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DYNAMICS OF VITREORETINAL INTERFACE CHANGES IN DIABETIC MACULAR EDEMA DURING REGULAR ANTIANGIOGENIC THERAPY

© D.H. Oskanov [1], S.V. Sosnovskii [1], E.V. Boiko [1, 2, 3], R.D. Berezin [1], T.V. Kotsur [1]

[1] S.N. Fedorov NMRC "MNTK "Eye Microsurgery", Saint Petersburg, Russia;
[2] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia;
[3] Military Medical Academy named after S.M. Kirov, Saint Petersburg, Russia

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✧ In the study, the state of the vitreoretinal interface (VRI) was investigated in diabetic macular edema (DME) at primary diagnosis and during regular antiangiogenic ranibizumab therapy. At primary diagnosis, pathological VRI changes were detected in 49.3% of cases. During regular antiangiogenic therapy, the transformation of initially normal VRI into pathological one occurs in 6% of cases, the transformation of initially pathological VRI into normal or other pathological one – in 15.8%. Initially pathological VRI is not an absolute indication for vitrectomy, since in no fewer than 7.9% of cases its transformation into normal VRI is possible.

✧ ***Keywords:*** diabetic macular edema; vitreoretinal interface; antiangiogenic therapy.

ДИНАМИКА ИЗМЕНЕНИЙ ВИТРЕОРЕТИНАЛЬНОГО ИНТЕРФЕЙСА ПРИ ДИАБЕТИЧЕСКОМ МАКУЛЯРНОМ ОТЁКЕ В ХОДЕ РЕГУЛЯРНОЙ АНТИАНГИОГЕННОЙ ТЕРАПИИ

© Д.Х. Осканов [1], С.В. Сосновский [1], Э.В. Бойко [1, 2, 3], Р.Д. Березин [1], Т.В. Коцур [1]

[1] Федеральное государственное автономное учреждение Национальный медицинский исследовательский центр «Межотраслевой научно-технический комплекс „Микрохирургия глаза" им. академика С.Н. Фёдорова» Министерства здравоохранения Российской Федерации, Санкт-Петербургский филиал, Санкт-Петербург;
[2] Федеральное государственное бюджетное образовательное учреждение высшего образования «Северо-Западный государственный медицинский университет им. И.И. Мечникова» Министерства здравоохранения Российской Федерации, Санкт-Петербург;
[3] Федеральное государственное бюджетное военное образовательное учреждение высшего образования «Военно-медицинская академия им. С.М. Кирова» Министерства обороны Российской Федерации, Санкт-Петербург

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✧ В работе изучено состояние витреоретинального интерфейса (ВРИ) у пациентов с диабетическим макулярным отёком при первичной диагностике, и его изменения в ходе регулярной антиангиогенной терапии ранибизумабом. При первичной диагностике патология ВРИ выявляется в 49,3 % случаев. На фоне регулярной антиангиогенной терапии изменение исходно нормального ВРИ в патологический происходит в 6 % случаев, в нормальный или другой патологический — в 15,8 % случаев. Исходно патологический ВРИ не является абсолютным показанием к витрэктомии, так как не менее чем в 7,9 % случаев возможен его переход в нормальный ВРИ.

✧ ***Ключевые слова:*** диабетический макулярный отёк; витреоретинальный интерфейс; антиангиогенная терапия.

INTRODUCTION

Diabetic macular edema (DME) is one of the main causes of visual acuity impairment in patients with diabetes mellitus [1–3]. With the widespread introduction in ophthalmologic clinical practice of a high-tech and highly informative method of optical coherence tomography (OCT), whose major assets are noninvasiveness and objectivity of results, the diagnosis of DME has become easy and affordable [4]. OCT enables the microstructural changes both in the retina itself and at the vitreous body and the retina interface to be visualized *in vivo* [1, 4, 5]. Due to the clinical importance of the ratios of the vitreous body and retina boundaries region for the pathogenesis of a number of ophthalmic diseases, the term vitreoretinal interface (VRI) is widely used to designate this boundary [4, 6, 7].

