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OPTICAL COHERENCE TOMOGRPAPHY IN DIFFERENTIAL DIAGNOSIS OF RETINAL ARTERIOLAR MACROANEURYSMS

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✧ ***Aim.*** To study the prevalence and topographical distribution of retinal exudation in eyes with retinal arteriolar macroaneurysms (RAM) and in those with macular branch retinal vein occlusions (mBRVO). ***Methods.*** The prevalence of optical coherence tomography (OCT) signs (different types of retinal hemorrhages and accumulation of fluid as well as hard and soft exudates) was evaluated in 28 eyes with RAM (22 males, 6 females, mean age 66.0 ± 9.9 years) versus 17 eyes with mBRVO (9 males, 7 females, mean age 56.9 ± 10.5 years). Topographical distribution of retinal exudation on OCT retinal maps was evaluated in 7 RAM eyes (6 males, 1 female, mean age 66.0 ± 11.7 years) and 8 mBRVO eyes (5 males, 3 females, mean age 60.1 ± 19.2 years). The measures were 1) position of the point of the maximum retinal thickness in relation to the macular center and RAM, 2) difference between maximum retinal thickness in the macular center and that at the site of RAM localization (surrogate control point in mBRVO eyes). ***Results.*** Soft exudates and intraretinal fluid accumulation were mostly associated with mBRVO ($p = 0.007$ and $p < 0.001$, respectively), while hard exudates were found almost exclusively in RAM eyes ($p < 0.001$). Central retinal thickness in RAM eyes was lower than that of mBRVO eyes, 453.1 ± 148.6 μm and 797.5 ± 179.6 μm, respectively ($p = 0.001$). The point of maximum retinal thickness was found at the site of RAM localization in 8 out of 9 RAM cases (88.9%), and within the central subfield in 8 out of 8 mBRVO cases (100%). The difference between maximum retinal thickness in the macular center and at the site of RAM localization (surrogate control point in mBRVO eyes) was −77.9 ± 174.1 μm and 148.3 ± 100.4 μm for RAM and mBRVO eyes, respectively ($p < 0.001$). ***Conclusions.*** Evaluation of exudative signs and their topographic distribution based on OCT data may be used for differential diagnosis and laser treatment planning in RAM.

✧ ***Keywords:*** retinal arteriolar macroaneurysm; branch retinal vein occlusion; macular edema; optical coherence tomography.

ОПТИЧЕСКАЯ КОГЕРЕНТНАЯ ТОМОГРАФИЯ В ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКЕ РЕТИНАЛЬНЫХ МАКРОАНЕВРИЗМ

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✧ ***Цель*** — изучить частоту встречаемости и топографическое распределение экссудативных признаков ретинальных артериолярных макроаневризм (РАМ) в сравнении с окклюзиями макулярных ветвей центральной вены сетчатки (мОВЦВС). ***Материал и методы.*** Частоту ОКТ-признаков (различные виды кровоизлияний и аккумуляции жидкости, а также твёрдые и мягие экссудаты) анализировали на группе из 28 глаз с РАМ (22 мужчины, 6 женщин, средний возраст — 66,0 ± 9,9 года) и группе из 17 глаз с мОВЦВС (9 мужчин, 7 женщин, средний возраст — 56,9 ± 10,5 года). Топографическое распределение экссудативных признаков по данным оптической когерентной томографии оценивали у пациентов с РАМ (7 глаз, 6 мужчин и 1 женщина, средний возраст — 66,0 ± 11,7 года) и пациентов с мОВЦВС (8 глаз, 5 мужчин, 3 женщины, средний возраст — 60,1 ± 19,2 года): 1) положение точки максимальной толщины сетчатки относительно центра макулы и РАМ; 2) разность максимальной толщины сетчатки в центре макулы и в точке локализации РАМ (суррогатной контрольной точке у пациентов с мОВЦВС). ***Результаты.*** Мягкий экссудат и интраретинальное скопление жидкости были более типичны для мОВЦВС ($p = 0{,}007$ и $p < 0{,}001$ соответственно), в то время как твёрдый экссудат — для РАМ ($p < 0{,}001$). Толщина сетчатки в центре макулы у пациентов с РАМ была меньше, чем у пациентов с мОВЦВС, — 453,1 ± 148,6 и 797,5 ± 179,6 мкм соответственно ($p = 0{,}001$). Точка максимальной толщины сетчатки у пациентов с РАМ совпадала с локализацией РАМ в 8 из 9 случаев (88,9 %), а у пациентов с мОВЦВС с центральным подполем в 8 из 8 случаев 100 %. Разница толщины сетчатки в центре макулы и в месте локализации РАМ (или суррогатной точке для мОВЦВС) была −77,9 ± 174,1 и 148,3 ± 100,4 мкм для пациентов с РАМ и мОВЦВС соответственно ($p < 0{,}001$). ***Заключение.*** Анализ экссудативных признаков и их топографического распределения с помощью оптической когерентной томографии может быть применён для дифференциальной диагностики и планирования лазерного лечения РАМ.

