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Prevention and Treatment of Age-Related Macular Degeneration Against Peripheral Uveitis

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Abstract: A series of experiments was performed on 50 sexually mature male rats of the line with an initial body weight of 200-250 g. In animals of the 1st group (n = 25), the pathological process was induced by intravitreal injection of functionally active blood mononuclear cells. The obtained material was fixed for light microscopy. All studies during the experiments and the collection of material were carried out at the same time of day - from 12.00 to 15.00. Experimental modeling of the mechanism of intraocular proliferation in vitro. Methods of cell cultivation in vitro are currently increasingly used to study the biological and structural features of cells that form periretinal proliferative membranes.

Keywords: age-related macular degeneration, human mononuclear cells, age-related macular degeneration, peripheral uveitis.

Introduction. Age-related macular degeneration (AMD) is one of the leading causes of blindness in people over 60 years of age and is the leading cause of central vision loss in developed countries. In recent years, this disease has been diagnosed not only in the elderly, but also in relatively young people, leading to primary thalamic degeneration in 11% of cases in people of working age and in 28% of cases in the elderly. In European countries, AMD is one of the most common eye diseases among the elderly population - from 20 to 40% of the population of Great Britain and Finland aged 50 years and older suffer from this disease. In Russia, the incidence of AMD is more than 15 people per 1000 population. Since the clinical picture and course of the disease are very diverse, the issues of the etiology and pathogenesis of AMD have been the subject of discussions among domestic and foreign scientists for many years (Sdobnikova S.B., 2008; Khoroshilova-Maslova I.P. et al., 2010;Campochiaro P.A., 2007; Dunker S. et al., 2009; Harbour J.W. et al., 2008;Limb G.A. et al., 2010). Experimental and clinical studies indicate the importance of local changes in homeostasis with the development ofmetabolic acidosis caused by the activation of free-radical processe sand intensification of lipid peroxidation (Evgrafov V.Yu., 2010; Etherington D., 2009). Metabolic products, accumulating in tissues, have a damaging effect on the cells of the chorioretinal structures (Travkin A.G., 2011; Griersonl., 2011; Yuetepi.M., 2010). A significant role in the pathogenesis of dystrophic changes in the retina is given to atherosclerosis. Many patients with AMD have biochemical abnormalities characteristic of atherosclerosis: hypercholesterolemia, elevated levels of p-lipoproteins, abnormal lecithin-cholesterol index (Shilkin S.V., 1979; Shlopak T.V., 1982). According to T.N. Selitskaya (1985), the damage to the fibro-elastic tissues of the eye and Bruch's membrane in AMD is identical to the nature of the damage to the muscular-elastic arteries in atherosclerosis. According to some researchers, AMD is a genetically determined disease with an autosomal dominant type of inheritance (Meyers S.M., 2005; Seddon J.M., 2009; Silvestri G., 2008). A significant role in the development of pathological changes in the macular region is attributed to biologically active substances (growth factors) that stimulate cell migration, their adhesion and proliferation, the production of other growth activators, as well as neovasculogenesis (Campochiaro P.A., 2009; Folkman J. et al., 2011; Forrester J.V. et al., 2009; Sebag J. et al., 2009; Vinores S.A. et al., 2011; Yamamoto S. et al., 2010). In the literature of recent years, more and more attention has been paid to the role of chronic inflammation (Chen M., Xu H., 2012, Parmeggiani F. et al., 2012). In particular, the immune system plays a central role in the pathogenesis and progression of both forms of AMD. The main genetic polymorphisms associated with the risk of developing and progressing AMD are found in

genes that regulate inflammation, especially in the gene of complement factor H (locus lq32) (Seddon J.M. et al., 2006), as well as in the locus 10q26 (Boyko E.V. et al., 2013). Thus, scientific studies of the pathogenesis of AMD at the present stage are distinguished by the lack of a systematic approach to the study of the phenomena underlying the development of pathological changes in the posterior part of the eyeball. All of the above creates the prerequisites for formulating a number of research tasks aimed at a more in-depth study of the cellular mechanisms of the development and progression of AMD, as well as at creating a comprehensive treatment and prevention regimen for the disease. The aim of the study is to study, on the basis of comprehensive research, the clinical and pathogenetic patterns of development and progression of age-related macular degeneration against the background of peripheral uveitis and to develop principles for their correction.