The key role of pathological changes in the VRI in retinal diseases, such as macular hole, epiretinal fibrosis, and vitreomacular traction syndrome, has been proven [7–12]. The International Vitreomacular Traction Study Group has developed a nomenclature and classification of abnormal changes in the VRI based on OCT data [13]. According to this classification, there are four main pathological conditions of the VRI: vitreomacular adhesion (VMA), vitreomacular traction (VMT), epiretinal membrane (ERM), and macular hole. Thickening of the retina in these cases is caused not by impairment of the permeability of its own vessels due to retinal dysregulation of vascular endothelial growth factor (VEGF), but by anteroposterior or tangential traction. As a rule, the increase in vascular permeability and thickening of the retina detected in this case are secondary.

According to the literature, the frequency of VRI pathology in diseases such as central retinal vein occlusion, uveitis, high myopia, Irvine – Gass syndrome, macular hole, age-related macular degeneration, and others, is 31.8% to 47% [14], whereas that with DME is 6% to 52.1% [15, 16].

In the study of Wong et al. [15] on the pathology of VRI in antiangiogenic therapy of DME, a variant of pathological VRI in the form of an eccentric ERM, not included in the results of the International Research Group of Vitreomacular Traction, was described. In this condition, the ongoing proliferative process in the eccentric ERM leads to contraction of the membrane and the emergence of radial tangential trajectories that create tension along the retinal inner surface, which leads to deformity of the contour and thickening of the retina with formation of the "folded" profile. The authors characterized eccentric ERM and ERM with involvement of the center of the macula as two different clinical conditions, but the practical significance of this separation was not considered. In our work, we showed the clinical significance of this type of VRI pathology in its effect on the efficacy of antiangiogenic therapy in DME, based on the criterion of central retinal thickness (CRT) changes, which implies the difference between the initial parameters and the data 1 month after intravitreal anti-VEGF administration [16]. The change in CRT in eyes with retinal folds associated with an eccentric ERM did not significantly differ from that in eyes with normal VRI. In eyes with VRI pathologic conditions including ERM, VMA, and VMT, the change in CRT was significantly less than that in eyes with normal VRI [16].

With the advent of VEGF inhibitors in the toolkit of ophthalmologists [17, 18] and the definition of the role of impaired regulation of VEGF in the pathogenesis of DME, intravitreal anti-VEGF treatment has become the first-line therapy of this ocular diabetic pathologic condition. Antiangiogenic therapy, with its pathogenetically oriented effect, is characterized by high efficacy [1, 2, 5, 19–21]. Maintenance of achieved functional and anatomical effects requires, first, regular monitoring of patients with mandatory OCT control of the anatomical state of the retina, and second, repeated, sometimes multiple, intravitreal anti-VEGF injections in the presence of signs of retinal edema. However, sometimes it is not possible to achieve complete relief of DME, even with compliance with follow-up and protocol of antiangiogenic therapy [22]. In such cases, the treatment of choice is a change in the direction of therapy to influence the pathogenetic mechanisms of DME, other than VEGF dysregulation. One such pathogenetic mechanism with a proven role in the development of DME is inflammation mediated by the expression of numerous proinflammatory cytokines in the retina [23]. Currently, the ophthalmologist's range of tools includes the glucocorticoid implant Ozurdex (dexamethasone, 0.7 mg, Allergan Pharmaceuticals, Ireland), created specifically for IVA, whose effectiveness against DME has been proven in numerous studies [24]. Another pathogenetic mechanism of DME, which may reduce the efficacy of antiangiogenic therapy, is the traction effect on the retina by pathologically altered VRI. Currently, due to the widespread introduction of vitrectomy in routine clinical practice, ophthalmologists are paying more attention to pathological changes of the VRI in DME [6, 22, 25–27]. A number of Russian studies have demonstrated the influence of VRI pathological changes on the efficacy of antiangiogenic therapy in DME [1, 16]. The literature presents mainly data on the pathological changes of the VRI at the diagnosis of this process, but it is not clear what changes in the VRI occur during treatment, in particular with the use of antiangiogenic therapy.

This study *aimed* to analyze options of changes in the VRI in DME patients, not only at the initial diagnosis, but also during regular antiangiogenic therapy.

MATERIALS AND METHODS

A total of 136 patients (175 eyes) diagnosed with DME underwent follow-up ranging from 4 to 65 months (average, 10.6 ± 11.2 months).