✧ ***Ключевые слова:*** ретинальная артериолярная макроаневризма; окклюзия ветви центральной вены сетчатки; макулярный отёк; оптическая когерентная томография.

A retinal macroaneurysm is a local dilation of the retinal vessel with the risk of local functional decompensation of the vascular wall, manifested by exudative and/or hemorrhagic complications [1]. Several conditions are associated with the development of macroaneurysms, including occlusion of the of the central retinal vein branches (branch retinal vein occlusion, BRVO) and Coats retinitis [2, 3]. However, macroaneurysms are most often idiopathic in nature, developing in systemic arterial hypertension [4]. In the latter case, the macroaneurysm is localized at the level of the arterial link of the retinal vascular bed and is called a retinal arterial macroaneurysm (RAM) [1, 4]. The clinical significance of macroaneurysms is determined mainly by exudation, which causes an accumulation of intraretinal and subretinal fluid, and a RAM is also associated with the risk of hemorrhagic complications (preretinal, intraretinal, and subretinal hemorrhages) [5].

In a significant proportion of cases, a RAM can be diagnosed based on the ophthalmoscopic pattern as local dilation of the secondary or tertiary branch of the central retinal artery. However, fluorescein angiography (FA), which allows the visualization of macroaneurysms of any etiology and size, is the most informative method in the diagnosis of RAMs and macroaneurysms in general. Nevertheless, in the presence of hemorrhagic complications (those associated with RAMs and those with BRVO patterns for secondary macroaneurysms), ophthalmoscopic and even FA identification could be difficult. Additionally, FA involves a risk of adverse reactions and is labor intensive and time consuming [7, 8]. Under these conditions, it seems rational to withdraw from FA in favor of noninvasive diagnostic methods based on optical coherence tomography (OCT).

Another important problem associated with RAMs is their differential diagnosis with BRVO, since RAMs have a number of common symptoms associated with BRVO (retinal edema and thickening at the center of the macula, hemorrhagic manifestations, and deposition of hard exudate). This refers primarily to cases of RAMs with a hemorrhagic component covering a macroaneurysm, in which it is impossible to visualize the macroaneurysm even with the aid of FA. In contrast, the differentiation of such macroaneurysms is especially difficult in the case of macular BRVO, in which disturbances in the blood supply and associated changes (primarily edema and hemorrhage), as in the case of RAMs, are limited to the area within the vascular arcades [9, 10].

Obviously, since the sources of exudation in BRVO and RAM are completely different, the pattern of distribution of exudative changes should also vary. Although data on the topographic distribution of exudative signs could improve the diagnosis (and, probably, laser treatment planning), such data could not be found in the available literature.

Based on the data above, this study aimed to identify the characteristics of the frequency and topographic distribution of exudative signs of retinal macroaneurysms to improve their differential diagnosis with BRVO and laser treatment planning.

MATERIAL AND METHODS

This single-center, cross-sectional study enrolled patients with idiopathic symptomatic RAM. The exclusion criteria were absence of complaints of decreased vision; visual acuity ≥20/20; aneurysms located beyond the central vascular arcades; low transparency of optical media, which impedes the performance of OCT; and OCT signal strength <6/10.

At the time of inclusion, all patients underwent standard ophthalmological examination, including OCT, FA, and fundus photography. The best corrected visual acuity (BCVA) was evaluated using the Snellen chart and converted to LogMAR for analysis. FA was performed using the F-10 scanning laser ophthalmoscope (SLO) (Nidek, Japan), according to a standard procedure with the intravenous administration of 5 mL of 10% fluorescein sodium solution. Fundus photography was performed using an SLO included in the Navilas laser system.

