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REVIEW

PATHOGENETIC PECULIARITIES OF COMPLICATED MYOPIA AND MODERN METHODS OF INVESTIGATION

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ABSTRACT

Based on analysis of scientific data sets the author summarizes traditional and modern views on a number of clinical features of progressive myopia. Therewith, common and some less explored aspects of disease-specific pathogenesis are carefully differentiated. Modern diagnostic capabilities for characterization of isolated features and groups of clinical signs and manifestations of complicated myopia are considered.

The conclusion is drawn that in spite of a sufficient number of modern objective and subjective methods and techniques for myopia examination, as well as diagnosis of certain features of its display, the verification of accommodative myopia transition into axial and thus into a complicated type of disease currently raises difficulties both in the aspect of targeted application of diagnostic procedures, and, mainly, in the absence of the objectified diagnostic algorithm for the early diagnosis at the pre-manifestation stage of the myopic disease.

The author emphasizes that the specified issues might be considered relevant to modern ophthalmology and, in particular, to pediatric ophthalmology.

Keywords: *progressive myopia, myopic chorioretinitis, anterior-posterior axis of the eye, rigidity of sclera, intraocular pressure.*

Myopia is the most commonly observed defect of vision. In developed countries its frequency is 19-42%, while in some regions of the East it reaches 50-70% [*Shamshinova A., 2001*]. Different terms are used to define progressive myopia accompanied by marked changes in the fundus: "complicated", "degenerative", "pathological", "malignant". Such a set of definitions suggests that many problems related to etiology and pathogenesis of this disease are not entirely investigated [*Curtin B., 1985*]. Recently, the term "pathological myopia" is most commonly used, and the condition is defined as a progressive pathology process. According to some authors [*Curtin B., 1985*], such definition as "degenerative myopia" is less appropriate, as it reflects only a certain stage of the pathological process. In some patients with pathological myopia the degenerative changes might be lacking up to the age of 20, but their further development is highly probable.

The term "malignant myopia" is even less acceptable, as it is depriving of hope and causing unnecessary associations.

According to various sources [*Curtin B., 1985; Blacharski P., 1988*], the share of high myopia in the general population makes 1.7-2.1%. Complicated myopia takes the 1st to 3rd place among the nosological causes of primary vision-related disability. The analysis of disability causes in high myopia shows that it most frequently develops as a result of dystrophic changes in the macular region, because of retinal detachment, as well as due to complicated glaucoma and cataracts.

It is believed that progressive myopia is a hereditary disease transmitted in the autosomal recessive or, rarer, in the autosomal dominant manner [*Curtin B., 1985; Avetisov E., 1986; Panteleeva O., 1997*].

Recent genetic studies confirm the polygenic

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nature of myopia inheritance, not excluding the possible influence of some modifying factors on its course. The adverse environmental effect might be manifested both *in utero* and *post partum*. Thus, myopia might be referred to a group of eye diseases with hereditary predisposition, when heredity is pathogenic or a conditionally etiological factor [*Shamshinova A., 2001*]. Risk factors include rubella, toxoplasmosis, toxicosis of pregnancy, which often cause prematurity. In the later period the influence of acute and chronic infections, especially those long-lasting and accompanied by high temperature and body weight decrease are distinguished; the lack of complete proteins is also significant [*Avetisov E., 1986*].

In recent years, hormonal disorders – arising from infringed light pulse passage from the retina to diencephalic-pituitary region manifested in steroid hormones imbalance – are considered the key factors in the etiopathogenesis of myopia. The endocrine pathology leads to disruption of collagen metabolism and stretching of the sclera [*Balacco-Gabrielli C., 1983*].

Several theories of myopia origin were proposed. Nowadays, three-factor theory of E.S. Avetisov (1986) should be considered the most scientifically substantiated. Accordingly, three basic links are identified in the mechanism of myopia development:

- visual work at close range caused by weakened accommodation;
- genetically conditioned predisposition;
- weakened sclera and probable changes of intraocular pressure (IOP).