The criteria for inclusion of patients in the study were DME confirmed by OCT (CRT > 250 μm), compensated glycemia level (from 7% to 10% glycated hemoglobin), and receiving antiangiogenic therapy according to indications. The exclusion criteria were diseases accompanied by VRI pathological changes (tractional retinal detachment, macular hole, or vitreomacular traction syndrome); the presence of other diseases of the retina, the pathogenesis of which is mediated by an impairment of VEGF regulation (occlusion of the central retinal vein or its branches, neovascular form of age-related macular degeneration, myopic choroidal neovascularization, etc.); vitrectomy at any stage of the study; and receiving treatment other than antiangiogenic therapy for DME (macular laser photocoagulation, steroids).

At the initial diagnosis and at each control examination, each patient underwent a standard ophthalmologic examination, which included determining the best corrected visual acuity using Golovin – Sivtsev charts, and fundus biomicroscopy, as well as OCT with analysis of the VRI. Control examinations were performed 1 month after each intravitreal anti-VEGF injection and at least once every 3 months in the DME remission period.

Antiangiogenic therapy consisted in ranibizumab intravitreal injection according to the standard protocol at a dose of 0.5 mg. The indication for ranibizumab intravitreal injection was macular edema confirmed by OCT (CRT > 250 μm).

Spectral OCT was performed on an SD-OCT RTVue 100 (Optovue, Fremont, CA, USA) using the 3D Reference and Line protocols. On the tomograms of the Line protocol, the state of the VRI in the central subzone was evaluated, as well as the thickness of the retina in the center of the macula, which was defined as the distance from the internal limiting membrane to the retinal pigment epithelium in the center of the fovea. On the tomograms of the 3D Reference protocol, the state of the VRI outside the central subzone was evaluated. When assessing the VRI, we determined the nature of the contour of the retinal inner surface and the state of the posterior hyaloid (PH). An increase in CRT with cystic changes in the neurosensory retina (NSR) without disturbing the contour of the retinal surface, the internal limiting membrane, and the PH was considered as normal VRI. All other conditions were regarded as pathological VRI.

All cases with pathological VRI were categorized into four typical variants (Fig. 1):

- Wave-shaped impairment of the profile of the boundary of the NSR – the vitreous body, or folding of the retina [16, 28].

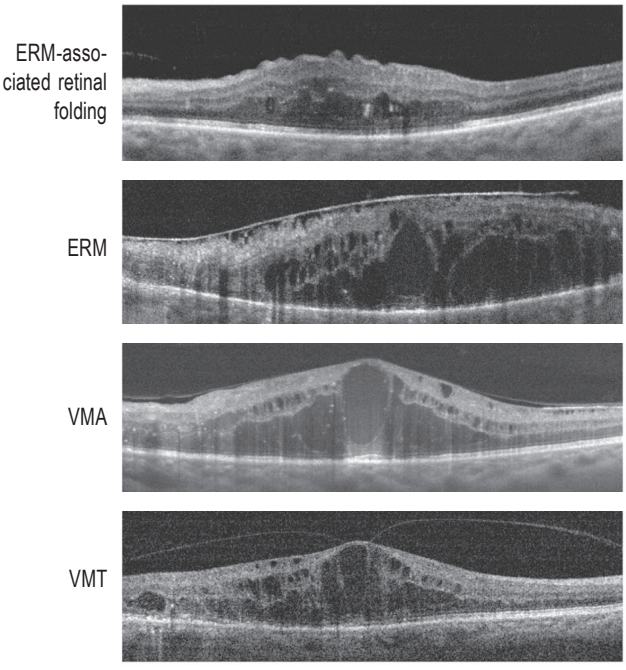

Fig. 1. Types of pathological vitreoretinal interface in DME

Рис. 1. Варианты витреоретинального интерфейса при диабетическом макулярном отёке. ЭРМ — эпиретинальная мембрана, ВМА — витреомакулярная адгезия, ВМТ — витреомакулярная тракция