Spectral OCT was performed using the Copernicus REVO tomograph (Optopol, Poland) or RTVue 100 (Optovue, USA). In performing OCT using Copernicus REVO, we used a 3D retinal scan (7 × 7 mm, including 163 B-scans of 320 A-scans each) located at the center of the macula and a line scan (7 mm, 50 B-scans of 1024 A-scans each) passing through the macroaneurysm. In performing OCT using RTVue 100, we used the Enhanced Macular Map 5 retina thickness map (11 horizontal and 11 vertical scans, 5 mm long; and 6 horizontal and 6 vertical scans, 3 mm long with 0.5-mm increments, with a total of 19,496 points) and obtained the background pseudo-SLO image using the protocol 3D-reference (132 B-scans with 512 A-scans each) and additionally received a structural OCT image in the projection of the macroaneurysm using the line protocol.

The frequency of OCT signs of RAM was analyzed in 28 patients, 28 eyes (22 men and 6 women, with an average age of 66.0 ± 9.9 years), using data from the RTVue 100 and Copernicus REVO tomographs. The control group included 16 patients with macular BRVO (9 men and 7 women, with an average age of 56.9 ± 10.5 years) examined using the Copernicus REVO tomograph.

In all patients, in the 3D protocols, through a revision of all the B-scans included in them, the presence of (1) preretinal hemorrhages, (2) intraretinal hemorrhages, (3) subretinal hemorrhages, (4) intraretinal cystic fluid accumulation, (5) subfoveal accumulation of fluid, and (6) hard exudate was evaluated.

The data obtained only with the Copernicus REVO tomograph were used to analyze the topographic distribution of exudative signs of RAM on OCT maps of the retinal thickness. The following aspects were evaluated in patients with RAM: (1) the position of the point of maximum retinal thickness relative to the center of the macula and RAM, and (2) the difference (magnitude) in the maximum thickness of the retina at the center of the macula and the maximum thickness of the retina at the point of RAM localization. The data of patients with RAM (7 patients, 7 eyes, 6 men, and 1 woman, with a mean age of 66.0 ± 11.7 years) were compared with the data obtained in patients with macular BRVO (8 patients, 8 eyes) of similar sex (5 men and 3 women) and age (average age of 60.1 ± 19.2 years), which were obtained using the Copernicus REVO tomograph. Macular BRVO was defined as BRVO involving the macular center, with a pronounced hemorrhagic component, but without signs of impaired blood circulation outside the vascular arcades. In patients with BRVO, the position of the point of maximum retinal thickness relative to the center of the macula was assessed, and the magnitude of the retinal thickness was determined as the difference between the maximum thickness of the retina at the center of the macula and the retinal thickness at the surrogate point of the maximum thickness of the retina at the virtual source of exudation (defined as the maximum thickness of the retina in the occlusion area at the distance of two diameters of the optic disc from the center of the macula) (Fig. 1).

The retinal thickness at the center of the macula and the maximum thickness of the retina were measured in all patients.

Moreover, the presence and distribution of solid exudate in the RAM or BRVO areas in color images were evaluated.

In the statistical analysis, the MedCalc 18.4.1 software package (MedCalc Software, Belgium) was used. The data were presented as the mean ± standard deviation. To assess the statistical significance of the differences in the frequency of exudative OCT signs between the RAM and BRVO groups, a χ^2 test was used. To assess the statistical significance of differences in the BCVA, the maximum thickness of the retina at the point of RAM localization, the maximum thickness of the retina at the center of the macula, and the magnitude of the retinal thickness in patients with RAM and BRVO, the Mann–Whitney test was used. The results were considered statistically significant at a *P*-value <0.05.