At weakened accommodation the enhanced visual work in close proximity becomes an unbearable load to eyes. In these cases, the organism is forced to change the optical system of eyes in order to adapt its work at close range without accommodation strain. This is mainly achieved by extending the anterior-posterior axis of the eye during the period of its growth and formation of refraction.

The genealogical analysis allows considering that myopia might be inherited in both autosomal dominant and autosomal recessive manner. In dominant type of inheritance myopia occurs at a later age, proceeds more favorably and, as a rule, does not reach the high degree. Myopia inherited according to the recessive type is characterized by phenotypic polymorphism, earlier onset, stronger tendency to progression and complications frequently combined with a number of congenital diseases of the eye [*Curtin B., 1985; Vo T. et al., 1986*].

The third link in the mechanism of myopia development is the weakened sclera and its possible effects to IOP. According to E.S. Avetisov. gradual stretching of the anterior-posterior axis of the eye is an inadequate response of the weakened connective tissue to the impact of IOP, even if the latter is not increased [*Avetisov E., 1986*].

Defining features of degenerative myopia are pathological changes of the fundus developing on the background of increasing size of the eyeball compared to norm. As recently found, in myopia not only the anterior-posterior, but also the horizontal and vertical dimensions of the eye increase. This process involves both the area of the equator and the posterior pole of eyes [*Shamshinova A., 2001*].

The extensive clinical experience acquired in the last decades indicates to the association between the frequency of origination and severity of changes in the fundus and the process of myopia progression, as well as to the occurrence of delayed ophthalmoscopic changes regarding the processes of the eyeball elongation. Accordingly, it might be supposed that changes in the fundus are secondary phenomena caused by stretching of eye membranes and, primarily, of the sclera. Changes in the biomechanical properties of the sclera due to its structural and metabolic disorders underlie myopia progression [*Volkolakova R., 1980; Avetisov E., 1986*].

Sclera is a type of connective tissue; therefore, it can be assumed that system diseases occurring as connective tissue lesions can also occur as scleral lesions, and the changes of the scleral membrane in myopia also present manifestation of collagenosis. The myopic disease, beginning from its mild degree, is accompanied by changes in the connective tissue of the scleral membrane: by the impairment of collagen fibers and the extracellular matrix worsened alongside the progression of myopia [*Vinetskaya M., 1979; Volkolakova R., 1980; Iomdina E., 1984*].

The main structural components of the sclera providing its support function are fibrillar ones: collagen, elastin and extracellular matrix – the cement substance, in which they are located. The mechanical stress, strength and elasticity that make biome-

chanical properties of the sclera depend on concentration of collagen, density of its fibers packing and their architectonics: the composition and structure of proteoglycan complexes, the type of their relationship with the fibers, the presence of stabilizing intra- and intermolecular bonds in these biopolymers [*Volkolakova R., 1980; Iomdina E., 1984*]. However, precisely the changes of extracellular matrix form the basis of destructive changes in the collagen framework of the sclera. They manifest in identified free glycosaminoglycans and reduction of their content in the sclera alongside with increasing refraction, while in glaucoma the level of glycosaminoglycans in the sclera increases. All this is reflected in the biomechanical properties of the myopic sclera, which is losing its strength and becomes extensible through the accumulation of residual microstrain due to periodic overloads, in particular, fluctuations in ophthalmotonus: daily, orthoclinostatic, pulse, converged, respiratory, muscular, etc. [*Andreeva L., 1981; Khojabekyan N., 1997*].

Distraction of sclera in the sagittal direction leads to thinning of the sclera and weakness of the cribriform plate and other supporting structures of the optic nerve; this latter explains the susceptibility of the optic nerve disk to glaucomatous changes in myopic disease. The increasing length of an eye in myopia is now considered a consequence of metabolic disorders of sclera, regional hemodynamic changes. It must be emphasized that high myopia is characterized by the expansion of the scleral canal due to general stretching of the posterior chamber of an eye and the weak development of the supporting tissues of the optic nerve. This leads to a marked flattening of the optic nerve and, in some cases, development of small and flat excavation [*Avetisov E., 1986*].

