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Identification of Diabetic Macular Oedema Patients and Compilation of an Algorithm for Differential Treatment with Brolucizumab

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Abstract: Among the generally recognised methods of diabetic macular oedema (DMO) diagnosis, optical coherence tomography (OCT) is the most sensitive one, which provides reliable, reproducible, objective retinal images, replacing subjective assessments, and is considered as a kind of lifetime retinal biopsy. In contrast to the applied clinical studies, OCT allows to detect structural changes of the retina at early stages of AMD, during laser treatment, to quantify them with the lowest variability of parameters, to identify retinal layers with high resolution.

Keywords: diabetic macular oedema, brolucizumab, optical coherence tomography.

The aim of the study was to develop a method of early detection and differential diagnostics of macular oedema type in patients with DMO.

Introduction. A method based on optical coherence tomography (OCT) data is proposed, which allows diagnosing the presence and type of diabetic macular edema according to the following scale: 18.0-19.5 - focal oedema, 19.6-21.1 - diffuse oedema; and 21.2 and above - cystic macular oedema.

Keywords: diabetic macular oedema, optical coherence tomography, diagnosis.

Introduction. The coincidence of histological and reti-notomographic pictures of retinal damage has been established, which allows us to consider OCT as an adequate lifetime method of retinal examination, including in the early stages of the disease [3].

There are a number of ways to diagnose AMD using OCT. There is a known method of macular edema diagnosis by scanning the retina using the grid 5 method of MG5 sample, which minimises the gaps between scans quite uniformly within 5 mm from the centre of the retina compared to standard OCT (Stratus OCT) [7]. The method is based on comparing normative retinal thickness maps and areas of abnormal retinal thickness in the macula exceeding two standard deviations to identify suspected areas of retinal oedema, which will allow identification of clinically significant macular oedema with appropriate software. Its disadvantage for mass use is the need for significant financial and material resources to purchase the appropriate hardware and software.

Another method of diagnosing changes in the central retinal thickness uses logarithmic transformations of OCT data rather than absolute values and takes into account the baseline thickness and similar parameters of normal eyes [6]. The disadvantage of the method is that only the parameters of the central zone are taken into account, without taking into account other zones of the MO. The method of early diagnosis of macular edema in DR deserves attention, in which after OCT the foveolar thickening coefficient is additionally calculated by means of the ratio of foveo-lar thickness and maximum fovea thickness, and if the coefficient is more than 0.8, the preclinical stage of macular edema development is judged [2].

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A negative point in its use at present is the lack of characterisation of subclinical forms of edema by OCT and treatment tactics in these lesions. In addition, thickness measurements within small central areas do not detect types of DMO in which retinal edema does not involve the centre of the macula.

Thus, there remains a need for improved methods and tools to detect and diagnose macular oedema.

Material and methods of research: A total of 184 eyes of 92 healthy individuals with no history of DM and no ophthalmopathology, used as a normative base, and 184 eyes of 109 DM patients with nonproliferative DR diagnosed with DMO were studied by random sampling method. Since the mean macular retinal thickness and volume in right and left eyes showed statistically significant correlation ($r=94$, $p<0.01$) any eye of the study subjects was randomly selected for further analysis. All groups were commensurate in terms of age and sex, $p>0.05$.

To include patients in the study, the following were determined: diagnostic selection criteria, similarity of groups by the most significant parameters, exclusion criteria, number of patients and eyes. Exclusion criteria were previous laser treatment, presence of other vascular eye diseases, uncontrolled AH (systolic BP>165 mm Hg, diastolic BP>90 mm Hg), intravitreal injections of vascular endothelial growth factor inhibitors in anamnesis.

All patients underwent a comprehensive ophthalmological examination: visometry, non-contact tonometry, retinal biomicroscopy using Goldmann and Meinster fundus lenses, colour stereophotography of the ocular fundus, fluorescence angiography (FAG) of the retina and OCT of the macular area. The presence of DMO was confirmed by retinal biomicroscopy, FAG and OCT.

FAG was performed using a fundus camera F450 (Carl Zeiss Meditec, AG, Germany). OCT was performed on a Stratus OCT 3000 (Carl Zeiss Meditec, Dublin, CA, USA) using the 'Fast Macular Thickness Map' scanning protocol. The obtained results were entered into a computer database. To analyse retinal thickness, the foveolar zone with a radius of 0.5 mm and two concentric zones were identified: the parafoveolar zone with a radius of 1.5 mm and the perifoveolar zone with a radius of 3 mm.

The thickness of the macular area (MO) in microns (μm) and the volume in mm3 were displayed using the software. Statistical processing was performed on the data obtained from the study using STATISTICA version 6.1 (StatSoft) analysis. The results are presented as mean (M) ± standard deviation (SD). The Spear-man correlation coefficient (rs), analysis of variance (ANOVA), regression analysis were used to determine the relationship between the indices, the coefficient of variation was used to determine the relative variability of the indices, and the multiple determination coefficient (R2) was used to determine the degree of influence of the considered factors on the treatment outcome [1, 5]. The probability of error-free prognosis equal to 95% ($p<0.05$) was taken as the critical level of significance for testing statistical hypotheses in this study.

Results and Discussion: The role of different sectors (separate zones) of the macula in the formation of DME and, accordingly, the influence on visual acuity is different. In this connection, the variables of the total variance caused by different factors (mean thickness of the foveolar, para- and perifoveolar zones of the macula) were identified by the method of principal component factor analysis.