- The epiretinal macular membrane – changes in the VRI in the form of a hyperreflective membrane partially adjacent to the uneven surface of the NSR [29].
- Vitreomacular adhesion – changes in the VRI in the form of partial detachment of the PH at an angle to the surface of the retina, without structural disorders of the retinal surface and with preservation of the adjacent zone in the macular zone [13].
- Vitreomacular traction – changes in the VRI in the form of a combination of the PH partially adjacent to the surface of the NSR and partially exfoliated, together with a disorder of the retinal surface as a "macular hole" [13]. Moreover, the structural state of the NSR itself is important. In the presence of structural deformities of the NSR according to the type of foveoschisis or ectasia combined with partially adjacent and partially exfoliated PH, a diagnosis of vitreomacular traction syndrome was established [13, 29], which was an indication for vitrectomy. In accordance with the exclusion criteria, patients with vitreomacular traction syndrome were excluded from the study.

Statistical analysis was performed using the Statistics 10.0 program (StatSoft, Tulsa, OK, USA). Differences were considered statistically significant at $p < 0.05$. All data are presented as mean ± standard deviation.

RESULTS

A total of 90 patients (144 eyes) met the inclusion criteria. Some patients discontinued participation in the study because their remote location made it difficult for them to be monitored regularly or because of concomitant cardiovascular pathology. The average age of the patients included in the final study was 64.8 ± 12.4 years, and the ratio of men to women was 43/47 (47.8%/52.2%). The level of glycated hemoglobin did not exceed the level of 7% to 10%. During the study, each patient received 2 to 10 intravitreal anti-VEGF injections (average, 2.6), for a total of 583 intravitreal anti-VEGF injections.

The average visual acuity was 0.33 ± 0.22 before treatment and 0.34 ± 0.25 at the end of the follow-up period ($p > 0.05$). The average CRT was 564.8 ± 142.4 μm before treatment and 440.5 ± 112.9 μm at the end of the follow-up period ($p < 0.05$).

At the initial diagnosis, normal VRI was detected in 73 eyes (50.7%), and pathological changes in the VRI were detected in 71 eyes (49.3%). Over the entire period of the study, OCT before each subsequent intravitreal anti-VEGF injection detected pathology of the VRI in 251 of 583 cases (43%) (Fig. 2).

During follow-up monitoring, in the course of regular antiangiogenic therapy, transition from normal VRI to one of the pathological types was recorded in 20 cases (6% of all cases of normal VRI). The average time of onset of the transition was 12.2 ± 6.8 months from diagnosis after an average of 2.4 ± 1.4 intravitreal anti-VEGF injections. The reverse transition from any type of pathological VRI to normal status was recorded in 20 cases (7.9% of all cases of pathological VRI). The average time of onset of the transition to VRI normalization was 8.8 ± 7.4 months from diagnosis after an average of 2.5 ± 1.8 intravitreal anti-VEGF injections. Transition from one type of pathological VRI into any other type of pathological VRI was recorded in 20 cases (7.9% of all cases of pathological VRI). The average time of onset of such transition was 11.8 ± 8.4 months from diagnosis after an average of 2.7 ± 1.9 intravitreal anti-VEGF injections.

Figure 3 shows the quantitative indicators of changes in the type of VRI with regular antiangiogenic therapy of DME. Figure 4 shows the period from the start of antiangiogenic therapy of DME to changes in the type of VRI. Figure 5 shows the number of intravitreal anti-VEGF injections from the start of antiangiogenic therapy of DME until a change in the type of VRI.

DISCUSSION

Antiangiogenic therapy is nowadays the first-line treatment of DME. The efficacy and safety of intravitreal ranibizumab injections have been proven in multicenter trials RESTORE [21] and DRCR.net [30], and the efficacy and safety of aflibercept have been proven in the multicenter trials VIVID and VISTA [2]. Subject to the treatment regimen, angiogenesis inhibitors enable a significant and persistent increase in best corrected visual acuity and a decrease in CRT.

However, these studies did not take into account the state of the VRI. Different types of VRI pathological conditions have different effects on the efficacy of antiangiogenic therapy [16, 28]. In our previous studies, the primary CRT findings in patients with normal and pathological VRI were not significantly different, which indicates that changes in the VRI do not play a major role in the increase in CRT. The average decrease in CRT during antiangiogenic therapy with folding of the retina was 119.5 ± 131.0 μm; with ERM, it was 65.0 ± 87.4 μm; with VMA, it was 44.3 ± 85.7 μm; and with VMT, it was 17.9 ± 89.7 μm.