MATERIAL AND METHODS OF EXPERIMENTAL RESEARCH

Experimental modeling of the inflammatory-reparative process in the posterior segment of the eye. Two types of autologous blood mononuclear cells were used in the experiment: freshly isolated cells and cells cultured under hypothermia. In the first case, we studied the secretory function of autologous blood mononuclear cells, necessary for the development of intraocular connective tissue, in the second case, the cells were studied as a source of biologically active substances provoking the development of a reaction similar to inflammation. A series of experiments was performed on 50 sexually mature male rats of the line with an initial body weight of 200-250 g. In animals of the 1st group (n = 25), the pathological process was induced by intravitreal injection of functionally active blood mononuclear cells. Under ether anesthesia, each animal received intravitreal injections: 0.05 ml of isotonic sodium chloride solution containing mononuclear cells at a rate of 3.0 • 10^mm^ was injected into one eye through the flat part of the ciliary body, 0.05 ml of isotonic sodium chloride solution was injected into the second eye for control. Mononuclear cells taken from the blood of the experimental animal were isolated using a ficoll-verografin gradient. In animals of the 2nd group (n = 25), the pathological process was induced by intravital introduction of blood mononuclear cells, cultured under hypothermia at a temperature of 0-1 "C for 24 hours, into the vitreous body. After maintaining the mononuclear suspension under hypothermia, the viability was 49%. During the experiments, indirect ophthalmoscopy was performed with a Heine Omega 180 binocular head ophthalmoscope on the 3rd, 7th, 14th and 21st days after injection under drug-induced mydriasis (instillation of Solutio Tropicamidi 1%). After each ophthalmoscopy, 5 animals from the experimental groups were decanted under deep ether anesthesia. The experimental animals were slaughtered in compliance with the rules and regulations, prescribed in the European Community directives (86/609 EEC) and the Declaration of Helsinki. Enucleation of both eyes was performed.

The obtained material was fixed for light microscopy. All studies during the experiments and the collection of material were carried out at the same time of day - from 12.00 to 15.00. Experimental modeling of the mechanism of intraocular proliferation in vitro. Methods of cell cultivation in vitro are currently increasingly used to study the biological and structural features of cells that form periretinal proliferative membranes. The device is a closed system with a chamber containing a semipermeable filter. The system was pre-filled with a nutrient medium containing 200.0 ml of RPMI 1640 nutrient medium and a 4% solution of gentamicin. A series of experiments on culturing cells of the mononuclear population under various conditions were performed. The object of the study was mononuclear cells from the blood of healthy volunteer donors, isolated by the fractionation method on a ficoll-verografin density gradient. The obtained cells were brought to a final concentration of 12 3-10® mononuclear cells/ml with a nutrient medium, introduced into the chamber using a syringe and placed on the filter. After turning on the roller pump, a uniform directed movement of the nutrient medium at a speed of 2.1 2.4 mm^/min was created in the system. The primary culture of blood mononuclear cells was incubated for 24-48 hours with constant movement of the liquid nutrient medium, observing the cultivation conditions. As a control, the studied cells were cultured on a semipermeable filter placed in a 35-mm Petri dish with the required nutrient medium with strict adherence to the temperature regime (37 °C), CO2 content (5-7%) and humidity level (100%). At the end of cultivation, the filters were removed from the system and dried in air. The cellular material on

the filter was fixed in formalin vapor for 30 s and examined using cytochemical methods. Viewing and photographing the results of staining on transparent substrates were carried out at the morphologist's workplace, which included an IBM PC Pentium, an Epson digital camera, and a Karl Zeiss-Yena microscope. Optical microscopy of opaque objects was performed in reflected light on a metallographic microscope Olympus GX-71 at a magnification of 400. The number, area of stained cells and their optical density were determined by computer morphometry of digital images using the PhotoShop 6.0 program. Under ether anesthesia, each animal first underwent photocalibrometry of the vessels of the bulbar conjunctiva and retina of both eyes, recording their initial state. Then, the left common carotid artery was isolated and a catheter was inserted into its distal section, and a ligature was applied to the proximal section. After the blood flow through the main vessel ceased, photocalibrometry of the vessels of the bulbar conjunctiva and retina of both eyes was repeated, recording the reaction of the vessels of the microcirculatory bed of various parts of the eyeball to acute obstruction of the main main artery. At the next stage of the experiment, the ligature was removed from the proximal section of the carotid artery of the animal and the blood was drained into a separate container until the heart stopped completely, after which photocalibrometry of the vessels of the bulbar conjunctiva and the retina of both eyes was again performed, recording the reaction of the vessels of the microcirculatory bed of the eyeball to complete blood loss. At the end of the experiment, the vascular bed of the eyeball was filled with ink under a pressure of 100 mm Hg and photocalibrometry of the vessels of the anterior and posterior segments of the eyeball was repeated. Photoregistration of the vessels of the anterior segment of the eye was performed using a digital camera for a DCM 130 microscope (1.3M pixels, USB2.0). An indirect binocular ophthalmoscope Omega 2c (Heine) with an analog video camera was used to photograph the vessels of the retina. The images were processed using a digital video camera "SONY Handycam" DCR-HC-42E. In the 2nd series of experimental studies, in order to study the structural and functional features of the vessels of the microcirculatory bed of the anterior segment of the eyes of rabbits, vasotonometry was carried out in combination with photocalibrometry. Vasotonometry was carried out using a device whose operation is based on the Seidel effect. The vasotonometer was installed on the studied vessel, its initial state was photographically recorded, and then photography was taken after the vessel was exsanguinated or pulsation disappeared when it was compressed. Photographing of the vessels of the eyeball was performed using a digital camera for a DCM 130 microscope. The results of vasotonometry were converted into mm Hg according to special calculation tables. All studies during the experiments were carried out at the same time of day - from 15.00 to 17.00. The slaughter of experimental animals was carried out in compliance with the rules and regulations prescribed in the directives of the European Community (86/609 EEC) and the Declaration of Helsinki.

