Magnetic Luminex Performance Assay 4-plex kit (R&D Systems, USA). The study was carried out using flow-through field fluorometry on a Bio-Plex 200 double-beam laser analyzer (Bio-Rad, USA).

Results. The study showed a statistically significant increase in the levels of matrix metalloproteinase-2 and tissue inhibitors of matrix metalloproteinases-1, -2, -3, -4 in the aqueous humor of patients with moderate POAG compared with patients with uncomplicated cataract.

Conclusion. The obtained data on high concentrations and imbalance in the levels of matrix metalloproteinases and their tissue inhibitors in the aqueous humor of patients with moderate POAG confirm the role of local inflammation, as well as impairments in the structure of the extracellular matrix and its remodeling in the mechanisms of development of this pathology.

Key words: primary open-angle glaucoma, pathogenesis, matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases, aqueous humor.

Conflict of interest. The authors declare the absence of obvious and potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to surgery, collection of the aqueous humor, as well as the use of the study data for scientific purposes. The study was approved by the Biomedical Ethics Committee at the Novosibirsk Branch of S. Fyodorov Eye Microsurgery Federal State Institution (Protocol No. 2 of 02.09.2018).

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Особенности содержания матриксных металлопротеиназ 2, 3, 9 и тканевых ингибиторов матриксных металлопротеиназ 1, 2, 3, 4 во внутриглазной жидкости пациентов с первичной открытоугольной глаукомой

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РЕЗЮМЕ

Цель – изучить содержание матриксных металлопротеиназ (MMP) 2, 3, 9 и тканевых ингибиторов матриксных металлопротеиназ (TIMP) 1, 2, 3, 4 во внутриглазной жидкости пациентов с развитой стадией первичной открытоугольной глаукомы.

Материалы и методы. Обследованы 47 пациентов с верифицированным, на основании офтальмологического обследования, диагнозом развитой стадии первичной открытоугольной глаукомы, которые составили основную группу. Контрольную группу составили 26 пациентов с диагнозом «неосложненная катаракта».

Концентрацию MMP-2, MMP-3, MMP-9 определяли с использованием набора Luminex Performance Human MMP Magnetic Panel (3-Plex) (R&D Systems, США), определение концентрации TIMP-1, TIMP-2, TIMP-3, TIMP-4 проводили с помощью набора Human TIMP Magnetic Luminex Performance Assay 4-plex (R&D Systems, США). Исследование проводилось методом проточной флуориметрии на двухлучевом лазерном анализаторе Bio-Plex 200 (Bio-Rad, США).

Результаты. Установлена статистически значимо высокая концентрация матриксной металлопротеиназы-2 и тканевых ингибиторов матриксных металлопротеиназ 1, 2, 3, 4 во внутриглазной жидкости пациентов с развитой стадией первичной открытоугольной глаукомы относительно данных, полученных при исследовании внутриглазной жидкости лиц с неосложненной катарактой.

Заключение. Полученные в исследовании данные о высоких концентрациях и нарушении баланса содержания матриксных металлопротеиназ и их тканевых ингибиторов в внутриглазной жидкости пациентов с развитой стадией первичной открытоугольной глаукомы подтверждают роль местного воспалительного процесса, а также нарушений структуры внеклеточного матрикса и его ремоделирования в механизмах развития патологического процесса.

Ключевые слова: первичная открытоугольная глаукома, патогенез, матриксные металлопротеиназы, тканевые ингибиторы матриксных металлопротеиназ, внутриглазная жидкость.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование проводилось за счет средств государственного задания, тема НИР «Изучение патогенеза открытоугольной глаукомы на основе оценки дисбаланса цитокинов и факторов роста» (№ АААА-А18-118082290059-3), а также в рамках договоров о научно-практическом сотрудничестве между НМИЦ «МНТК "Микрохирургия глаза" им. акад. С.Н. Федорова» и НИИКЭЛ – филиал ИЦиГ СО РАН, НИИКЭЛ и Федеральным исследовательским центром фундаментальной и трансляционной медицины СО РАН.

Соответствие принципам этики. Все пациенты подписали информированное согласие на проведение операции, забор внутриглазной жидкости, а также использование данных исследования в научных целях. Исследование одобрено комитетом по биомедицинской этике Новосибирского филиала НМИЦ «МНТК "Микрохирургия глаза" им. акад. С.Н. Федорова» (протокол № 2 от 02.09.2018).

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INTRODUCTION

Primary open-angle glaucoma (POAG) is widely spread in all countries of the world, and its increasing prevalence has significant medical and social consequences for patients and the community [1–4]. The ophthalmological community is to a certain extent unsatisfied with results of treatment for this pathology, which makes POAG a pressing issue of modern ophthalmology. A thorough study of the development of pathological mechanisms in this disease is a significant research task which would allow to elaborate pathogen-specific treatment.

According to the analysis of publications devoted to POAG pathogenesis, morphological and structural changes in the eye drainage system leading to impaired aqueous humor outflow and an increase in the intraocular pressure (IOP) are some of the main causes of POAG [5–9].