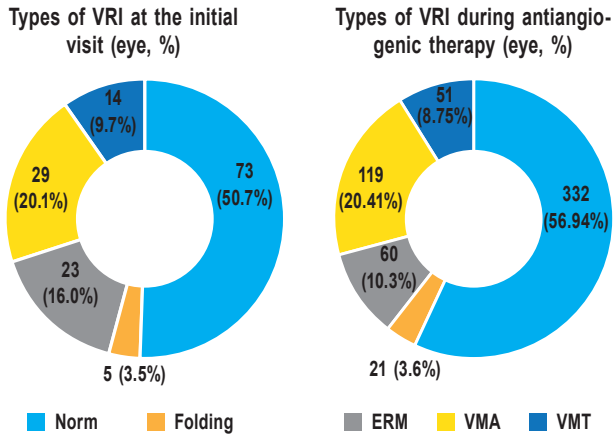

Fig. 2. Quantitative and fractional distribution of VRI types at the initial diagnosis and during antiangiogenic therapy of DME

Рис. 2. Количественное и долевое распределение различных типов витреоретинального интерфейса при первичной диагностике и в ходе антиангиогенной терапии диабетического макулярного отёка. ВМТ — витреомакулярная тракция, ВМА — витреомакулярная адгезия, ЭРМ — эпиретинальная мембрана

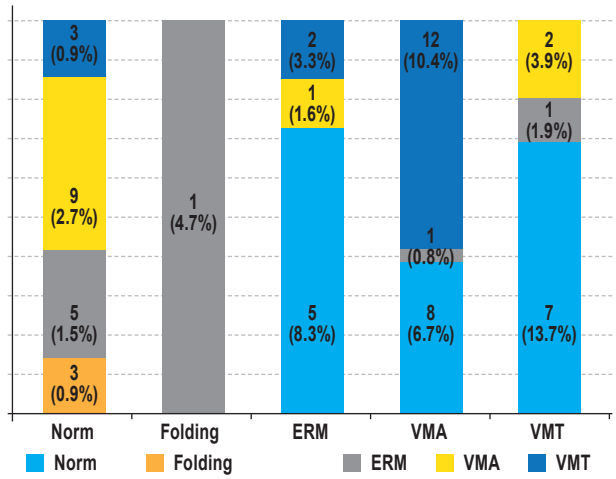

Fig. 3. The number of VRI type change cases in DME 1 month after intravitreal administration of angiogenesis inhibitor

Рис. 3. Число случаев изменения типов витреоретинального интерфейса через 1 мес. после интравитреального введения ингибитора ангиогенеза. ЭРМ — эпиретинальная мембрана, ВМА — витреомакулярная адгезия, ВМТ — витреомакулярная тракция

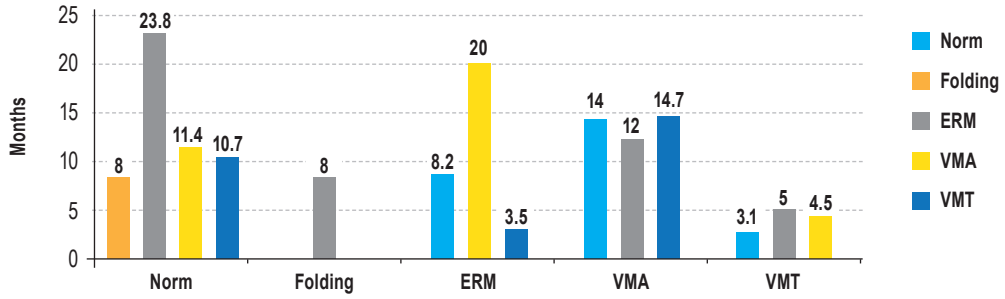

Fig. 4. Times of VRI type transitions

Рис. 4. Сроки переходов типов витреоретинального интерфейса. ЭРМ — эпиретинальная мембрана, ВМА — витреомакулярная адгезия, ВМТ — витреомакулярная тракция

