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MODERN APPROACH TO THE DIAGNOSIS OF NORMAL TENSION GLAUCOMA TAKING INTO ACCOUNT THE FEATURES OF ITS PATHOGENESIS

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✧ Normal tension glaucoma was isolated as a separate clinical form of primary open-angle glaucoma at the end of the 20th century. In the article, various points of view on the development of this most difficultly diagnosed variety of glaucoma, as well as modern concepts of the pathogenesis of normal tension glaucoma which determine the strategy of a new approach to its diagnosis, are reviewed in the historical aspect.

✧ ***Keywords:*** normal tension glaucoma; trans-laminar cribrosa pressure gradient; lamina cribrosa thickness; lamina cribrosa depth; optic nerve subarachnoid space width.

СОВРЕМЕННЫЙ ПОДХОД К ДИАГНОСТИКЕ ГЛАУКОМЫ НОРМАЛЬНОГО ДАВЛЕНИЯ С УЧЁТОМ ОСОБЕННОСТЕЙ ЕЁ ПАТОГЕНЕЗА

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✧ Глаукома нормального давления была выделена в отдельную клиническую форму первичной открытоугольной глаукомы в конце XX в. В статье в историческом аспекте рассмотрены различные точки зрения на развитие этой наиболее труднодиагностируемой разновидности глаукомы, а также современные концепции патогенеза глаукомы нормального давления, определяющие стратегию нового подхода к её диагностике.

✧ ***Ключевые слова:*** глаукома нормального давления; трансмембранный градиент давления; толщина решётчатой пластинки; глубина решётчатой пластинки; ширина субарахноидального пространства зрительного нерва.

INTRODUCTION

Glaucoma is one of the main causes of irreversible blindness and vision disability worldwide, claiming the first position as a leading cause in Russia. The most common type of primary open-angle glaucoma (POAG) is hypertensive form, which is characterized by a high level of intraocular pressure (IOP). However, glaucoma is not always accompanied by an increase in ophthalmotonus. At the end of the 20th century, normal tension glaucoma (NTG) was identified as a separate clinical form, in which all the signs characteristic of glaucoma (specific atrophy of the optic nerve head (ONH) in the form of advanced cupping and, as a consequence, characteristic disorders in the visual field) developed without an increase in the IOP level [1, 2].

In the 1970s, V.V. Volkov was the first in the global ophthalmology to develop the concept of glaucoma pathogenesis. According to this concept, glaucomatous optic neuropathy (GON) occurs because of deflection of the cribriform membrane (CM)/cribriform plate (CP) (CM/CP) of the sclera due to a disorder in the transmembrane pressure gradient (TMPG) between IOP and tissue liquor pressure [3]. The main risk factor for the development of hypertensive POAG is an increased level of IOP. However, according to

V.V. Volkov's concept, the important risk factor for NTG is a lowered level of intracranial pressure (ICP) and, accordingly, a lowered pressure of cerebrospinal fluid (CSF) in the subarachnoid space (SAS) of the ON; therefore, V.V. Volkov defined this form of POAG as optical-liquor hypotensive POAG. In addition, the CP deflection can be facilitated by changes in its biomechanical properties, which aggravate due to age-related degenerative restructuring of the CP matrix biochemistry and the surrounding sclera from changes in the composition of collagen. In this case, even the normal TMPG becomes excessive, and according to V.V. Volkov, it leads to the development of membrane-dystrophic POAG.

ROLE OF BLOOD AND INTRACRANIAL PRESSURE IN THE DEVELOPMENT OF NORMAL TENSION GLAUCOMA

A majority of scientists considers glaucoma as a set of multifactorial diseases with a threshold effect, that is, it occurs in cases where the combination of unfavorable factors (risk factors) exceeds the threshold for the implementation of the disease scenario. The reasons contributing to the development of glaucoma are not fully understood. However, several theories have been developed to explain the pathogenesis of GON. The most famous of these theories are of mechanical (biomechanical, in the current interpretation), vascular, and metabolic nature. The earliest ones are mechanical (H. Müller, 1858) and vascular (E. Jaeger, 1858) theories [4, 5].