The results of clinical studies also signify to thinning of the eye membranes in the progression of myopia. The decreased thickness of sclera from 1.2 *mm* in emmetropia to 0.6 *mm* in high myopia, and the total thickness of the posterior chamber of an eye from 2.34 *mm* at high hyperopia to 0.75-0.54 *mm* in high myopia [*Guthoff R. et al., 1987; Shirshikov Yu., 1997*].

Until now, the causal role of elevated IOP in the genesis and progression of myopia is not entirely proved. The elevated IOP causes stretching of weakened, genetically defective or thinning sclera. Some authors considered that increased IOP in myopia might be the result of myopic process rather than its cause [*Bonomi L. et al., 1982; Phillips C., 1990; Kragha I., 2004*]. On average, the level of ophthalmotonus in myopic eyes (without glaucoma) is increased by 1.5-2.0 *mm Hg*.

Structural inadequacy of the scleral tissue in myopia is the cause of reduced rigidity, often proportional to myopia degree and the length of the anterior-posterior axis. The more pronounced is chorioretinal degeneration, the lower is eye rigidity. Some authors mention the increase of sclera rigidity coefficient in myopia above 18.0 dioptres (*D*) [*Curtin B., 1985*]. This effect is explained by the fact that at very high degrees of myopia the stretching of sclera obviously reaches its limit resulting in increased rigidity.

Currently, the following clinical classification of myopia is applied: according to degree – mild or low (up to 3.0 *D*), moderate (3.25 *D* to 6.0 *D*) and severe or high myopia (≥6.25 *D*); according to pathogenesis – genuine or axial, false or pseudomyopia; according to the time of onset – congenital and acquired; according to disease course – stable (annual increase no more than by 0.5 *D*), slowly progressing (annual increase up to 1.0 *D*) and rapidly progressing (annual increase of myopia degree ≥ 1.0 *D*).

Myopia progression can be slow and end with the completion of the organism growth (18-20 years old). Sometimes myopia is progressing continuously and reaches high degrees (35-40 *D*); it is accompanied by a number of complications (detachment of retina is the most dangerous one) and a significant decrease in vision. This is called a malignant myopic disease [*Volkolakova R. 1980; Avetisov E., 1986*].

The complicated and uncomplicated myopia are distinguished by the presence of complications; respectively, by the localization of complications progressing myopia is classified as follows: scleral; scleropapillary (peri-disk); chorioretinal; macular; vitreous; hemorrhagic; mixed; total.

According to functional changes (corrected visual acuity) four stages are distinguished:
- stage I – corrected acuity makes 0.8-0.5;
- stage II – corrected acuity achieves 0.4-0.2;
- stage III – corrected visual acuity equals 0.1-0.05;
- stage IV – corrected visual acuity is 0.04 and lower.

In myopia the following scleral and sclera-papillary changes might be differentiated in the posterior pole of the eye: myopic cone; oblique position of the disk; supertraction of the optic nerve disk. The latter, to a certain extent, is due to staphylomas formation. The cone is one of the most common clinical manifestations of myopia. Formerly, the question related to the origin of cones was the subject of debate. Some authors considered cone a congenital malformation that might occur with any type of refraction. However, it was proved that the cone is formed in myopia as a consequence of stretching the posterior pole of the eye [*Avetisov E., Flick L., 1974*].

Staphyloma is a true protrusion of sclera in the posterior of an eye. It is rarely recorded: only at a very high degree of myopia. The edge of staphyloma is a fold in the fundus, especially on the temporal half; passing through it, the retinal vessels bend. The border of staphyloma is observed as a sharp curved line concentrically arranged towards the optic nerve [*Avetisov E., 1986*].

Progressive myopia is frequently accompanied by a chorioretinal changes that are degenerative in nature and result from stretching of the posterior pole of the eye. According to localization the central chorioretinal and peripheral vitreochorioretinal changes are distinguished. At present, specialists use the classification of central chorioretinal changes according to E. Avetisov and L. Flick (1974) and apply the classification proposed by E.O. Saksonova and co-workers for peripheral vitreochorioretinal changes [*Saksonova E. et al., 1979*].