RESULTS

Twenty-eight eyes of 28 patients (22 men and 6 women, with a mean age of 66.0 ± 9.9 years) with symptomatic RAM did not show statistically sig-

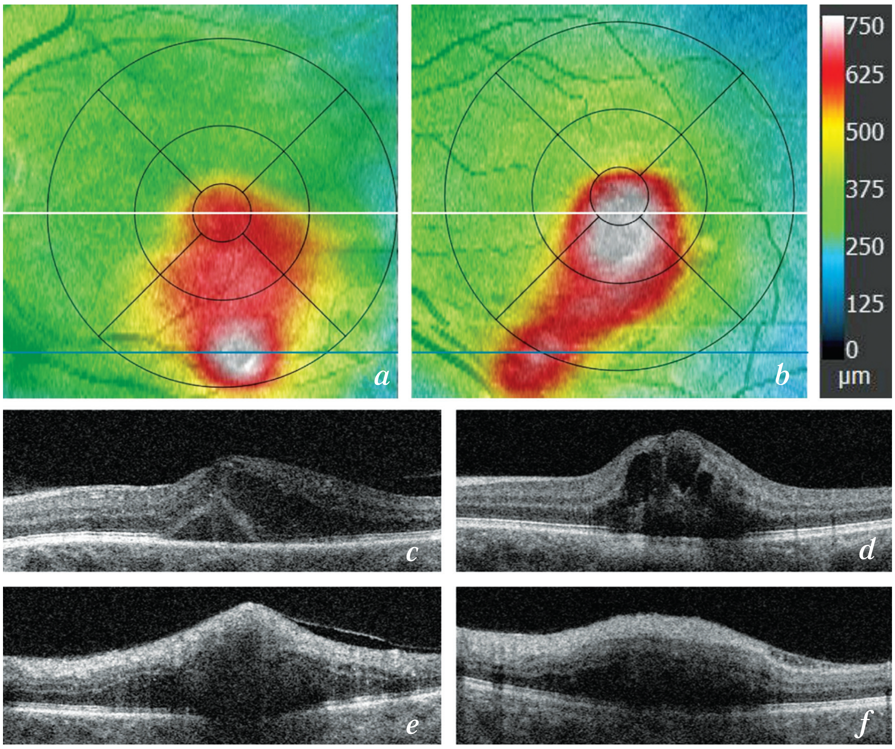

Fig. 1. Representative example of evaluation of topographical distribution of retinal exudation in patients with retinal arteriolar macroaneurysm (RAM) (*a*, *c*, *e*) and macular branch retinal vein occlusion (mBRVO) (*b*, *d*, *f*). The white and blue lines represent positions of OCT cross-sectional scans crossing the macular center (*c*, *d*) and the RAM (*e*) or the surrogate control point in mBRVO eye (*f*)

Рис. 1. Репрезентативный пример оценки топографического распределения экссудативных изменений сетчатки у пациентов с ретинальной артериальной макроаневризмой (*a*, *c*, *e*) и макулярной окклюзией ветвей центральной вены сетчатки (*b*, *d*, *f*). Белая линия отражает положение ОКТ-скана через центр макулы (*c* и *d*), синяя линия — положение скана через ретинальную артериальную макроаневризму (*e*) и репрезентативную зону у пациента с окклюзией ветвей центральной вены сетчатки (*f*)

nificant differences in visual acuity compared with 17 eyes of 16 patients (9 men and 7 women, with an average age of 56.9 ± 10.5 years) with BRVOs of 0.6 ± 0.27 LogMAR (average 0.3 according to the Snellen chart) and 0.43 ± 0.32 LogMAR (average 0.45 according to the Snellen chart), respectively ($p = 0.18$). The analysis of the frequency of OCT signs of macroaneurysms is presented in Table 1.

The retinal thickness at the center of the macula in patients with RAM was significantly less than that in patients with BRVO (453.1 ± 148.6 and 797.5 ± 179.6 μm, respectively; $p = 0.001$) (Fig. 2).

The retinal thickness at the RAM localization and surrogate points in patients with BRVO did not have significant differences (542.1 ± 121.7 and 649.3 ± 136.8 μm, respectively; $p = 0.15$).

The point of maximum retinal thickness in patients with RAM coincided with the localization of RAM in 8 of 9 cases (88.9%). In one case of parafoveal localization of RAM, the point of maximum thickness coincided with the center of the macula. In all patients with BRVO (8 eyes, 100%), the point of maximum retinal thickness was localized within the central subfield of the Early Treatment Diabetic Retinopathy Study map ($p < 0.001$ compared to the frequency of localization of the point of maximum retinal thickness at the center of the macula in patients with RAM).