S. Drance [6], known for his research on the NTG pathogenesis, attached great importance to systemic arterial hypotension, in which the perfusion pressure in the blood vessels of the eyeball, including those supplying the blood to the intraocular and retrobulbar parts of the ON, is lowered. The systemic arterial hypotension is the primary cause of the development of GON; hence, it is the guiding idea of the contemporary interpretation of the vascular theory of NTG pathogenesis. Using color Doppler imaging, Y. Yamazaki and S. Drance [7] studied the blood flow velocity in the system of the posterior short ciliary arteries and the central retinal artery in POAG patients with normal and increased IOP. The study revealed that in NTG patients with progressive deterioration in the visual field, the blood flow velocity in the central retinal artery and posterior short ciliary arteries was significantly lower ($p = 0.04$) than that in patients with a stabilized course of NTG. The authors did not find such a difference in patients with hypertensive form of POAG with stabilized and nonstabilized course. N. Plange et al. came to a similar conclusion in their studies [8]. The authors studied the relationship between blood flow parameters (peak systolic velocity, end diastolic velocity, and blood flow resistance index) in the ophthalmic artery, the central retinal artery, measured using color Doppler imaging, and defects in filling the capillaries of the optic nerve head (ONH) with fluorescein in NTG patients and the control group. As a result, lower ($p < 0.05$) blood flow velocity and higher ($p < 0.01$) blood flow resistance index were registered in NTG patients compared with patients of the control group. Accordingly, the number of defects in filling of the ONH blood vessels with fluorescein was significantly higher ($p < 0.01$) in NTG patients.

Earlier, scientists have found the relationship between arterial hypotension and its adverse effect on visual functions in patients with glaucoma. Therefore, in 1959, D. Harrington noted deterioration in the visual field (appearance of scotomata in the Bjerrum area, nasal step, and narrowing of the peripheral boundaries) in three patients after consuming the antihypertensive drug, reserpine [9]. Similarly, R. Sachsenweger [10] and R. Ebner [11] noted a more rapid deterioration in the visual field in patients with glaucoma and low blood pressure (BP) than in those with normal or high BP. J. Tielsch et al. [12] studied a large sample of the general population (5308 patients of 40 years and above). They noted a lower IOP level in patients with arterial hypotension (i.e., systolic blood pressure (SBP) below 110 mmHg and diastolic blood pressure (DBP) below 60 mmHg) than in hypertensive patients. Moreover, based on the data obtained, the authors calculated the perfusion pressure, which turned out to be lower in POAG patients compared with that in healthy people.

S. Hayreh et al. [13] performed daily monitoring of BP in POAG patients with elevated and normal IOP and in patients with anterior ischemic optic neuropathy. The authors revealed a more pronounced decrease in DBP in NTG patients ($p = 0.0044$) than in patients with anterior ischemic optic neuropathy. In addition, it was noted that in hypertensive patients who received oral antihypertensive therapy, there was a statistically significant relationship ($p = 0.0445$) between the nighttime decrease in BP and deterioration in the visual field. In a similar study, S. Graham et al. [14] performed daily monitoring of BP in POAG patients with normal and increased IOP and in healthy individuals from the control group. They did not obtain a statistically significant difference between the mean values of the parameters under study (daily SBP and DBP at night and daytime) in NTG patients and hypertensive POAG patients.

Additionally, they identified two groups of patients from the nature of the glaucoma process course (presence or absence of progression in changes in the visual field). In the group of patients with non-stabilized course of glaucoma, nocturnal decreases in the studied BP parameters were registered more often (in 29 out of 37 patients) and were more pronounced ($p = 0.001$) than in the group of patients with stabilized POAG [14].

J. Melgarejo et al. studied the effect of BP level on the glaucoma progression [15]. The authors revealed that GON patients had lower DBP values than that of healthy individuals ($p < 0.014$). However, according to the authors, it is the significant decrease in SBP and/or DBP at night (more than by 20% of the level of daytime indicators) that contributes to the development and progression of GON ($p < 0.007$).