According to classification, the following basic forms of central chorioretinal changes might be differentiated: "dry" (atrophic) and "wet" (transudative) macular dystrophy, lacquer cracks, Fuchs central pigmented spot, "Dry"' form of the central chorioretinal dystrophy is characterized by blanching of fundus, the presence of initially small rounded white-yellow foci of lesions, sometimes with pigmented edges – areas of focal chorioretinal atrophy [*Averbach F., 1987*].

The transudative or "wet" form of macular dystrophy in myopia is accompanied by a sudden loss of vision, sometimes with the appearance of the central or paracentral scotomas. "Wet" form is much rarer than the "dry" one; however, it is characterized by the relatively early onset and severe course. As a rule, this disease develops before the age of 50 years and is more often in women [*Vodovozov A., 1979; Averbach F., 1987; Mizgireva A., 1990*].

The share of serous (edematous) forms in patients with transudative myopic maculopathy makes 30.6%, fibrinous – 1.4%, hemorrhagic – 68.0% [*Averbach F., 1987*].

Peripheral vitreochorioretinal dystrophy is observed in all types of refraction; however, in patients with myopia the frequency is 2-3 times higher than in those with emmetropia and hyperopia [*Karlin D., Curtin B., 1976; Zakharova G., 1983*].

In formation of the peripheral vitreochorioretinal dystrophy three structures are involved: the vitreous body, choroid and retina. According to the classification of E.O. Saksonova and co-workers, the following types of peripheral vitreochorioretinal dystrophy are distinguished: equatorial (lattice, isolated ruptures of the retina, pathological hyperpigmentation); paraoral (cystoids, retinoschisis, chorioretinal atrophy); mixed forms [*Saksonova E. et al., 1979*].

Changes of the vitreous body present almost constant symptoms of high myopia, N.B. Shulpina (1974) found the specified pathology in 73% of patients with myopia. Initially, changes are localized in the posterior part and then capture all the vitreous body. These changes are caused by decay products of the eye inner membranes – cellular elements and pigment cells – in-flowing to this site.

An important role in disorders of physicochemical properties of the vitreous body also belongs to the fact that under the excessive extension of eye membranes it is stressed, but does not "grow" together with them.

At patient examination it is important to get a comprehensive understanding of the clinical features and course of myopia. Surveys begin with visometry, biomicroophthalmoscopy, then the static and dynamic refraction of the eye is explored, as well as the presence of anisometropia, and the annual gradient of myopia growth is calculated. At the annual gradient below 1.0 *D/year* myopia is considered a slowly progressing one, with a gradient of 1.0 *D/year* or above – a rapidly progressing. Re-measuring the length of eye axis with the use of ultrasound biometry can help in assessing the dynamics of myopia [*Avetisov E., 1986*].

Perimetry is a method of determining the field of view. Peripheral vision is much more volumi-

nous compared to the central one; therefore, it is difficult to quantify it. The aim of examining the field of view is to define the outer boundaries of vision by the peripheral retina, as well as various characteristics of vision in this region. Perimetry and campimetry also allow revealing central and paracentral defects in the visual field. The interpretation of data relevant to field of view is important for setting diagnosis of diseases, their localization in the visual pathways between the retina and the occipital cortex of the brain, recording progression, stability or remission of the disease.

Kinetic and static perimetry are distinguished. In static perimetry the intensity of stimulus varies at the same position of the object. Upon kinetic perimetry the location of an object changes. In complicated myopia static and kinetic perimetry reveal narrowing of the peripheral boundaries of the field of view, reduction in retina sensitivity, central, paracentral, absolute or relative scotomas.

It is nearly half a century that A-B mode ultrasound is widely used in ophthalmology to determine various diseases of the eye and orbit. A-scan allows to measure the distance between individual peaks (respectively, between different structures) with high accuracy. B-scan allows obtaining two-dimensional ultrasound picture more convenient for interpretation. This method of investigation gives an idea about the location, size, shape and acoustic characteristics of the pathology focus and its relationship with neighboring structures. Other types of ultrasound for eye research involve: high frequency ultrasound – to visualize the anterior segment of the eye; Dopplerography – for determination of blood flow in vessels; three-dimensional ultrasound – to measure the volumetric characteristics.