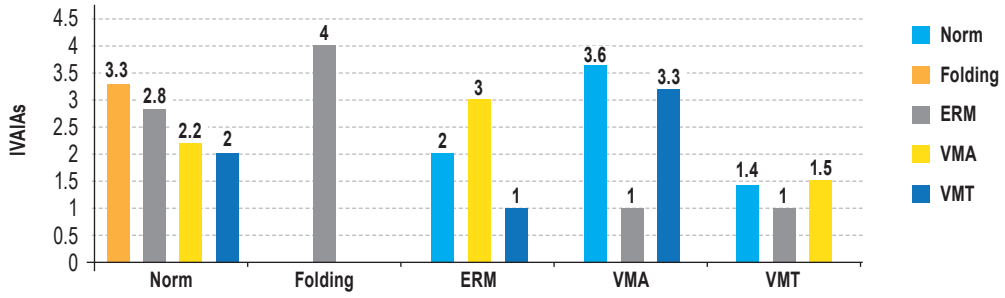

Fig. 5. The number of intravitreal angiogenesis inhibitor administrations before the transformation into another vitreoretinal interface type in DME

Рис. 5. Количество интравитреального введения ингибитора ангиогенеза до перехода в другой тип витреоретинального интерфейса при диабетическом макулярном отёке. ЭРМ — эпиретинальная мембрана, ВМА — витреомакулярная адгезия, ВМТ — витреомакулярная тракция

It should be noted that the IVA procedure, although a minimally invasive manipulation, causes microcavitation of the vitreous body and can enhance vitreoretinal traction [31–33]. With repeated occurrences, such an effect can induce changes in the state of the VRI; in our study, three patients withdrew for vitrectomy for this reason.

In the present study, we studied the VRI state at the initial diagnosis of DME and its changes during antiangiogenic therapy. In almost half of DME

patients, pathological VRI was found at the initial diagnosis. In most cases, the initial state of the VRI did not change with antiangiogenic therapy. Conversion of normal VRI to a pathological variant during intravitreal anti-VEGF therapy was recorded in only 6% of cases, and initially pathological VRI converted to normal in only 7.9% of cases. Conversion of normal VRI to a pathological variant during intravitreal anti-VEGF treatment occurred relatively quickly, at an average of 12.2 ± 6.8 months after the start of follow-up monitoring, whereas conversion of pathological VRI to normal occurred at an average of 8.8 ± 7.4 months. Most often, the conversion to normal VRI occurred with VMT-type VRI (13.7% of VMT cases). The conversion to normal VRI occurred least often with folding of the retina, which was not detected at all, although this result could be compromised by the small number of cases with this type of VRI pathology. The most variable were VMA and VMT, which, in the presence of regular antiangiogenic therapy, converted to normal in 17.9% and 19.5% of cases, respectively. The pathological VRI of the retinal folding type changed less often (4.7%).

This study has a number of limitations. First, the study was retrospective. Second, only morphological changes (changes in CRT), and not visual acuity, were considered as criteria for the efficacy of treatment. However, it should be remembered that the efficacy of anti-VEGF therapy does not clearly correlate with the functional outcome, since the functional outcome can be compromised by structural changes in the foveal retina, including destruction of the ellipsoid zone or ischemic maculopathy. Finally, current results do not permit to give deterministic recommendations on the choice of treatment (antiangiogenic therapy or vitrectomy).

CONCLUSION

At the initial diagnosis, diabetic macular edema is accompanied by pathological changes in the vitreoretinal interface in 49.3% of cases. In the presence of regular antiangiogenic therapy, a change from the initially normal vitreoretinal interface to a pathological one occurs in only 6% of cases, whereas a change from an initially pathological vitreoretinal interface to a normal interface or another type of pathological interface occurs in 15.8% of cases. An initially pathological vitreoretinal interface is not an absolute indication for vitrectomy, since spontaneous disappearance of pathological changes in the vitreoretinal interface is possible in at least 7.9% of cases during follow-up monitoring.

Conflict of interest. The authors declare no conflicts of interest.

Transparency of financial activities. None of the authors has a financial interest in the materials or methods presented. All authors declare that they have read and approved the article, and all authorship requirements are met. All authors state that the manuscript reflects the work actually performed.