In addition to reduction in the perfusion pressure in the ophthalmic artery system, the tendency of the vascular system to vasospasm is a significant factor in glaucoma patients. One of the manifestations of vasospastic reactions is migraine. For the first time, C. Phelps and J. Corbett paid attention to this fact, noting that headaches are more common in patients with NTG than those with hypertensive POAG and healthy people ($p = 0.01$ and $p = 0.02$, respectively) [16]. Later, this fact was confirmed by S. Drance et al. [17, 18], who studied the capillary blood flow in the subungual space in POAG patients with normal and high IOP and healthy individuals of the control group. The blood flow velocity was found to be lower in NTG patients compared with those in the control group ($p < 0.05$); whereas, this difference increased ($p < 0.0005$) after using the cold test [17, 18]. A special role of vasospasm in the development of NTG was noted by J. Flammer [19], who introduced the concept of "primary vascular dysregulation" or Flammer's syndrome, which refers to inappropriate narrowing and/or dilation of morphologically healthy blood vessels in response to mechanical, physical, or stress-inducing stimuli. With primary vascular dysregulation, instability in the blood supply of the ONH is noted, and the processes of ischemia and reperfusion alternate, which results in increased apoptosis of retinal ganglion cells [20–24].

Thus, many authors believe that vascular failure is the main factor in the development of NTG. However, similar to hypertensive POAG, a loss of the nerve fiber layer, increase in the size of cupping, and peripapillary atrophy of the retina, which is not noted in ischemic optic neuropathies, occur in NTG [25]. Therefore, scientists continued to search for new factors affecting the development of GON in individuals with NTG.

In the early 20th century, K.I. Noishevsky, Privatdozent of the Department of Ophthalmology at the Military Medical Academy, wrote in his monograph "Glaucoma, Its Etiology and Treatment" (1915) that "in one case, the pressure of 27 mmHg does not cause glaucomatous changes in the eye, while in other cases, they are caused by a pressure below 27 mmHg. Can we smooth over these contradictions only by disrupting the balance between intraocular and intracranial pressure?" This finding appears to be the first attempt to explain the pathogenesis of glaucoma with normal IOP. K.I. Noishevsky came to this conclusion based on the results of his own experiments performed in the laboratory of I.P. Pavlov. This study included two dogs that had bilateral glaucomatous excavation, which was confirmed by not only ophthalmoscopic but also histological examination, a month after craniotomy. K.I. Noishevsky explained the results obtained from the lymph flow disorder, believing that "in the normal state of the eyeball hydrostatics, lymph flows from the vascular membrane and the ciliary body toward the anterior chamber, and only 1/50 of the total flow of lymphatic fluid is directed to the optic papilla. With decrease in ICP as well as with an increase in intraocular pressure, the lymph flows in the opposite direction, that is, to the optic papilla" [26].

In 1974, R.I. Korovenkov under the guidance of Prof. V.V. Volkov was the first in the world to measure experimentally the pressure of the CSF in the intermembrane spaces of the ON and confirm the existence of TMPG. This study was performed under the conditions of a technically complex experiment using a micropipette that was inserted through the dura mater into the SAS of the ON of a rabbit and a specially designed device for measuring fluid pressure in small volumes. As a result, the CSF pressure was within the range of 6.0–10.5 mmHg [27].

Twenty years later, W. Morgan et al. [28] measured the retrolaminar tissue liquor pressure in dogs using a special pipette, which was inserted through the flat part of the ciliary body directly into the center of the OND. The authors confirmed that the IOP and tissue liquor pressure differential occurs in the plane of the CP. In his further studies, W. Morgan determined that the CSF pressure (7.7 ± 0.7 mmHg) in the ON membranes is insignificantly lower than that in the lateral ventricles of the brain (8.9 ± 2.8 mmHg), and these two indicators are in direct relationship ($p < 0.001$) [29].

According to the Monro – Kellie doctrine, "in the cranial cavity, there should be a dynamic balance of

three constituent components, namely brain tissue, CSF, and blood, the relationship of which determines the level of ICP (A. Monro, 1783; G. Kellie, 1824)" [30]. According to M. Albeck et al. [31], the range of normal ICP values in the prone position depending on age is 7–15 mmHg in healthy adults, 3–7 mmHg in children, and 1.5–6 mmHg in infants. In a sitting position, ICP value decreases to below 0 mmHg in adults [32]. The study by D. Fleischman et al. confirmed that there is a tendency for a decrease in CSF production with age, and accordingly, a minor decrease in the level of ICP [33]. The authors revealed that the ICP level decreases from 11.56 mmHg at the age of 20–49 years to 11.26 mmHg at 50–54 years and up to 8.46 mmHg in people aged over 90 years.

