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Literature Review

Pathogenetic Features of the Development of Retinal Dystrophic Processes in Myopia Accompanying Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD), causing a progressive decrease in vision, can lead to blindness mostly in elderly people. In recent years, there has been a tendency to "rejuvenate" AMD, as well as various refractive errors. According to statistics, myopia affects from 28.4% to 35% of the world's population. Complicated myopia is a medical and social problem, which is associated with a high frequency of its occurrence in the population, the development of irreversible changes of the fundus and a significant decrease in vision in young and working age. Estimation of the stage and evolution of AMD, developing in eyes with moderate to high myopia is often difficult due to changes in the fundus. The article highlights the contemporary aspects of the etiology and pathogenesis of the development of degenerative processes of the retina in both diseases. Particular attention is paid to the features of the formation of choroidal neovascularization (CNV) in the case of both pathologies.

Keywords: *AMD; Myopia; CNV*

Introduction

The last decade of the century is connected with a great interest of ophthalmologists in a growing amount of myopic ametropy all over the world and its tendency to progression makes this pathology leading among most common visual disorders. It is known that complicated myopia can be the reason of disability in people of young and workable ages (1st - 2nd places) [1,2]. Statistics shows that 28,4 - 35% of people on the planet are myopic [3].

According to American Academy of Ophthalmology if is awaited that the amount of myopic people on the Earth will be 5 milliards by 2050 [4]. In the USA more than 25% of people are myopic when in Asia this number is 80% (according to WHO) [5].

Modern ophthalmologists recognize some main factors of the origin and progression of myopia such as violation of accommodative ability, a hereditary predisposition, a weakening at the stage of progression of supporting (biomechanical) properties of the scleral membrane of the eye, caused by metabolic disorders of its collagen and other protein structures [6-8].

The following fact is interesting: in progressive myopia, a decrease in the total protein content in the cerebrospinal fluid correlates with a significant decrease in the content of the main protein, collagen in the sclera. In past works on the study of sclera *in vitro* it was shown that a violation of the metabolism, structural and biomechanical properties of sclera with progressive myopia is mainly happens due to damage of the collagen structures of its extracellular matrix

In particular, in the posterior equatorial section of the sclera in eyes with medium and high myopia, the content of total collagen is reduced and the level of its soluble fractions is simultaneously increased. This indicates to the relative immaturity of the myopic sclera. Disruption of collagen metabolism is accompanied by a significant decrease in the content of glycosaminoglycans - the main component of the sclera cementing substance, and the number of transverse intra- and intermolecular bonds stabilizing the connective tissue structures of the sclera [8].

Authors describe various classification systems for myopia. When considering changes affecting the fundus we use the classification of myopia proposed by E.S. Avetisov (1999). Thus, myopia is divided into weak (up to 3.0 diopters); average (3.25 - 6.0 diopters); high (more than 6.25 diopters). According to the flow, it can be stationary; slowly progressing (less than 1.0 diopters per year); rapidly progressing (1.0 diopters and more per year). By the presence or absence of complications it can be divided into uncomplicated; complicated: chorioretinal (near-optic nerve head (ONH), macular, peripheral, common); vitreal; haemorrhagic; mixed; complicated by glaucoma; complicated by cataract.

As a rule, the initial stages of myopia development are not accompanied by visibly rude changes of the fundus, except for myopic cones in the optic disc. More often, weak or moderate myopia is formed, which can remain stationary throughout the life. In case when the eyeball continues to increase in the anteroposterior size, a degree of myopia also increases, which is accompanied by pathological changes in mediums and membranes of the eye. First of all, the area of the optic nerve head (ONH) is affected. The myopic cones (existing here earlier or newly arising) gradually increase in size and cover the optic discs in the form of a ring that can often be with an irregular shape. Sometimes the ONH itself changes its configuration: it looks enlarged or reduced, elongated, flatter, acquires a greyish tint. In very high degrees of myopia, in 35% of cases in the posterior pole of the eye, true protrusions or staphylomas sometimes occur [9].

