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Research Article

Keratoconus and Pathological Changes in the Retina and Optic Nerve, as Manifestations of Undifferentiated Dysplasia of the Connective Tissue of the Body

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Abstract

Introduction: In this study shows evidence of the influence of undifferentiated connective tissue Dysplasia of the body at risk of Keratoconus and development of pathological changes of optic nerve and retina.

Purpose: Comparative study of morphometric parameters of optic nerve and retina in patients with Keratoconus, depending on the availability of undifferentiated connective tissue dysplasia.

Materials and Methods: 186 patients with verified diagnosis of Keratoconus (186 eyes) were analyzed using optical coherence tomography of the posterior segment of the eye, on the basis of the results obtained were formed 3 clinical groups and comparative analysis morphometric indices of the optic nerve and retina. In 1 group included 40 patients (40 eyes) having expressed morphometric parameters of optic nerve and retina, into 2 group-the 50 patients (50 eyes) with insignificant deviations from a multiyear average. The comparison group consisted of 96 patients (96 eyes) without any changes in the fundus, according to optical coherence tomography.

Results and Discussion: The average thickness of retinal nerve fiber layer was statistically highly reliably less than patients of other groups (80.15 ± 1.29 against 91.70 ± 1.09 and 95.50 ± 0.81, respectively) (1-2 $P \leq 0.0001$; 1-3 $P \leq 0.0001$; 2-3 $P = 0.003$). Retinal nerve fiber layer thickness on separate segments (SNIT) Group 1 patients also was statistically significantly less. Identified significant differences in the volume of excavation of optic disc and rim area. Reliable differences in average and the vertical size of the optic disc excavations between patients of different clinical groups have been identified. Group 1 patients, unlike the 2 and the comparison group, have reliably smaller optic disc (1.712 ± 0.059 μm against 1.825 ± 0.047 and 1.966 ± 0.036 μm, respectively) ($P = 0.04$ 1-2; 1-3 $P = 0.0001$; 2-3 $P = 0.01$).

Conclusion: Undifferentiated connective tissue dysplasia is a risk factor for Keratoconus and pathological changes of optic disc and retinal. Patients with keratoconus on the background of connective tissue dysplasia need neuroprotective, stabilizing collagen therapy and constant medical supervision.

Keywords: *Keratoconus; Morphometric Changes Drive the Optic Nerve; Retina; Optical Coherence Tomography*

Introduction

The problem of keratoconus has been acute in recent decades due to the high prevalence in the world and in Russia, as well as due to the susceptibility of young, able-bodied persons to this pathology. Being the structure of the connective tissue (CT) of the body and the main refractive medium of the eyeball, the cornea must have biomechanical stability, which is determined by the state of collagen fibers, intercollagen bonds and their architecture [1-3]. The basis of pathological changes in the cornea in keratoconus are violations of the synthesis and maturation of collagen. With the development of keratoconus, the collagen fibers of the cornea change their orientation from perpendicular to oblique, tangential or circular [4-6] and the volume fraction of all four types of collagen decreases by 3.6 - 6.0 times compared to the norm [7-11].

Connective tissue (CT) is the only tissue present in the body in 4 types - fibrous, hard, gel-like and liquid. In addition to ligaments, bones, cartilage, joints and their bags, tendons, fascia, muscular vaginas, etc. CT is also neuroglia, microglia, vessels and capillaries, intercellular fluid, cornea, sclera, iris, lens and much more. Collagen fibers are a characteristic component of CT, which accounts for 25 - 33% of the total protein of the adult body, or 6% of his body weight. There are 19 types of collagen known, the genes encoding them are localized on 14 chromosomes. Elastin, which is the main protein component of elastic fibers, differs from collagen in chemical composition and molecular basis. An important role is played by fibrillin, which is especially abundant in the intercellular matrix of the cornea, lens, Cinn ligaments, vascular walls of all tissues and organs. The inferiority of collagen, elastin and fibrillin leads to a violation of the structure of tissues and the functions of target organs, one of which is the human eye [12-16].

The relevance of the problem of connective tissue dysplasia is determined by the wide prevalence of signs of impaired morphogenesis (the frequency of occurrence varies in the range of 13 - 70%), the difficulties of differential diagnosis and the peculiarities of the course of individual clinical forms [17,18]. Connective tissue dysplasia is characterized by a polymorphic clinical picture, including pronounced lesions of the lungs, heart and blood vessels, intestines and kidneys [19,20]. The entire clinical variety of undifferentiated connective tissue dysplasia is interpreted in a syndromic manner, most patients have several syndromes, while the very presence of syndromes and their combination make it possible to identify a systemic violation of CT [17-20]. Analyzing the data of the literature, we came to conclusions about the identity of the processes of impaired synthesis and maturation of collagen in keratoconus and undifferentiated connective tissue dysplasia, which made it possible to put forward a hypothesis about the currently undescribed connection between these conditions.