The clinical section of the research work was carried out at the base of the ophthalmology department of the Samarkand Medical University. The study involved 171 patients (69 men and 102 women) (195 eyes) with various types of exudative macular degeneration. The patients were divided into four groups: 1a - the main group and 16 - the comparison group with a diagnosis of "wet" AMD (90 people); 2a -the main group and 26 - the comparison group with exudative macular edema(82 people). The inclusion criteria for the 1a main group and 16 comparison group at stage of the study were: age over 45 years, "wet" AMD, a history of complaints at a young age of periodic redness of the eyes, blurred vision, a feeling of seeing as if "through water". The exclusion criteria were: the presence of severe concomitant somatic and ophthalmological pathology. At the second stage of the study, 2 a main group and 26 comparison group were formed, where the inclusion criteria were: age from 18 to 45 years, the presence of edematous maculopathy against the background of peripheral uveitis. The exclusion criteria were the presence of high degrees of refractive errors.

Conclusions

1. In an in vivo experiment, it was established that intravitreal administration of autologous blood mononuclear cells induces the development of periretinal proliferation, the severity of which depends on the morphofunctional activity of the cells of this population. Functionally active mononuclear cells cause the development of pronounced destructive proliferative changes in the

posterior pole of the eyeball. Mononuclear cells inactivated under hypothermia initiate the proliferative process in the cavity of the eyeball.

2. An in vitro experiment has shown that when culturing human mononuclear cells under conditions of directed movement of the nutrient medium, similar to the movement of fluid in the cavity of the eyeball, there is a significant increase in their enzymatic activity and acceleration of the processes of maturation and differentiation into mature forms.
3. An in vivo experiment has shown that the constancy of transmural pressure in the vessels of the microcirculatory bed of the tissues of the eyeball is ensured by myogenic autoregulation of blood flow. Under conditions of chronic inflammation, due to a violation of this mechanism, an increase in transmural pressure and the development of edema in the central parts of the fundus are noted.
4. During clinical studies, the main clinical and morphological forms of chronic peripheral uveitis in patients with age-related macular degeneration were identified and characterized in detail.
5. Application of a new combine reatment of the "wet" form of age-related macular degeneration provides a significantly faster - 1.5 times - primary anatomical topographic reattachment of the retina in the macular region. At the same time, the period of restoration of the normal thickness of the retinal tissue in the central sections of the fundus is reduced by 1.6 times.
6. Combined transscleral cryocirclage of the peripheral parts of the retina and intravitreal injection of Lucentis in the treatment of the "wet" form of age-related macular degeneration promotes a significant (up to 10 times) and stable improvement in visual acuity, as well as a more significant (3 times) reduction in the area of the central scotoma in the postoperative period compared to the traditional administration of angiogenesis inhibitors.
7. The use of laser coagulation of the outer parts of the retina in the complex treatment of macular edema against the background of peripheral uveitis significantly (2 times) accelerates the resorption of retinal tissue edema in the central parts of the fundus, ensuring a 1.5-fold acceleration of the restoration of the normal thickness of the retina in the macular region.
8. Complex treatment of macular edema against the background of peripheral uveitis with laser coagulation of the retina near the ora serrata provides a significant (2.85 times) and stable improvement in visual functions in comparison with traditional pharmacotherapy.

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