Some researchers suggest that these morphological and structural changes in the eye drainage zone may be manifestations of the local aseptic destructive and inflammatory process in patients with POAG, the development of which depends on the imbalance and content change of various biologically active molecules with proinflammatory and fibrotic activity (cytokines, growth factors, etc.), as evidenced by publications of recent years [10–14]. In order to understand the role of local destructive and inflammatory process in POAG development, it is important to determine changes in the local content and balance of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMP), which play an essential role in degradation of extracellular matrix proteins degradation and tissue remodeling [15–20], as well as in ophthalmic disorders [21].

In addition, the publications provide data on the ability of a number of cytokines to affect MMP and TIMP production and participate in regulation of MMP and TIMP synthesis [22–24].

Currently, few publications contain data on high concentrations of various MMPs and TIMPs in both the aqueous humor and tear and tissue structures of the eye affected by POAG. Based on the conducted studies, the authors of the publications suggest that excessive production of MMPs and TIMPs is associated with the active synthesis of various classes of cytokines, and the resulting imbalance in the studied biologically active molecules can lead to disturbances of the extracellular matrix and remodeling of the trabecular meshwork and lamina cribrosa of the sclera with impaired aqueous humor outflow and development of glaucomatous process. The authors also suggest possible role of MMP in the mechanisms of apoptosis in retinal ganglion cells and glaucomatous optic neuropathy [25–30].

However, it is not always possible to interpret the data presented in the literature unequivocally, which allows to conclude on the relevance of further study of the content and balance of MMP and TIMP in the aqueous humor of POAG patients to understand the molecular mechanisms of POAG development, as well as to formulate the aim of this study.

The aim of the study was to investigate the content of MMP-2, 3, 9 and TIMPs-1, 2, 3, 4 in the aqueous humor of patients with moderate POAG.

MATERIALS AND METHODS

The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association “Ethical principles for medical research involving human subjects”, the Federal Law

of the Russian Federation of November 21, 2011 No. 323 FL "On the basics of protecting the health of citizens in the Russian Federation", as well as the requirements of the Federal Law of July 27, 2006 N 152-FL (as amended on July 21, 2014) "On Personal Data" (as amended and supplemented, entered into force on September 1, 2015).

The study examined 73 patients. The experimental group consisted of 47 patients who underwent clinical and instrumental examination, including best visual acuity, binocular ophthalmoscopy, spheroperimetry, echoopthalmography, optical coherence tomography (OCT), and intraocular pressure (IOP) measurement. Moderate POAG and uncomplicated cataract were revealed. There were 16 (34.0%) men and 31 (66.0%) women in the experimental group. The average age of patients was 64.3 ± 5.9 years. The control group included 26 patients with uncomplicated cataract. There were 8 (30.8%) men and 18 (69.2%) women in the group, the average age of patients was 67.1±3.2 years. Thus, the studied groups did not differ in terms of age and gender.

Exclusion criteria from both groups were acute and chronic eye disorders, diabetic retinopathy, neovascular glaucoma, uveitis of various etiology and localization, hemophthalmus, and autoimmune diseases and cancer of any localization. The study excluded patients who, in order to normalize intraocular pressure, took medications containing prostaglandin analogs, capable of affecting the activity of the local destructive and inflammatory process.

Samples of the aqueous humor (AH) (100–150 μL) were collected from all patients at the initial stages of surgical treatment. The samples were frozen and stored at –70 °C until the study was conducted.

Determination of the concentration of matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs) in AH

Once frozen, AH was defrosted to room temperature before the study. To remove the sediment, it was centrifuged at 4°C, 10,000 rpm, for 10 min. The concentrations of MMP-2, MMP-3, and MMP-9 were determined using the Luminex Performance Human MMP Magnetic Panel 3-plex kit (R&D Systems, USA). The levels of TIMP-1, TIMP-2, TIMP-3, and TIMP-4 were identified using the Human TIMP Magnetic Luminex Performance Assay 4-plex kit (R&D Systems, USA). The study was conducted using flow-through field fluorometry on a two-beam laser analyzer Bio-Plex 200 (Bio-Rad, USA).

Bio-Plex manager Software version 4.1 was used for data processing. Data analysis was performed using the Statistica 10 software package (StatSoft Inc., USA). The concentrations were measured in ng/ml. The use of the Kolmogorov – Smirnov and Lilliefors tests for normality allowed to establish the absence of normal distribution in the obtained samples. In this regard, the study used the methods of non-parametric statistics. The significance of differences in variation series in unrelated samples was assessed using the Mann–Whitney *U*-test. Data were presented as the median and upper (75%) and lower (25%) quartiles, *Me* (*Q1–Q3*). The differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

As a result of this study, we identified the presence of a significantly higher concentration of MMP-2 in the AH of patients with moderate POAG compared with the data obtained in the AH of patients with uncomplicated cataract ($p = 0.001$, Table).