Staphylomas are usually delimited by an arcuate line. This line is located concentrically towards the optic disc, the vessels of the retina can bend over it. Due to the increasing atrophy of the choroidal and retinal elements degenerative changes are becoming more common. Stripes of whitish-yellow color appear first, and then appear rounded or irregularly shaped white foci, often with clumps of pigment. These foci merge and affect a significant area of the fundus. Due to depigmentation and the disappearance of the layer of small and medium vessels, the fundus becomes unevenly colored or acquires an albinotic appearance with a rare network of choroidal vessels. The accumulation of pigment in the intervascular spaces in the form of elongated spots or triangles can imitate a picture of so called “parquet” or tessellated fundus.

As described above, a high myopia is an anomaly of refraction of at least -6.00D or can be defined as the axial length of the eyeball more than 26.5 mm [10]. In general, it is a bilateral condition associated with multiple eye diseases, such as cataract, glaucoma, and retinal detachment [11]. Pathological or degenerative myopia is considered to be a high myopia with any myopically related posterior pole pathologies, developing as a result of lengthening of the eyeball [10,12]. This condition affects 3% of the global population. Loss of vision in pathological myopia plays an important clinical, medical and social role in connection with the tendency to a progressive, irreversible nature of disease and limitates professional adaptation. Myopia of a high degree requires constant spectacle or contact optical correction, reduces the quality of life of people and affects them in their most productive years of life. One of the most serious complications of myopia is a myopic maculopathy [13]. This includes lacquer cracks, posterior staphyloma, spotty atrophy, choroidal neovascular membrane (CNV) and geographical atrophy [14-16]. Studies indicate to the connection between the increase in severity of maculopathy and the

lengthening of the eyeball, as well as with the aging process [20,21]. With the time, lacquer cracks expand and, thus, areas of choriocapillary atrophy increase, as well as chances of CNV ingrowth from damaged areas of the Bruch's membrane, CNV can develop in 10% of the eyes with degenerative myopia [17,18].

According to literature reviews, CNV often complicates the course of age-related macular degeneration (AMD) [19-22]. Every 5 representative over 65 has involutional changes in macular zone. More than 30 million people in the world, including more than 12 million of Europeans lost their sight due to AMD [22]. AMD is characterized by the loss of visual acuity caused by degeneration of the choriocapillaries, retinal pigment epithelium (RPE) and photoreceptors. At the very beginning of the disease, druses and changes in the Bruch's membrane are formed [23]. Domestic and foreign ophthalmologists unanimously consider AMD to be a multifactorial disease and its development is influenced by age, smoking, ethnicity, hereditary factors, a burdened family history, etc. [24-26]. A significant role in the development of AMD is assigned to the pathology of the cardiovascular system. Cherney EF., *et al*. (2001) note that the risk of damage of the macular region increases 3 times with atherosclerosis, while in patients with hypertension the risk increases 7 times [27]. P Penfold., *et al*. (1985) were among the first who suggested that AMD can be the result of chronic inflammation by detecting by electron microscopy an accumulation of macrophages, fibroblasts, lymphocytes and mast cells in areas of Bruch's membrane damage, thus, determining the role of immunocompetent cells in the formation of a neovascular membrane [28]. Most scientists have pointed to the dominant role of inflammation in the development of AMD and its transition from dry to wet form. However, some authors do not abandon attempts to find a direct "provocateur" or trigger of inflammation and *Chlamydia pneumoniae, Toxoplasma* and herpes viruses are considered to be as "applicants" for this role [29,30]. The role of cytomegalovirus (CMV) as a trigger for inflammation with the subsequent development of vascular pathology (atherosclerosis, vasculitis) has been confirmed by many researchers [31-34]. A number of authors have suggested the possible participation of CMV in the development of AMD and the transition of the dry form of the disease to the exudative one by finding in patients with AMD increased titers of immunoglobulins G (IgG) to CMV in serum [26,35].

In the Russian Federation, in clinical practice, doctors often use to the classification developed by L. Katznelson with co-authors which is based on the stages of development of the dystrophic process. The classification provides for 3 forms of the disease:

- Non-exudative (dry) form: Retinal druses, defects of the RPE, redistribution of the pigment, atrophy of the RPE and the choriocapillary layer.
- Exudative (wet) form: Stage of exudative detachment of the RPE; stage of exudative detachment of neuroepithelium; stage of exudative-haemorrhagic detachment of pigment and neuroepithelium.
- Cicatricial stage.