By means of multiple regression, a multiple correlation coefficient ($R=0.98$; $p<0.001$) was determined, which indicates a strong relationship between the thickness of the foveolar, para- and perifoveolar retinal zones with the total macular thickness and is a high estimate of prediction quality. This is confirmed by the coefficient of determination ($R2=0.95$) as an indicator of the degree of model fit to the data and explaining almost all the variability in the variables (95% of retinal area thickness) [5].

The estimation of the variance of individual components was used to determine their share in the total variance. The obtained relative values of the variance components as a percentage of the total variance indicate the leading role of the foveal thickness in forming the of the foveolar zone thickness, which explains 70.9% of the total variance. Significantly lower significance of other variables: parafoveolar

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(18.0%) and perifoveolar (6.1%) thickness. The presented variables explain 95% of the variability of DMO thickness and only 5% are unaccounted factors [5, p. 295].

Taking into account the degree of influence of each component on the final index, their ranking was performed: Rf=12.0; Rv=3.0; Rn=1.0 (Rf, Rv, Rn - rank of the foveolar, para- and perifoveolar zones of the macula, respectively).

Having the normal parameters of retinal zones in healthy individuals based on our large-scale study [12] and having measured the thickness of the foveolar (F), parafoveolar (Pf) and perifoveolar (Pn) zones of the macula, we calculate the thickness proportionality coefficients Kf, Kv and Kn for each zone of the macular retina by correlating the corresponding values in diabetic patients and healthy individuals: Kf=F:193, Kv=B:266, and Kn=H:234.

The final severity index (It) of macular oedema is equal to the sum of products of thickness proportionality coefficients by their rank. The mathematical model of calculation can be presented in the form of formula 1:

It = (KfhRf) + (KvhRv) + (KnhRn)

(1),where It is the macular oedema severity index; Kf is the coefficient of proportionality of the foveolar zone thickness; Kv is the coefficient of proportionality of the macula parafoveolar zone thickness; Kn is the coefficient of proportionality of the macula perifoveolar zone thickness; Rf, Rv, Rn are the rank of the corresponding zones.

Substituting the values of average thickness of foveolar, para- and perifoveolar zones of the macula of a healthy eye and rank places of the corresponding zones, we obtain formula 2:

It=(F:193)x12 + (B:266)x3 + (H:234)x1(2)

where F is the thickness of the foveolar zone (μm), B is the thickness of the parafoveolar zone of the macula (μm), H is the thickness of the perifoveolar zone of the macula (μm).

If the It value is within 18.0-19.5, focal oedema is diagnosed, within 19.6-21.1 - diffuse oedema, with the value of 21.2 and higher - cystic oedema of the macula.

Here is a concrete example confirming the possibility of using the developed method.

Example. Patient P., born in 1956, has been suffering from type 2 diabetes for 14 years. He came to the ophthalmological centre with complaints of blurred images of objects for the last three months. Objectively: visual acuity OD=0.7. The retina was examined using OCT. The retinal thickness in the foveolar zone was 260 μm, in the parafoveolar zone - 303 μm and in the perifoveolar zone - 262 μm.

It = (260:193*)x12 + (303:266*)x3 + (262:234*)x1 = 6.2+3.4+1.1 = 20.7

The diagnosis was diffuse DMO, which was confirmed by retinal biomicroscopy.

To evaluate the diagnostic method and to accept it for practical application in clinical conditions, its approbation was carried out. A blinded study, in which the personnel performing DMO diagnosis was shielded from information about the presence or absence of DR in the patient, as well as independent of the results of other diagnostic methods. Consistency between clinicians was achieved to harmonise the interpretation of clinical test results using different retinal examination methods. Macular oedema was classified as focal, meaning clinically significant macular oedema (CSMO), which is defined as retinal oedema involving or threatening the centre of the macula even without a reduction in OD. Diffuse macular edema was diagnosed when retinal edema with an area of 2 or more optic disc diameters with involvement of the foveolar zone.

The results of retinal biomicroscopy with retinal lenses as the most common universal diagnostic method used in clinical practice were used as a control test, with which the tested method was compared when assessing the diagnosis of AMD according to the proposed method. The ‘blind’ method was used in the evaluation of the results regardless of the presence or absence of the disease, as well as in the interpretation of the results of the control and test methods.

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OCT method as the most universal diagnostic test in detecting diabetic retinal lesions was taken as a reference. The results of biomicroscopy and our developed method of DMO diagnostics were evaluated in relation to it. The used methods of DMO diagnostics have errors to some extent. For this reason, a number of indicators were calculated to determine the diagnostic accuracy of the method [1]. The proposed method showed an optimal balance of sensitivity (98%) and specificity (93%), which is statistically significantly ($p=0.04$) higher compared to the results of biomicroscopy (86% and 84%, respectively). The advantage of the developed method is confirmed by another characteristic - diagnostic accuracy (efficiency), which depends on the prevalence of the disease. In general, the diagnostic accuracy of the developed method is 93.7% versus 84.1%, according to retinal biomicroscopy through retinal lenses ($p<0.001$).

The predictive value of the positive result, reflecting the percentage of detected patients who really suffer from a particular pathology, is of great importance for the detection of the disease. This indicator is 21.8% higher ($p<0.001$) in the tested method relative to the traditional one. The result of the new method is a positive likelihood ratio, combining sensitivity and specificity in a single number, equal to 13.8 and indicating that a positive result is 13.8 times more likely for patients suffering from DMO than in its absence. The similar figure in the control group (5.3) is 2.6 times lower ($p=0.001$). Finally, the odds ratio that the disease will be diagnosed by the proposed method is 17.2 times higher than the alternative method ($p<0.001$).

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