However, age is not the only factor that can influence ICP levels. L. Pasquale et al. [34] examined more than 78,000 women and revealed a lower ($p = 0.01$) risk of developing glaucoma in patients with an increased body mass index (BMI) compared with those whose BMI was lower or within the normal values. J. Berdahl et al. [35] performed lumbar puncture in POAG patients with elevated and normal IOP levels, patients with ophthalmic hypertension (OH), and a control group of healthy individuals. A lower level of ICP was revealed in NTG patients compared with those having the OH form of POAG (8.7 ± 1.16 and 9.1 ± 0.77 mmHg, respectively; $p < 0.01$). Moreover, the ICP level was found to be higher in patients with OH than in the control group (12.6 ± 0.85 and 11.8 ± 0.71 mmHg, respectively; $p < 0.05$) [36]. The authors suggested that the imbalance between IOP and ICP plays an important role in the pathogenesis of glaucoma and contributes to its development.

R. Ren et al. [37] examined patients with NTG and hypertensive POAG and healthy individuals. According to the data of lumbar puncture, the ICP level in NTG patients was significantly lower than that in patients with hypertensive POAG and healthy individuals (9.5 ± 2.2, 11.7 ± 2.7, and 12.9 ± 1.9 mmHg, respectively; $p < 0.001$). In addition, R. Ren et al. [38] examined patients without glaucoma but with various neurological diseases that did not affect the ICP level. All patients underwent lumbar puncture to assess ICP levels. As a result, a higher level of ICP was noted in patients with a higher BMI ($p < 0.001$) and a higher level of IOP ($p < 0.001$). After the analysis of more than 4000 case histories of patients who underwent lumbar puncture, J. Berdahl et al. [39] revealed a positive relationship between BMI and ICP levels ($p < 0.001$). It was observed that with an increase in BMI from 18 to 39 kg/m^2, the ICP level increased by 37.7% (from 8.6 ± 2.1 to 14.1 ± 2.5 mmHg). However, there was no correlation between IOP and BMI ($p = 0.14$).

H. Killer et al. [40] investigated the movement of CSF between the basal cisterns in the brain and the SAS of the ON in patients with NTG and healthy individuals using computed cisternography along with the administration of a contrast agent. The authors measured the density of the contrast agent in the CSF and revealed its significant decrease in the SAS of the ON compared with the basal cisterns in patients with NTG; while in healthy individuals, such a difference in the density of the contrast agent was not revealed ($p = 0.003$). The authors concluded that in patients with NTG, there is a metabolic imbalance of CSF at the level of the intracranial part of the ON. In the subsequent work of the same authors, the aspects of the movement of the CSF in the SAS in different parts of the ON were studied in patients with NTG and healthy individuals. In patients with NTG, the density distribution of the contrast agent in the CSF of the ON was significantly lower than that in the control group, and with a significantly lower content of contrast agent in the CSF of the retrobulbar section of the ON ($p < 0.001$). The results of this study confirmed that patients with NTG have a disorder of the CSF dynamics in the ON and mainly in the area of its retrobulbar region, which undoubtedly may be a significant factor in the development of NTG [41].

Transmembrane pressure gradient

According to V.V. Volkov's concept on the pathogenesis of glaucoma, due to the normal TMPG (the difference between IOP and tissue liquor pressure at the CP level), not only the flow of venous blood from the posterior segment of the eyeball beyond its limits but also the axoplasmic flow along the axons of the ON to the brain is provided. A faster neurotrophin flow toward it is noted. The CSF flows from the brain to the eye through the intermembrane spaces of the ON. The pressure of the CSF normally determines the lower level of tissue liquor pressure in the retrolaminar field of the OND in comparison with the prelaminar field [1, 3, 42].

In 1979, M. Yablonsky et al. [43], in fact, repeated the experiment of K.I. Noishevsky [26], performing craniotomy of animals (cats). However, these authors installed a cannula into the anterior chamber of the cat's left eye immediately after craniotomy for a dosed decrease in the IOP level and registered the development of glaucomatous excavation of the OND, but only in the right eye. Using the anterior chamber

cannula, the increase in TMPG was eliminated; therefore, in the left eye, in contrast to the right eye, glaucoma excavation of the OND did not develop. The results of this original study demonstrated very clearly and convincingly the pathogenetic relationship between lowered ICP and the development of GON.