Purpose of the Study

The purpose of the study is to study the features of the retina and optic nerve in keratoconus, which occur in patients against the background of the presence of undifferentiated connective tissue dysplasia.

Materials and Methods

186 patients with all stages of keratoconus (186 eyes) were examined. Depending on the changes detected on the fundus during optical coherence tomography (OCT), three clinical groups were formed. The first clinical group included 40 patients (40 eyes) with pronounced changes in morphometric parameters according to optical coherence tomography. The second clinical group consisted of 50 patients (50 eyes) with insignificant, close to normal ("paranormal") values of any of the morphometric parameters of the optic nerve and/or retina. The third clinical group (comparison group) included 96 patients (96 eyes) without changes in the fundus according to optical coherence tomography.

By gender-age indicators, the groups were representative. In group 1 there were 32 men (80%) and 8 women (20%), in group 2 men were 39 (78%), women - 11 (22%), in group 3 (comparison group) there were 76 men (79%) and 20 women (21%). The mean age of all keratoconus patients examined was 27.74 ± 0.68 years. In group 1, the mean age was 27.01 ± 0.64, in group 2 - 28.02 ± 0.43 years, in group

3 (comparison group) - 27.27 ± 0.32 years, statistically significantly not differing (P ≥ 0.05). The diagnosis of keratoconus was established after a comprehensive examination of patients: viscometry (automatic for opter "RT-5100, NIDEK Co., Ltd"); autokeratorefractometry (keratorefractometer "HRK-7000, Huvitz"); examination of the cornea with WaveLight® Oculyzer™ II "Alcon" (Schempflug camera); indirect ophthalmoscopy with a lens 78D "Volk" (USA); direct ophthalmoscopy (ophthalmoscope "Heine EN 100-12"); ophthalmobiomiocroscopy ("XCEL-255, REICHERT, "Carl Zeiss Jena"), etc. Clinical groups of patients with keratoconus were representative of the refraction and length of the anterior-posterior axis of the eyes (P ≥ 0.05).

It should be noted that the OCT of the retina and optic nerve is not a traditional method of examination of patients with keratoconus and is not included in the list of mandatory examinations for it. With OCT of the posterior part of the eyes, first used by us to examine patients with keratoconus, traditional morphometric parameters were calculated: the average thickness of the layer of nerve fibers of the retina (RNFL, μm); symmetry of the layer of nerve fibers of the retina (RNFL, %); area of the neuro-retinal girdle (mm^2), area of the optic nerve disc (Rim area, mm^2); the average ratio of the excavation of the optic disc to its diameter (Cup/disc ratio, abs. value); the ratio of vertical excavation of the optic nerve disc (Vertical cup/disc ratio, abs. value), the volume of excavation of the optic disc (Cup volume, mm^3), the thickness of the layer of nerve fibers of the retina by segments (SNIT, μm). OCT studies were conducted on the "Cirrus HD-OCT" apparatus ("Carl Zeiss Meditec", Germany) by one specialist, under the same conditions. In cases where keratoconus was present in both eyes, only the worst eye was included in the study.

Statistical processing of the results of the study included the calculation of average values and their error (M ± m), σ - standard (root mean square) deviation, the Student's criterion, with the calculation of the level of confidence (P). Statistically significant were the differences corresponding to them (P ≤ 0.05).

Criteria for inclusion in the study: Patients with a verified diagnosis of keratoconus of all stages, both sexes, with sufficiently transparent eye environments for optical coherence tomography, without age restrictions. Exclusion criteria: the study excluded patients with secondary keratectasia and acute keratoconus, post-traumatic changes in the cornea, the consequences of previous injuries of the eyeball, acute and chronic inflammatory eye diseases, patients with glaucoma and with suspected glaucoma, with all stages of cataracts (with the exception of the initial one), patients who had previously undergone surgical (with the exception of crosslinking) or laser operations in the anterior and/or posterior parts eyeball, patients with endocrine ophthalmopathy, with pathology of the retina and optic nerve, patients with diabetes mellitus, cardiovascular diseases, other clinical conditions that may affect the purity of the study. All patients gave informed consent to the studies and were made aware of their rights.