The magnitude of the retinal thickness at the center of the macula and in RAM localization in patients with RAM was significantly different from the magnitude of the maximum thickness of the retina at the center of the macula and the surrogate point in patients with BRVO (−77.9 ± 174.1 and 148.3 ± 100.4 μm, respectively; $p < 0.001$) (Fig. 3).

In 7 of 9 patients (78%), a hard exudate was observed, located perifocally to the macroaneurysm (Fig. 4).

DISCUSSION

RAM must be differentiated from a large number of hereditary and acquired conditions, which may have similar ophthalmoscopic and FA manifestations,

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Table 1 / Таблица

Distribution of optical coherence tomography findings in eyes with retinal arteriolar macroaneurysms and macular branch retinal vein occlusions
Распределение признаков, обнаруженных на изображениях оптической когерентной томографии, в группах глаз с ретинальными артериолярными макроаневризмами и макулярными окклюзиями ветвей центральной вены сетчатки

Features	РАМ (n = 28) RAM (n = 28)	ОВЦВС (n = 16) BRVO (n = 16)	p
Преретинальное кровоизлияние Preretinal hemorrhage	2 (7 %)	0 (0 %)	0,52
Интраретинальное кровоизлияние Intraretinal hemorrhage	25 (89 %)	15 (94 %)	0,28
Субретинальное кровоизлияние Subretinal hemorrhage	3 (11 %)	0 (0 %)	0,28
Интраретинальное скопление жидкости Intraretinal cystic fluid	18 (64 %)	16 (100 %)	0,007
Субретинальное скопление жидкости Subretinal fluid	12 (43 %)	9 (56 %)	0,53
Твёрдый экссудат Hard exudates	22 (79 %)	2 (13 %)	< 0,001
Мягкий экссудат Soft exudates	0 (0 %)	13 (81 %)	< 0,001

Примечание. РАМ — ретинальная артериальная макроаневризма; ОВЦВС — окклюзия ветвей центральной вены сетчатки.
Note: RAM, retinal arterial macroaneurysm; BRVO, occlusion of the central retinal vein branches

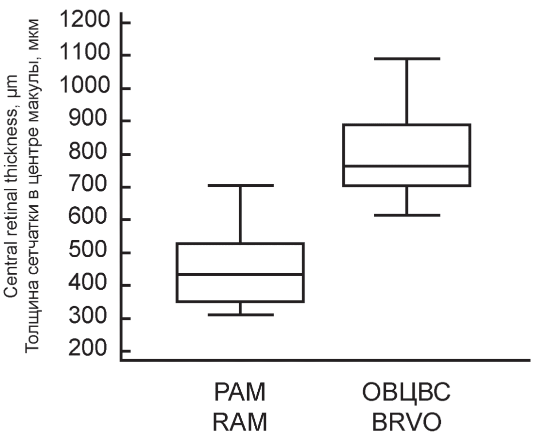

Fig. 2. Box-and-whiskers plot showing central retinal thickness in eyes with retinal arteriolar macroaneurysms and macular branch retinal vein occlusions: RAM — retinal arteriolar macroaneurysm; BRVO — branch retinal vein occlusion

Рис. 2. Толщина сетчатки в центре макулы у пациентов с ретинальными артериолярными макроаневризмами и макулярными окклюзиями ветвей центральной вены сетчатки: РАМ — ретинальная артериальная макроаневризма; ОВЦВС — окклюзия ветвей центральной вены сетчатки

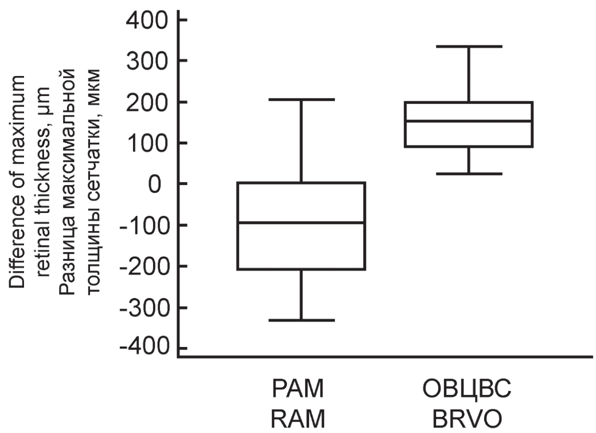

Fig. 3. Box-and-whiskers plot showing difference of maximum retinal thickness in the macular center and control point in eyes with retinal arteriolar macroaneurysms and macular branch retinal vein occlusions : RAM — retinal arteriolar macroaneurysm; BRVO — branch retinal vein occlusion