V.V. Volkov's concept on the TMPG role in the glaucoma pathogenesis was confirmed and further developed in the studies by distinguished international scientists as early as in the 21st century. At the International Symposium in Moscow in 2014, the famous German scientist, J. Jonas, emphasized in his report "Cerebrospinal Fluid Pressure: The 'X Factor' in Glaucoma" the international priority of V.V. Volkov in creating a new concept of glaucoma pathogenesis, taking into account the value of TMPG that increases with both an increase in IOP and a decrease in ICP [44].

Under the guidance of J. Jonas, a group of authors evaluated TMPG in a large population of healthy individuals and POAG patients, first in India (9301 and 121 eyes, respectively), and then in China (6184 and 234 eyes, respectively). In India, the average TMPG was 3.64 ± 4.25 mmHg in healthy individuals and 9.65 ± 8.17 mmHg in POAG patients. In glaucoma, the authors revealed a significant relationship ($p < 0.001$) between an increase in TMPG and the presence of GON, and there was no correlation between the level of IOP and the presence of GON ($p = 0.08$) [45]. In Chinese residents, TMPG values averaged 5.8 ± 4.1 mmHg in healthy individuals and 7.9 ± 4.9 mmHg in POAG patients, and the difference was significant ($p < 0.001$) [46].

R. Ren et al. [47] compared IOP and ICP values measured during lumbar puncture in OH patients and healthy people of the control group. The authors found a higher ICP level in OH patients compared with those in the control group (16.0 ± 2.5 and 12.9 ± 1.9 mmHg, respectively; $p < 0.001$) and concluded that in OH patients, GON does not develop because TMPG is within normal values due to higher ICP indicators. Y. Wang et al. [48] determined the TMPG values in the general population without POAG by calculating the ICP level using their own mathematical formula. As a result of these studies and calculations, higher ICP values were detected in patients with higher IOP levels ($p < 0.001$).

The clinical case of NTG described by B. Chen et al. [49] is of great interest. A 93-year-old female patient with previously diagnosed NTG in both eyes underwent a neurosurgical intervention in the form of installation of a ventriculoperitoneal shunt for normotensive hydrocephalus to improve the outflow of CSF. One month after the surgery, the ophthalmologist diagnosed the progression of GON in the patient based on the deterioration of the OND (the appearance of hemorrhages and expansion of the excavation) and the visual field. The authors concluded that the decrease in ICP values after the neurosurgical procedure led to the progression of NTG due to an increase in TMPG.

In 2011, J. Jonas took on a leadership role in the large-scale Beijing Eye Study conducted in the general population (3468 individuals) of China to investigate the relationship between the values of ICP, IOP, TMPG, height indicators, BMI, BP (systolic and diastolic), and heart rate. As a result, a reliable relationship was revealed between the ICP value and BMI level calculated according to the mathematical formula developed by the authors ($r = 0.67$, $p < 0.001$), as well as the BP level ($r = 0.75$, $p < 0.001$) and less pronounced with high height ($p = 0.002$) and increased heart rate ($p < 0.001$). In this study, the mean TMPG value was 5.9 ± 4.2 mmHg and its increase was, as a rule, associated with low growth rate, BMI, and BP level [50].

C. Linden et al. [51] performed a lumbar puncture and determined ICP and TMPG values in 13 NTG patients and 11 healthy individuals. The authors did not reveal a significant difference between the average values of ICP (7.0 ± 2.9 and 6.6 ± 1.4 mmHg, respectively; $p = 0.24$) and TMPG (13.7 ± 3.8 and 12.3 ± 2.2 mmHg, respectively; $p > 0.05$). S. Lee et al. [52] calculated ICP using the well-known formula [48] and determined TMPG in healthy individuals and NTG patients, having distributed the latter into two groups according to the IOP level (Group 1 with IOP less than 15 mmHg and Group 2 with IOP within 15–21 mmHg). The authors found a significant difference between the mean values of TMPG in healthy individuals and NTG patients of the Group 2 (2.31 ± 0.06 and 6.48 ± 0.27 mmHg, respectively; $p = 0.006$), and the difference between these parameters in healthy individuals and NTG patients of the Group 1 was not significant (2.31 ± 0.06 and 2.11 ± 0.24 mmHg, respectively; $p = 0.636$).