American Academy of Ophthalmology recommends classification which was developed during the Age-Related Eye Disease Study (AREDS).

Dystrophic and age-related changes in fundus structures occur in people with emmetropia, as well as with various refractive errors. Some studies indicate the prevalence of AMD in hyperopia compared with emmetropia [36,37]. In eyes with moderate and high myopia the assessment of the stage and evolution of AMD often causes difficulties, since changes in the fundus with far-reaching stages of both pathologies have similar characteristics: presence of the destruction of the RPE, the formation of CNV, microcirculation disorders in the retina and choriocapillary layer and others [5,38,39]. Myopic choroidal neovascularization (mCNV) occurs in approximately 62% of patients younger than 50 years old and differs from CNV appearing in other diseases, for example, in AMD [40]. Complicated myopia is mainly characterized by classical subretinal neovascular membranes associated with a focus of atrophy or with lacquer cracks (zones of ischemia). Their localization can be subfoveolar in 58% of cases, juxtafoleolar (1 - 199 μm from the center to the foveal avascular zone)

in 23% and extra foveolar (at least 200 μm from the center to the foveal avascular zone) in 19% of cases. In all cases edema extends to foveola. Moreover, detachment of the RPE and neuroepithelium may not be determined by stereoscopic biomicroscopy [41-43]. As a rule, mCNVs have no pronounced prominence, less than 1 diameter of the optic disc (less than 1,000 μm) in size, have a greyish tint and hyperpigmented borders. They are located in the subretinal space, unlike CNV in AMD, when the membrane is located under the pigment epithelium and is accompanied by the presence of haemorrhages or exudates [41,44].

In early stage of the development of mCNV with serous neuroepithelium detachment it is possible to evaluate a light area of small sizes surrounded by a dark hyperpigmented ring in the foveal center at biomicroscopy. The integrity of walls of retinal vessels is sometimes disturbed, especially in presence of lacquer cracks and could be accompanied by retinal haemorrhages. After haemorrhages the so-called Fuchs spot may appear in fovea - a large pigmented lesion surrounded by a light rim [45]. The dark color of Fuchs spots is caused by haemoglobin degradation products and hyperplasia of RPE cells surrounding CNV [46]. They look like rounded or elliptic foci, often dark coloured, but may also have grey, yellow, red or green color. Over time, a ring of chorioretinal atrophy appears in the center of the macula around the Fuchs spot (in 74% and 96% of the eyes after 3 and 5 years after initial examination), which continues to increase and may involve a large area of the posterior pole [47]. Data on the development of CNV in both eyes are of great interest and still remain controversial. So, Fried M. and Siebert A. recorded bilateral neovascular membranes in only 12% of myopic eyes [48]. At the same time, Hotchkiss M. revealed the presence of a Fuchs spot in both eyes in 40 - 52% of patients, and also noted an increase in the proportion of people with these manifestations over time (the average period before bilateral involvement was 2.4 years ranging from 0 to 8 years) [49]. The time between the appearance of changes in the paired eye varies from several days to many years. More often, the Fuchs spot is diagnosed in people older than 30 years (average age is 41 years), although it is also observed in children aged 14 years and in 5 - 10% of the eyes in general population of myopic people [41,50].

Curtin and Karlin report cases of various pathologies associated with myopia, where the length of the eyeball plays important role. They found that the temporal myopic cones, posterior staphyloma and chorioretinal atrophy increased in size along with the growth of the eyeball, but such changes did not occur in the presence of lacquer cracks and Fuchs spots [50]. In this study, it was found that mCNV did not develop in eyes with an axial length exceeding 33 mm. Ikuno., *et al*. suggested that axial growth itself does not cause the formation of a myopic neovascular membrane, and other hidden factors may exist. The anteroposterior size of the eye and the anomaly of refraction did not differ in eyes with mCNV and in the paired eye. According to some studies, the choroid in eyes with a neovascular membrane in the subfoveal area and below it has a significantly smaller thickness than in the paired eye [52]. It remains unclear how this can contribute to the formation of CNV. One possible explanation is that choroidal vessels indirectly supply outer layers of the retina. Thinning of choroid in fovea can lead to hypoxic changes in outer layers of the retina indirectly through factors induced by hypoxia [53].