Results and Discussion

In our previous study in 74 patients (136 eyes) with keratoconus of all stages, we examined the morphometric parameters of the optic disc and the peripapillary part of the retina [21-24]. The average value of the thickness of the layer of nerve fibers of the retina (RFNL) without division by stages of the disease was 92.60 ± 1.18 mμ (δ = 9.87), the minimum value was 63 mμ, the maximum - 118 mμ. The average excavation of the optic disc was in the range of 0.45 ± 0.01 (δ = 0.14), the minimum excavation value was 0.07, the maximum was 0.73 times the diameter of the optic disc. Vertical cup/disc ratio was larger - 0.58 ± 0.04 (δ = 0.29), the minimum size was 0.1, the maximum - 0.71 of the diameter of the optic nerve disc. The volume of excavation was in the range of 0.12 ± 0.01 mm^3 (δ = 0.13), varying from 0.01 to 0.7 mm^3. The thickness of the RNFL layer by individual sectors (SNIT) was as follows: in sector S - 112.17 ± 1.85 mμ (δ = 15.49), the minimum thickness - 61 mμ, the maximum thickness was 137 mμ; in sector N, the thickness of the RNFL was 71.93 ± 1.66 mμ (δ = 13.96), the minimum thickness was 52 mμ, the maximum was 122 mμ; in Sector I, the thickness of the RNFL was 120.53 ± 1.80 mμ (δ = 15.10), the minimum was 78 mμ and the maximum was 153 mμ; in sector T, the thickness of the RNFL was 64.76 ± 1.46 mμ (δ = 12.24), the minimum was 39 mμ and the maximum was 109 mμ. Thus, when analyzing the thickness of the RNFL by sectors, we paid attention to not so much the average values, since the average indicators are actually very average, always "average", our attention was drawn to the

maximum and minimum characteristics, significantly inferior to the normal values laid down in the optical coherent tomographic apparatus "Cirrus HD-OCT" [25]. To a greater extent, thinning of the RNFL was observed in the N and T sectors. For example, in the temporal segment - 39 mμ and in the nasal segment - 52 mμ.

The morphometric parameters of the optic disc were analyzed with the calculation of the average, maximum and minimum values of excavation depending on the stage of keratoconus. Already at stage I keratoconus, the excavation of the optic nerve disc could reach 0.71, which is characteristic of manifestations in glaucoma, but was not described earlier in patients with keratoconus! For all stages of keratoconus, the maximum values were in the range of 0.67 - 0.73, the average value of excavation in stage I keratoconus was in the range of 0.46. There were no statistically significant differences in the average values depending on the stage of the disease ($P \geq 0.05$). It is known that the excavation of the optic nerve more than 0.3 goes beyond the physiological and indicates, most often, glaucoma. In our study, we excluded patients with all forms and stages of any glaucoma. Thus, for the first time with the help of optical coherence tomography, we recorded such changes in the optic disc in patients with keratoconus.

There are few reports of morphometric parameters of the optic nerve and peripapillary retina in healthy young people, and data in keratoconus are isolated [25-29]. We compared the morphometric parameters of the retina and optic nerve in patients with keratoconus with and without connective tissue dysplasia. When analyzing the data, it turned out that, in addition to the group with obvious morphometric changes, the clinical group was determined with single subnormal, "paranormal" changes, isolated in a separate subgroup 2. Such unlike, but slightly different from the main group of cases of patients in mathematical circles are usually called "renegades". The comparison group included patients with a verified, as in other groups, diagnosis of keratoconus, but without any changes in the optic disc and retina according to OCT data. The results of a comparative analysis of the morphometric parameters of the structures of the posterior part of the eyes in patients with keratoconus are presented in table 1.

	Clinical groups of patients with Keratoconus						
Options OCT	**Group 1 (n = 40 eyes)**		**Group 2 (n = 50 eyes)**		**Comparison group (n = 96 eyes)**		**P ≤ 0,05**
	M ± m	**δ**	**M ± m**	**δ**	**M ± m**	**δ**	
Average RNFL thickness, μm	80,15 ± 1,29 [63; 100]	8,19	91,70 ± 1,09 [81; 112]	7,7	95,50 ± 0,81 [84; 125]	7,9	1-2 P≤0,0001; 1-3 P≤0,0001; 2-3 P = 0,003
RNFL symmetry, %	84,28 ± 1,44 [63; 96]	9,15	81,68 ± 2,07 [45; 97]	14,6	89,00 ± 0,53 [61; 97]	5,24	1-2 P = 0,16; 1-3 P = 0,0001; 2-3 P≤0,0001
Rim area, mm^2	1,27 ± 0,04 [0,79; 2,1]	0,21	1,42 ± 0,03 [1,00; 1,96]	0,24	1,58 ± 0,03 [1,15; 2,52]	0,25	1-2 P = 0,005; 1-3 P≤0,0001; 2-3 P = 0,0001
ONH area, mm^2	1,712 ± 0,059 [1,13; 2,57]	0,38	1,825 ± 0,047 [1,26; 2,57]	0,329	1,966 ± 0,036 [1,26; 2,82]	0,356	1-2 P = 0,04; 1-3 P = 0,0001; 2-3 P = 0,01
Cup/disc ratio, abs. value	0,444 ± 0,033 [0,07; 0,71]	0,21	0,430 ± 0,021 [0,08; 0,67]	0,154	0,406 ± 0,014 [0,07; 0,66]	0,141	1-2 P = 0,36; 1-3 P = 0,11; 2-3 P = 0,17
Vertical cup/disc ratio, abs. value	0,416 ± 0,034 [0,06; 0,71]	0,21	0,407 ± 0,021 [0,06; 0,64]	0,150	0,381 ± 0,014 [0,06; 0,64]	0,139	1-2 P = 0,4; 1-3 P = 0,12; 2-3 P = 0,14