G. Jaggi et al. [53] performed computed tomography (CT) of the head in 18 NTG patients and 17 healthy people to determine the diameter of the retrobulbar part of the ON (with membranes) in the axial plane. This diameter of the ON was significantly greater in NTG patients than in healthy individuals (7.96 ± 0.9 and 6.36 ± 0.5 mm, respectively; $p < 0.001$). The authors explained their results by thinning of the ON membranes due to the high

activity of inflammatory mediators and, as a result, their increased extensibility.

A. Pircher et al. [54] examined NTG patients and healthy individuals. Lumbar puncture was performed to all of them to determine the ICP level and measure the diameter of the ON with its membranes on axial CT images of the head at a distance of 3 mm behind the eyeball. In NTG patients, the mean value of the diameter of the ON with membranes was significantly greater (6.4 ± 0.9 mm, $p < 0.000$) than in healthy individuals (5.4 ± 0.6 mm), which the authors explained by the impairment of the anatomical connection between the intracranial and intraorbital sections of the SAS of the ON. The mean ICP value in the group of NTG patients amounted to 11.6 ± 3.7 mmHg, but no significant relationship between the diameter of the ON with the membranes and the level of ICP was found ($p = 0.72$).

CT is known to be the best method to assess bone structures; therefore, it was used in detecting bone damage, and magnetic resonance imaging (MRI) was developed to study the conditions of soft tissue structures in the 1980s. Therefore, in modern studies, the latest models of MRI tomographs with a magnetic field induction of 1.5 or 3 T are used, which provide clearer MR images of the ON with fewer artifacts, to measure the ON diameter with and without membranes.

The increased interest in assessing the CSF pressure when studying the NTG pathogenesis necessitated the development of noninvasive methods for determining ICP. There are numerous invasive methods for assessing ICP and some of them are quite precise, but all of them are associated with infectious and hemorrhagic risks for the patient, which limits their widespread use [55]. Therefore, various noninvasive methods have been developed and proposed. In 1989, R. Marchbanks proposed to evaluate ICP from the displacement of the tympanic membrane, considering this shift to be the result of a change in the pressure of the perilymph in the cochlear duct with a change in the level of ICP. However, the result of this method only roughly indicates the dynamics of changes in ICP in a particular patient [56]. One of the attempts to assess ICP was the interpretation of the data of transcranial Doppler imaging of the medial cerebral artery. To assess cerebral perfusion pressure, a computer analysis of the wave characteristics of BP and linear blood flow velocity in the medial cerebral artery was used, but the results had a large error (±10 mmHg) [57].

R. Firsching [58] suggested assessing the ICP level using ophthalmodynamometry. A study with intraventricular ICP monitoring was conducted, in which 22 patients with suspected hydrocephalus participated. Ophthalmodynamometry was used to measure the pressure level of the central retinal vein, and a strong correlation was revealed ($r = 0.983$, $p < 0.001$) by comparing it with real ICP indicators from the monitoring results. Based on the data obtained, a mathematical formula was developed to calculate the ICP level.

According to the literature, few studies used an ultrasonic method named "time-of-the-flight" technique, which was based on the assessment of the rate of an ultrasonic wave passage in the cranial cavity. However, this method lacked widespread use due to the large difference in the thickness of the skull bones in subjects, lack of standardization in the location of sensors, and low measurement accuracy [59].

In 2008, a group of Japanese scientists led by A. Watanabe conducted a study involving 12 patients with intracranial hypertension who required surgical treatment. ICP was measured in these patients using a manometer before, during (before opening the dura mater), and after the surgery. MRI of the orbits in the mode of adipose tissue suppression was performed to obtain transverse images of the sections of the ON. The authors estimated the diameter of the ON with membranes before (6.1 ± 0.7 mm) and after (4.8 ± 0.9 mm) the surgery using MR images and obtained a strong correlation between diameter and ICP level ($r = 0.879$, $p = 0.0036$). They also explained the significant decrease in diameter after surgery in terms of decrease in the ICP level [60].