Authors' contributions.

D.Kh. Oskanov performed the diagnostic examinations, surgical treatment, collection and processing of materials, and analysis of the data obtained, and wrote the text and the literature review;

S.V. Sosnovsky created the concept and design of the study, collected and processed the materials, performed surgical treatment, analyzed the data, and wrote the text;

E.V. Boyko created the concept and design of the study, performed analysis of the data, and wrote the text;

R.D. Berezin collected and processed the materials, performed surgical treatment, analyzed the data obtained, and wrote the text;

T.V. Kotsur collected and processed the materials, performed analysis of the data obtained, and wrote the text.

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Information about the authors

Dzhambulat H. Oskanov — Ophthalmologist. S.N. Fedorov National Medical Research Center MNTK "Eye Microsurgery", St. Petersburg Branch, Saint Petersburg, Russia. E-mail: oskanovd@mail.ru.

Sergei V. Sosnovskii — Assistant-Professor, PhD, MD of Highest Qualification, Ophthalmologist. S.N. Fedorov National Medical Research Center MNTK "Eye Microsurgery", St. Petersburg Branch, Saint Petersburg, Russia. E-mail: svsosnovsky@mail.ru.

Ernest V. Boiko — Professor, Doctor of Medical Science, Honored MD of Russian Federation, Director, S.N. Fedorov National Medical Research Center MNTK "Eye Microsurgery", St. Petersburg Branch, Saint Petersburg, Russia; North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia; Professor, Head, Ophthalmology Department, S.M. Kirov Military Medical Academy, Saint Petersburg, Russia E-mail: boiko111@list.ru.

Roman D. Berezin — PhD, Ophthalmologist. S.N. Fedorov National Medical Research Center MNTK "Eye Microsurgery", St. Petersburg Branch, Saint Petersburg, Russia. E-mail: berrom@yandex.ru.

Tat'yana V. Kotsur — MD, Ophthalmologist. Laser Microsurgery and Fluorescent Angiography Department. S.N. Fedorov National Medical Research Center MNTK "Eye Microsurgery", St. Petersburg Branch, Saint Petersburg, Russia. E-mail: tatiana781@yandex.ru.

Сведения об авторах

Джамбулат Хусенович Осканов — врач-офтальмолог отделения витреоретинальной хирургии. Санкт-Петербургский филиал, ФГАУ «НМИЦ «МНТК «Микрохирургия глаза» им. акад. С.Н. Фёдорова», Санкт-Петербург. E-mail: oskanovd@mail.ru.

Сергей Викторович Сосновский — канд. мед. наук, доцент, врач высшей квалификационной категории, врач-офтальмолог отделения витреоретинальной хирургии. Санкт-Петербургский филиал, ФГАУ «НМИЦ «МНТК «Микрохирургия глаза» им. акад. С.Н. Фёдорова», Санкт-Петербург. E-mail: svsosnovsky@mail.ru.

Эрнест Витальевич Бойко — д-р мед. наук, профессор, Заслуженный врач РФ, директор, Санкт-Петербургский филиал, ФГАУ «НМИЦ «МНТК «Микрохирургия глаза» им. акад. С.Н. Фёдорова», Санкт-Петербург; ФГБОУ ВО СЗГМУ им. И.И. Мечникова Минздрава России, Санкт-Петербург; профессор, заведующий кафедрой офтальмологии, ФГБВОУ ВО ВМА им. С.М. Кирова Минобороны России, Санкт-Петербург. E-mail: boiko111@list.ru.

Роман Дмитриевич Березин — канд. мед. наук, врач-офтальмолог отделения. Санкт-Петербургский филиал. ФГАУ «НМИЦ «МНТК «Микрохирургия глаза» им. акад. С.Н. Фёдорова», Санкт-Петербург. E-mail: berrom@yandex.ru.

Татьяна Владимировна Коцур — канд. мед. наук, врач отделения лазерной микрохирургии глаза и флюоресцентной ангиографии. Санкт-Петербургский филиал. ФГАУ «НМИЦ «МНТК «Микрохирургия глаза» им. акад. С.Н. Фёдорова», Санкт-Петербург. E-mail: tatiana781@yandex.ru.