The hemodynamic theory of the development of mCNV is associated with changes in choroidal perfusion and blood circulation in myopic eyes, such as delayed choroid filling and diffuse choroidal thinning [54,55]. Choroidal neovascularization is accompanied by a slowdown in the blood flow in the ophthalmic artery, central retinal artery and central retinal vein, short posterior ciliary arteries and an increase in peripheral resistance in the ophthalmic artery, which contributes to ischemia of eye tissues. It is believed that due to prolonged decrease in blood flow velocity a reduction in the lumen of blood vessels occurs, as well as decrease in the tone of the vascular wall with its secondary hypoplasia. The ischemia of the choroid and retina exacerbates with an increase in the number of insufficiencies of supplied zones. This leads to compensatory remodelling of choroid vessels and appearance of neovascularization zones. It is suggested that high IOP is a risk factor of CNV development in pathological myopia [56].

It is important to note that CNV with various diseases have their own characteristics. According to some reports, CNV most often complicates the course of AMD (in 4.6 - 20% of cases). Exudative form of AMD can be described as the appearance of newly formed choroidal vessels and connective tissue that causes a vision loss in patients with AMD in 90% of cases, according to Murphy RP and L Wu [20,22,57]. Changes in RPE lead to the accumulation of metabolic products inside cells themselves, and subsequently in the space under the pigment

epithelium with the formation of soft druses containing colloidal material. The presence of the latter leads to the separation of Bruch's membrane and RPE, its atrophy and appearing of defects in the structure of the Bruch's membrane. In case of the exudative form of AMD, the transudate formed as a result of increased permeability of the walls of choriocapillary vessels penetrates through the defects in the Bruch's membrane, leading to its detachment, and then to neuroepithelium detachment. Thus, retinal tissue ischemia occurs, which is accompanied by edema with subsequent development of neovascularization [58]. In myopia, the growth of newly formed vessels is primary during the formation of neuroepithelium detachment, comparing with AMD. As a result of axial lengthening of the eye, myopia depletes the RPE, leads to the choriocapillary layer atrophy, then cracks appear in the Bruch's membrane and newly formed choroidal vessels grow into the space under the RPE [59].

There are three types of development of newly formed vessels in the exudative form of AMD, according to L. Yannuzzi: CNV, subretinal neovascular membrane, developing as a classic or occult type, but, more often, a mixed form; retinal angiomatous proliferation (RAP); polypoid choroidal vasculopathy (PCV). With the development of CNV, newly formed vessels penetrate through the RPE into the sensorineural part of the retina. In some cases, the formation of anastomoses between the choroidal and retinal blood flows is possible (retinochoroidal anastomosis). This is clearly visible with the formation of a disciform scar. In recent years, it has been proven that a "reverse" growth of the retinochoroidal anastomosis from retinal vessels (capillaries) is also possible. With this outcome, the "vascular branch" "deepens" the retina towards the choroid, where it forms an anastomosis with choriocapillaries. This form of exudative AMD is called "retinal angiomatous proliferation" [59,60].

Conclusion

Some questions are still unresolved about the origin of changes in the retinal structures with a combination of degenerating processes of age and myopic origin. In case of developed stages, AMD and myopia mask each other, worsening the prognosis for visual functions and leading to irreversible vision loss. The severity of the course of degenerative processes of the retina in advanced stages of AMD and complicated myopia, the irreversible nature of visual impairment in these conditions necessitate the development of methods for predicting the course of diseases at the initial stage, which could greatly contribute to determining the optimal tactics of patient management. It should be noted that all the recommendations for the diagnosis and management of patients with AMD and high myopia, currently offered, reflect the current understanding of the pathogenesis of the disease and existing real treatment options.

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