Arterial hypotension, which is often detected in NTG patients, is known to be usually accompanied by a decreased level of ICP, which may result in decrease in the CSF filling between the meninx serosa and pia mater of the brain and the spinal cord, namely SAS, including ON, and, accordingly, narrowing of this space. In this regard, N. Wang et al. [61] studied the relationship between the width of the SAS of the ON and the level of ICP in POAG patients with high and normal IOP and in healthy individuals as well. For this purpose, the patients underwent MRI of the head with obtaining transverse sections of the ON at a distance of 3, 9, and 15 mm behind the eyeball. At all three measurement points, the width of the SAS of the ON was significantly lower ($p < 0.001$) in NTG patients (0.67 ± 0.16, 0.55 ± 0.09, and 0.51 ± 0.12 mm, respectively) than in patients with hypertensive POAG (0.93 ± 0.21, 0.70 ± 0.12, and 0.62 ± 0.11 mm, respectively) and in the control group (0.87 ± 0.15, 0.67 ± 0.07, and

0.61 ± 0.07 mm, respectively). The authors have developed mathematical formulas for calculating ICP, in other words, the pressure of the CSF in the SAS of the ON at the levels of 3, 9, and 15 mm behind the eyeball. In their further studies, the same group of authors confirmed these results by examining the ON using a modern ultrasonic device. In the B-scan mode with a frequency of 12.5 MHz, the area of the SAS of the ON was determined at a distance of 3, 5, and 7 mm behind the eyeball. This indicator was significantly lower ($p = 0.0008$) in NTG patients (5.15 ± 0.81 mm^2) than in patients with hypertensive POAG (6.24 ± 1.62 mm^2) and healthy individuals (6.40 ± 2.20 mm^2). The authors also explained the results obtained by the decreased ICP and the associated decrease in filling of the SAS of the ON with CSF and, accordingly, the narrowing of SAS in NTG patients [62].

BIOMECHANICAL PROPERTIES OF THE CRIBRIFORM PLATE OF THE SCLERA IN NORMAL TENSION GLAUCOMA PATIENTS

Based on the characteristics of the pathogenesis of glaucomatous failure of CP, V.V. Volkov identified three clinical forms of GON, namely hypertensive, optical-liquor hypotensive, and membrane dystrophic. Therefore, it is not only a matter of TMPG, but also the biomechanical properties of CP itself are the most significant as they worsen due to age-related dystrophic restructuring of the biochemistry of its matrix and the surrounding sclera due to changes in the composition of collagen. In this case, even the normal value of TMPG becomes excessive, and according to V.V. Volkov, leads to the development of membrane-dystrophic POAG [2].

The contemporary notion of the role of biomechanical factors in the onset and progression of GON is presented in the scheme developed by J. Downs et al. [63]. The risk of tissue deformity is determined by not only the level of IOP, but also the gradient of IOP and CSF pressure, the mechanical properties of the tissues themselves, which deteriorate due to age-related dystrophic changes in the CP, and the surrounding sclera due to changes in the collagen composition. Tissue deformity leads to the disorder of the axoplasmic flow and blood supply to the OND, and the latter further worsens the axoplasmic flow. All this complex pathology leads to damage in axons in the CP. Under conditions of ischemia and hypoxia, astrocytes and CP glial cells are activated, which leads to remodeling of connective tissue and deterioration of its biomechanical properties.

M. Sullivan Mee et al. [64] proposed to evaluate the viscoelastic properties of the corneoscleral membrane in patients with glaucoma in terms of corneal hysteresis. According to the authors, corneal hysteresis more accurately indicates the structural and functional state of CP in glaucoma than the indicator of the central corneal thickness. E.N. Iomdina et al. [65–67] studied the biomechanical properties of the sclera and CP in patients with glaucoma. The authors revealed that with POAG in the sclera, the levels of collagen types I and III increase, as well as the transverse connectivity of collagen structures increases, which leads to an increase in rigidity and a decrease in the permeability of the fibrous capsule of the eye.

In experimental studies on primates, A. Bellezza et al. [68] established that the deflection of the CP occurs at an early stage of induced glaucoma. Later, H. Yang et al. [69] conducted similar studies, which demonstrated that the upper temporal quadrant of CP is susceptible to the greatest deflection at the initial stage of experimental glaucoma due to the peculiarities of its anatomical structure.