Cup volume, mm^3	0,165 ± 0,028 [0; 0,531]	0,17	0,108 ± 0,014 [0; 0,363]	0,102	0,085 ± 0,007 [0; 0,326]	0,072	1-2 P = 0,03; 1-3 P = 0,0001; 2-3 P = 0,05
S	96,65 ± 2,36 [61; 136]	14,94	111,80 ± 2,21 [72; 143]	15,61	120,70 ± 1,20 [100; 155]	11,74	1-2 P≤0,0001; 1-3 P≤0,0001; 2-3 P≤0,0001
N	62,18 ± 1,84 [36; 84]	11,62	69,76 ± 1,93 [50; 119]	13,66	68,40 ± 1,24 [50; 119]	12,11	1-2 P = 0,003; 1-3 P = 0,003; 2-3 P = 2,6
I	103,05 ± 2,46 [63; 141]	15,61	119,34 ± 1,95 [95; 161]	13,77	124,10 ± 1,46 [102; 169]	14,33	1-2 P≤0,0001; 1-3 P≤0,0001; 2-3 P = 0,02
T	59,4 ± 1,76 [39; 93]	11,13	66,70 ± 1,82 [40; 101]	12,84	69,03 ± 1,14 [51; 107]	11,17	1-2 P = 0,002; 1-3 P≤0,0001; 2-3 P = 0,12

Table 1: *The results of a study of morphometric parameters of the optic nerve and retina in patients with Keratoconus, depending on the availability of undifferentiated connective tissue dysplasia (n = 186 eyes).*

Thus, the average layer thickness of the nerve fibers of the retina was statistically highly significantly less than in patients of other groups (80.15 ± 1.29 versus 91.70 ± 1.09 and 95.50 ± 0.81, respectively) (1-2 P≤0.0001; 1-3 P≤0.0001; 2-3 P = 0.003). The thickness of the RNFL by individual sectors (SNIT) in patients of group 1 was also statistically significantly less. Significant differences in the volume of excavation of the optic disc and the area of the neuro-retinal girdle were revealed. There were no significant differences in the average and vertical sizes of optic disc excavations between patients of different clinical groups. Patients of group 1, in contrast to representatives of group 2 and the comparison group, had significantly smaller optic disk sizes (1.712 ± 0.059 μm versus 1.825 ± 0.047 and 1.966 ± 0.036 μm, respectively) (1-2 P = 0.04; 1-3 P = 0.0001; 2-3 P = 0.01).

For the first time, we have put forward the assumption that keratoconus is a separate syndrome or part of the syndrome of pathology of the organ of vision in undifferentiated connective tissue dysplasia. In previous series of studies in patients with keratoconus with high frequency, we found valvar, vascular and arrhythmic syndromes of dysplasia connective tissue. The presence of mitral and tricuspital valve prolapses separately and in combination, as well as additional chords in the cavity of the left ventricle, as stigmas of congenital systemic pathology of CT, pathological changes in arteries and veins, heart rhythm disturbances, described in detail in [21], confirmed our hypothesis about the now clearly traceable connection of keratoconus with systemic damage to connective tissue.

Conclusion

Thus, morphometric changes in optic disk and retina in keratoconus are based on connective tissue insufficiency in its undifferentiated dysplasia Increased in size and deep excavation of the optic disc, reduced thickness of the layer of nerve fibers of the retina in the average values and/or in individual sectors of SNIT, currently not associated with keratoconus, from our point of view, are evidence of the presence of undifferentiated connective tissue dysplasia in the patient.

Clinical manifestations in keratoconus against the background of undifferentiated connective tissue dysplasia differ from the classical course of the disease - the combination is prognostic ally unfavorable, so all patients with suspected keratoconus should be additionally examined with OCT for early detection of morphometric changes in the optic disc and retina. In addition, it is necessary to consult a cardi-

ologist, since valvar, vascular and arrhythmic syndromes are considered marker syndromes of undifferentiated connective tissue dysplasia. When confirming the presence of connective tissue dysplasia, patients with keratoconus, along with the "gold" standard of treatment, need constant follow-up and collagen-stabilizing and neuroprotective therapy.

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