A-scan is used in ophthalmology, generally through echobiometry. Echobiometry is measuring the thickness of cornea and lens, anterior chamber depth, length of the vitreous body, other intraocular distances and the magnitude of the eye in general.

In recent years, the technique of ultrasound B-scan was developed; it allows intravital quantitative study of sclera features through measuring the amplitude of echo signal attenuation as reflected from the scleral capsule of an eye. The resulting figure is called the acoustic density of the sclera. A significant decrease in acoustic density of the sclera in myopia was revealed as compared to emmetropia, in high myopia compared with mild to moderate, in progressive myopia compared with the stationary, and in complicated myopia compared with the uncomplicated one [*Khojabekyan N., 1997; Tarutta E., Kushnarevich N., 1997*].

In the last decade works were published related to the use of color and power Doppler mapping for the diagnosis setting on vascular malformations, diseases of the optic nerve, tumors of the eye and orbit, as well as a variety of hemodynamic disorders in the *a. ophthalmica* system and orbital veins.

Pachymetry is the measurement of corneal thickness that is an indirect sign on the integrity of the corneal endothelium. Maximum thickness of the cornea is observed at the limb (0.7-0.9 *mm*). Normally, the central corneal thickness is 0.49-0.56 *mm*. and its increase above 0.6 *mm* might be indicative of endothelium pathology.

On average, human cornea thickness varies in a wide range. In men this index makes 542 μ*m*, in women – 551 μ*m*. The average value of daily fluctuations in the thickness of the cornea in humans is about 6 μ*m*. These measurements are obtained by pachymetry and depend on research method, by which pachymetry is done. These methods are divided into two types: optical and ultrasound. Optical methods of pachymetry are non-contact. They are used only on the transparent cornea. Ultrasound pachymetry methods are divided into contact and immersion methods of measurement.

The thickness of cornea plays an important role in precise and individual evaluation of IOP. Depending on the thickness of cornea, the IOP is evaluated with the corresponding correction factor.

Considering the fact that in myopia the synthesis of cartilaginous tissue is changed, the biochemical research methods of investigation (blood, urine analyses) seem promising. In children with progressive myopia the increased activity of alkaline phosphatase, reduced levels of total calcium and phosphorus in the blood serum were revealed. At myopia progression a substantial increase in excretion of chondroitin sulphate and acid mucopolysaccharides with urine, changes in the content of proline, oxyproline, as well as glycosaminoglycans in blood plasma were also recorded reflecting the intensity of degradation in connective tissue of the main protein, i.e. collagen [*Bikbov M. et al., 2009*].

Biochemical methods for determination of pro-

collagen and antibodies titers to different types of collagen are promising research methods as well [*Vinetskaya M., 1979*].

As obvious from data above, complicated development of the myopic process, to a greater or lesser extent, results *inter alia* in pathological changes of fundus-related complex, variations in IOP, scleral rigidity, central and peripheral vision, biochemical indices of certain organic components of tissue complexes, etc.

Unfortunately, the mentioned changes are recorded only at clinical stages of the disease even upon application of modern techniques; in practice, the standard generally accepted diagnostic algorithm used at the initial stage of pathologically significant progression does not involve the integrated application of diversified research procedures, their correlation interdependence both between each other and the early signs of the disease in itself was not previously studied as an entire complex.

Thus, the analysis of publications on pathogenetic mechanisms of progressive myopia development and methods of its study allows us to conclude that despite a sufficient number of modern objective and subjective methods and procedures of myopia investigation, the diagnosis of certain features of its display, the timely verification of accommodative myopia transition into the axial and thus into the complicated type currently cause known difficulties both in terms of diagnostic methods targeted application, and, mainly, due to absence of objectified clinical algorithm for early diagnosis of "pre-manifested" stage of the myopic disease. The specified issues might be obviously considered as relevant to modern ophthalmology and, above all. to pediatric ophthalmology.

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