Under the guidance of J. Jonas [70], histological sections of 42 eyes enucleated for choroidal melanoma without changes in the OND (control group) and 11 eyes enucleated for painful closed-angle glaucoma (main group) were studied. As a result, reliably ($p < 0.01$) thinner CP was revealed in patients with glaucoma (201.5 μm) compared with the control group (457.7 μm). In their studies, H. Park et al. [71, 72] measured CP thickness in POAG patients with high and normal BP and in healthy people. The measurements were performed using a spectral optical coherence tomograph, and in NTG patients, the CP thickness (175.1 ± 22.60 μm) was found to be significantly lower ($p < 0.001$) than that in healthy people (348.14 ± 23.41 μm) and in patients with hypertensive POAG (237.82 ± 40.32 μm). In their subsequent studies, the authors concluded that the measurement of the CP thickness in terms of diagnostic significance is comparable ($p = 0.001$) with the determination of the thickness of the retinal nerve fiber layer in patients with the initial stage of NTG. In the by K. Omodaka et al. [73], a significant ($p < 0.01$) difference was obtained in the CP thickness in healthy people (282.6 ± 20.6 μm), patients with preperimetric glaucoma (261.4 ± 15.8 μm), and NTG patients (232.6 ± 33.3 μm). The authors believed that the measurement of CP thickness may be an important criterion in diagnosis and study of glaucoma pathogenesis. At the same time, S. Yokota et al. [74], when examining patients with secondary

neovascular glaucoma and healthy individuals revealed no significant differences in thickness and depth of CP (155.0 ± 4.7 and 407.0 ± 22.9 μm; 156.9 ± 4.2 and 403.9 ± 20.1 μm, respectively) [74].

M. Kim et al. [75] measured the CP depth (the posterior displacement of the CP) in 66 patients with NTG and 100 patients with hypertensive POAG using an optical coherence tomograph and Humphrey perimeter tests were performed. The authors found that the CP depth was lesser in patients with NTG (539.4 ± 140.5 μm) than that in patients with hypertensive POAG (565.9 ± 143.2 μm), but only the group of patients with NTG showed a significant relationship ($p < 0.045$) between the mean values of the CP depth and the global MD index. R. Furlanetto et al. [76], investigating the depth of CP, found that in POAG patients, CP is displaced more posteriorly compared with healthy eyes (438 ± 102 and 353 ± 70 μm, respectively; $p < 0.03$). L. Li et al. [77] also concluded that the measurement of CP depth enables in differentiating glaucoma patients from healthy individuals because this indicator was significantly higher ($p < 0.01$) in patients with hypertensive POAG (538.8 ± 96.8 μm) than in NTG patients (403.8 ± 85.4 μm) and healthy individuals (336.4 ± 57.9 μm).

S. Lee et al. [78] compared the parameters of CP depth and curvature in POAG patients and healthy individuals. According to the measurement results, the CP depth in the former was significantly greater than that in the latter (527.0 ± 116.4 and 413.3 ± 80.4 μm, respectively; $p < 0.001$). To determine the CP curvature index, the authors used the average value of measurements of the curvature of its surface at seven different points. According to the authors, CP curvature index is more significant for diagnosis of POAG than the CP depth indicator. Y. Kim et al. [79] monitored POAG patients for 3 years, determining changes in CP depth and in the state of the visual field. At the end of the study, they were all distributed into three groups according to the increase, decrease, and lack of changes in CP depth. A significant relationship ($p < 0.001$) between the progression of changes in the visual field and CP was registered only in the Group 1 of patients (increase in CP depth). Therefore, the authors suggested using the CP depth index as a criterion for the progression of the glaucomatous process.

Thus, V.V. Volkov's concept on the pathogenesis of glaucoma, based on the fact that GON develops as a result of the scleral CP deflection due to a disorder of the gradient between IOP and ICP, has been confirmed thoroughly in modern works by distinguished international scientists. The emergence of new high-precision devices that enable to perform precise morphometric studies of structures that were previously inaccessible for measurement (thickness and depth of the CP and width of the SAS of the ON) and develop noninvasive methods for assessing the level of ICP and TMPG on the basis of the data obtained provides new perspectives for a modern approach in studying pathogenesis and improving the diagnosis of NTG, which is the most hazardous clinical form of POAG.

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