Рис. 3. Разница толщины сетчатки в центре макулы и суррогатной контрольной точке у пациентов с ретинальными артериолярными макроаневризмами и макулярными окклюзиями ветвей центральной вены сетчатки: РАМ — ретинальная артериальная макроаневризма; ОВЦВС — окклюзия ветвей центральной вены сетчатки

due to both the clinical presentation of the disease and secondary aneurysm complications. Thus, aneurysms can be secondary to BRVO [2], diabetic retinopathy [11], radiation retinopathy, and idiopathic retinovasculitis (arteritis) [12]. Angiomatous processes, namely, Coats retinitis [3], Hippel–Lindau disease [13], and other retinal capillary angiomas, can also resemble RAM. Moreover, pronounced

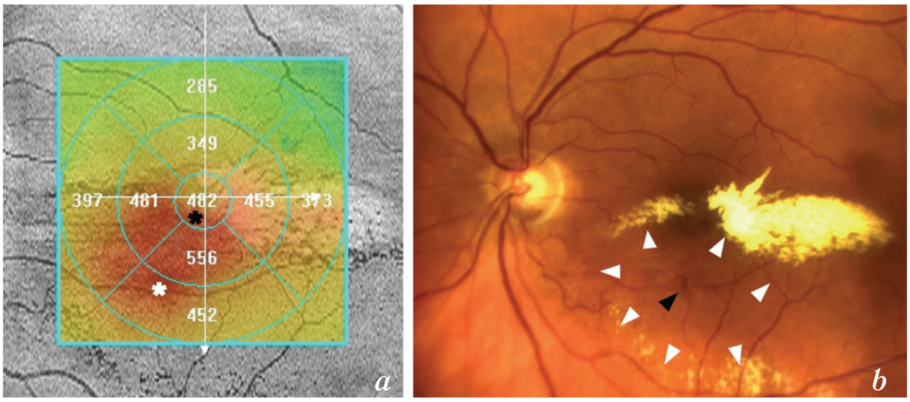

Fig. 4. Topographical distribution of retinal exudative findings in the left eye of the patient with a retinal arteriolar macroaneurysm (RAM). Retinal thickness map demonstrates an increase in retinal thickness from the macular center toward the microaneurysm. Maximum retinal thickness within central subfield (*black asterisk*) is of 450 µm and maximum retinal thickness at the RAM site (*white asterisk*) is of 525 µm. Color fundus photograph demonstrates centrifugal (from RAM (*black arrowhead*)) distribution of hard exudates (*white arrowheads*)

Рис. 4. Топографическое распределение экссудативных признаков у пациента с ретинальной артериальной макроаневризмой. Карта толщины сетчатки (*a*) демонстрирует увеличение толщины сетчатки по направлению от центра макулы к ретинальной артериальной макроаневризме, максимальная толщина сетчатки (*чёрная звездочка*) в пределах центральной подзоны — 450 мкм, максимальная толщина сетчатки в области ретинальной артериальной макроаневризмы (*белая звёздочка*) — 525 мкм. Цветная фотография глазного дна демонстрирует перифокальное по отношению к ретинальной артериальной макроаневризме (*чёрная стрелка*) распределение твёрдого экссудата (*белые стрелки*) (*b*)

exudation associated with RAM can be interpreted as diabetic macular edema or edema associated with BRVO, and subretinal and preretinal hemorrhages in the macula, typical of RAM, can be age-related macular degeneration manifestations.

It is the differential diagnosis between RAM and BRVO that is potentially of the outmost clinical interest and causes the greatest difficulties. First, the spectrum of ophthalmoscopic and FA manifestations in RAM and BRVO is almost similar, especially in cases of macular BRVO, and each of these conditions may be secondary to the other. Second, the diagnosis of diabetic retinopathy can be established easily based on bilaterality and local prevalence of changes on the fundus, and thus can be ruled out. Finally, the prevalence of angiomatous conditions is significantly less than that of venous occlusions [14], and they usually do not have hemorrhagic complications.