At the same time, when determining the content of MMP-3 and MMP-9 in the AH of patients in the examined groups, it was found that their levels did not differ statistically significantly ($p = 0.08$ and $p = 1$, respectively), and the samples in which the concentration of the studied biologically active molecules was higher than the lower limits of the sensitivity were isolated.

Table

Content of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases in the aqueous humor of patients with moderate POAG and uncomplicated cataract, ng/ml, *Me* (Q_1–Q_3)

Parameter	Patients with POAG, *n* = 47	Patients with uncomplicated cataract, *n* = 26	*p*
MMP-2	1.87 [1.43; 2.31] *	1.43 [1.09; 1.81]	0.001
MMP-3	0.06 [0.00; 0.09]	0.02 [0.00; 0.01]	0.08
MMP-9	0.00 [0.00; 0.00]	0.00 [0.00; 0.00]	1
TIMP-1	30,822.74 [23,320; 44,298] *	18,254.11 [14,058; 25,685]	0.001
TIMP-2	40,570.62 [33,690; 49,381] *	27,520.26 [24,159; 31,400]	0.001
TIMP-3	11,771.36 [10,788; 14,086] *	10,364.90 [8,097; 11,333]	0.012
TIMP-4	110.41 [80.03; 129.05] *	77.57 [69.83; 93.86]	0.001

* statistically significant differences compared with the group of patients with uncomplicated cataract.

When comparing the obtained data on the MMP content in the AH of patients in the examined groups with the results of other studies presented in the literature, the following can be noted.

Our data on significantly higher concentrations of MMP-2 in the AH of patients with POAG are similar to the results presented in the study by A.D. Nga et al., where comparable data were obtained on the content of this matrix metalloproteinase in the AH [26]. Our data are also consistent with the data presented by P. Sahay et al., in which high concentrations of MMP-2 were found in the lacrimal fluid of patients with POAG [27].

At the same time, we did not reveal significantly higher concentrations of MMP-3 in the AH of patients with moderate POAG, data on which were presented by A.D. Nga et al. [26]. We also could not confirm the conclusion made in the study by L. Markiewicz et al., who found high concentration of MMP-9 in the AH of POAG patients and regarded it as a marker of inflammation development [29].

The analysis of the data obtained in the study made it possible to state the following facts reflecting the content of TIMPs in the AH of patients in the examined groups. The concentrations of TIMP-1 in the AH of patients with moderate POAG were found to be significantly higher than in patients with uncomplicated cataract ($p = 0.001$). Similar results were obtained when examining the levels of TIMP-2 in the AH of the patients. The patients with moderate POAG had significantly higher values of the studied parameter compared with the data in the control group ($p = 0.001$).

The study also showed the presence of a significantly higher concentration of TIMP-3 and TIMP-4 in the AH of patients with moderate POAG relative to the values of the studied parameters in the AH of patients with uncomplicated cataract ($p = 0.012$ and $p = 0.001$, respectively).

When comparing the data on the content of TIMPs in the AH of the patients obtained in this work with the results of other studies presented in the literature, the following can be noted. Our data on statistically significantly higher concentrations of TIMP-1, TIMP-2, and TIMP-4 in the AH of patients with POAG are similar to the results presented in the study by E.L. Ashworth Briggs et al. There, comparable data were presented, and it was concluded that an imbalance between MMP and TIMP with a shift towards their increased levels was found in the AH samples, which can lead to inhibition of MMP activity with changes in the composition of the extracellular matrix in the trabecular meshwork with a subsequent increase in resistance to the AH outflow, as well as to increased intraocular pressure [31].

Additionally, higher concentrations of TIMP-1 and TIMP-2 in the AH of POAG patients were identified in the study by A.D. Nga et al. [26]. In the study by N. Fountoulakis et al., it was concluded that the most significant changes were established when TIMP-4 was determined in the AH; it was also established that this biologically active molecule was crucial in the pathogenesis of POAG [32]. The analysis of the data obtained in this study and research results presented in the literature on the content of TIMPs in the AH of POAG patients made it possible to state fewer discrepancies between them than in the analysis of data on the content of MMPs. However, a relatively small number of publications devoted to the study of MMPs and TIMPs indicates the need for further research in this area.

CONCLUSION

The conducted study allowed to establish that in patients with moderate POAG, significantly high levels of MMP-2 and TIMPs-1, -2, -3, -4 were identified. The study also confirms the importance of local inflammatory process and impairment of the extracellular matrix structure and its remodeling in the mechanisms of POAG development.

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Authors contribution

Chernykh V.V., Konenkov V.I. – conception and design, critical revision of the manuscript for important intellectual content, drafting of the article. Ermakova O.V. – selection and ophthalmic examination of patients, surgical treatment and sampling of the biomaterial for the study, analysis and interpretation of the data. Orlov N.B. – determination of biologically active molecules in the aqueous humor, statistical processing of the data. Trunov A.N. – substantiation of the manuscript, critical revision of the manuscript for important intellectual content, drafting of the manuscript.

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