Our study showed that the pattern of the distribution of exudative signs in RAM and macular BRVO is significantly different, and this can be useful in clinical practice, as, in some cases, when deciding whether macular edema was caused by RAM or BRVO (primarily the macular form), significant difficulties arise. This relates primarily to cases when the direct visualization of RAM is difficult or impossible. It is easy to rule out RAM as the cause of edema in patients with diabetic maculopathy, which is primarily due to the identification of common signs of diabetic retinopathy. Furthermore, the pattern of diabetic macular edema itself has characteristic differences, which, even when localized, has no connection with any separate vascular branch, especially the arcade, as is found in patients with BRVO and RAM. With BRVO, especially macular, similar to RAM, the sharply asymmetric pattern of edema shows a connection with one vascular arcade or branch, as it is caused by local vascular dysfunction, and therefore additional signs may also be useful in the diagnosis and treatment planning (primarily laser) of RAM. In this study, we identified several OCT signs of exudation, typical mainly for RAM. First, the point of maximum thickness of the retina in RAM tends to have an eccentric arrangement and coincides with the RAM localization area. Second, the retinal thickness at the center of the macula is not maximal with respect to the rest of the edema area. Another sign is the perifocal distribution of the hard exudate. We suggest that all these signs are due to the presence of a virtually point source of sufficiently intense exudation in RAM, while in BRVO, although the exudation is limited to the occlusion area, it is relatively diffuse in nature and localized mainly in the area of the terminal parafoveal vessels.

Despite the fact that the visual acuity in these two cohorts did not differ significantly, the retina at the center of the macula in patients with RAM was still significantly thinner. This can be explained by a less pronounced tendency of accumulation of intraretinal fluid in patients with RAM and a more pronounced tendency of accumulation of subretinal fluid in patients with macular BRVO. Although these signs are relative, they can also help establishing an initial diagnosis in complicated cases. In such case, attention should be paid to preretinal and subretinal hemorrhages, which are not observed in patients with BRVO, but are found in several patients with RAM. Mild exudates were one of the most reliable signs of BRVO, which are not found in RAM. This seems natural, because if the aneurysm was not a consequence of occlusion and did not lead to it, there should be no ischemic changes in the retina. In contrast, the signs of prolonged intense exudation, hard exudates, are more typical for RAM.

The significance of the application of the OCT differentiation algorithm in RAM and BRVO lies in not only the differential diagnosis between RAM and macular BRVO, which have similar ophthalmoscopic presentation, but also the identification of secondary macroaneurysms (possibly, large microaneurysms) if combined with BRVO. This will also reduce the need for FA in this cohort of patients and aid in planning navigational laser coagulation, which has been shown to be effective [15]. In this case, the target of laser coagulation may be an eccentric peak of thickening of the retina, presumably hiding macroaneurysms. All these patterns can be extrapolated to microaneurysms in diabetic retinopathy if diffuse exudation is absent or poorly expressed. There should, indeed, be no significant difference in the pattern of the distribution of exudative signs between one macroaneurysm and a group of microaneurysms localized in a limited area and a single relatively large microaneurysm.

CONCLUSION

In the present study, we revealed special aspects of the topographic distribution of exudative signs of RAM, in particular, the eccentricity of thickening of the retina with a peak in the RAM region and the distribution of the hard exudate that is perifocal with respect to RAM. Moreover, the presence of the hard exudate and the absence of soft exudates or a slight accumulation of intraretinal fluid indicate the presence of a macroaneurysm compared with macular BRVO. These signs not only contribute to the improvement of the differential diagnosis between RAM and macular BRVO but could also form the basis for laser treatment planning when the RAM cannot be visualized directly.

Conflict of interest

The authors declare no conflict of interest or material interest in this study.

Contribution of authors

D.S. Maltsev and *A.N. Kulikov* provided the study concept and design.

D.S. Maltsev, *A.A. Kazak*, and *M.A. Burnasheva* collected and processed the data.

D.S. Maltsev, *A.A. Kazak*, and *M.A. Burnasheva* wrote the manuscript.

A.N. Kulikov edited the manuscript.

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