ECRONICON OPEN ACCESS

EC OPHTHALMOLOGY
Research Article

Pathogenetic Classification of Primary Angle-Closure Glaucoma

Bakunina NA[1,2,3]* and Balashova LM[1,2]

[1]*International Scientific and Practical Center for Tissue Proliferation, Moscow, Russia*

[2]*Pirogov Russian National Research Medical University, Moscow, Russia*

[3]*N.I. Pirogov City Clinical Hospital №1, Leninskiy Prospect, Moscow, Russia*

***Corresponding Author:** Bakunina NA, International Scientific and Practical Center for Tissue Proliferation, Moscow, Russia.

Received: March 27, 2023; **Published:** June 12, 2023

Abstract

Purpose: The classification of primary angle-closure glaucoma (PSG) on the basis of genetic studies is proposed.

Methods: 30 patients (46 eyes) aged 40 to 65 years with various forms of angle-closure glaucoma were examined.

Results: Clinical and genetic analysis of patients with primary angle-closure glaucoma was carried out. It is noted that the classification based on biometric indicators does not take into account the genetic characteristics of patients with PACG, predisposition to which is inherent at birth. Indications for preventive laser iridectomy with appositional closure of the anterior chamber angle are substantiated.

Conclusion: The innate nature of PACG dictates the need for the formation of a pathogenetic classification of PACG.

Keywords: *Primary Angle-Closure Glaucoma; Classification; Genetic Polymorphisms*

Introduction

Currently, there are difficulties in the classification of primary angle-closure glaucoma (PACG). According to the European Guidelines (European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 2 (2017), the primary closure of the anterior chamber angle goes through three stages: Primary angle closure suspect (PACS), primary closure Primary angle closure (PAC) Primary angle closure glaucoma (PACG) all forms of PZUG. Primary angle closure (PZU, iridotrabecular contact with peripheral anterior synechiae) - Iridotrabecular contact with peripheral anterior synechiae (ITC with PAS) - eyes with iridotrabecular contact and anterior synechiae, may be with increased IOP, but without signs of glaucomatous neuropathy and changes in visual fields (PE) [1]. Angle closure implies that, on gonioscopy, the posterior pigmented trabecular meshwork was not visible at least 180° when the patient was looking straight ahead according to the P. Foster classification [2]. According to European guidelines, the term "glaucoma" - primary angle-closure glaucoma (PACG), primary angle-closure glaucoma (PACG) is used in the presence of glaucomatous optic neuropathy. According to the classification of Svend Wedel Kessing and John Tygesen, the classification of glaucoma includes pupillary block (PB) - pupil block (PB), iris plateau (PR) - plateau iris (PI) and a mixed mechanism, which includes eyes with pupillary block after laser iridectomy [3]. Mixed glaucoma includes the following types [4]:

- CPC is closed only in one segment and open in other departments;
- CPC is open, but it is very narrow, slit-like;
- The blockade of the APC by the root of the iris was subsequently superimposed on the previously installed OAG.

Combined glaucoma in foreign literature includes: pseudoexfoliative syndrome; eyes with open-angle glaucoma, in which angle closure may develop, either due to the natural development of pupillary block or due to increased miotic therapy [5]. We propose a pathogenetic classification of PACG and mixed glaucoma, taking into account the found genetic polymorphisms in PACG.

Purpose of the Study

The purpose of the work is to develop a pathogenetic classification of primary angle-closure glaucoma (PACG) based on genetic studies.

Materials and Methods

Retrospectively, 30 patients (46 eyes) were selected, aged 40 to 65 years, with various forms of angle-closure glaucoma in the initial, advanced, advanced and terminal stages of the disease, which were divided into 3 groups: 1) a group of patients with primary closure of the anterior chamber angle who underwent effective prophylactic laser iridectomy (LIE) (10 patients, (18 eyes), 4 men, 6 women aged 45 to 75 years) patients (12 eyes), 3 men, 5 women aged 45 to 75 years). 3) a group of patients with chronic angle-closure glaucoma (8 patients, 16 eyes) who underwent ineffective LIE.

The follow-up period ranged from 5 to 15 years. Laboratory diagnostic equipment was used for general clinical and biochemical analyses. General clinical: genetics consultation, family history, disease history, age of onset and rate of progression, physical examination. Clinical instrumental: viscometry, refractometry, gonioscopy, biomicroscopy, optical coherence tomography of the anterior and posterior segments of the eye, perimetry, pneumotonometry, ophthalmoscopy, OCT angiography. Molecular Genetic: Nextera Rapid Capture Exomev1.2 reagents (Illumina) were used for sequencing. Whole exome sequencing (WES) was performed on an Illumina NovaSeq 6000 sequencer using paired-end read (2x101 bp) with an average coverage of at least 70-100x. together with the Head of the genetic diagnostics project oftalmic.ru, PhD, ophthalmologist, leading project manager Direction "Gene Therapy" of the Scientific and Technological University "Sirius" Viner (Ivanova) M.E. For sample preparation, the technique of selective capture of DNA regions was used [6].

Bioinformatic analysis and in silico experiment, variant annotation were performed using standard and proprietary algorithms. With the help of bioinformatics processing of "raw" patient genetic data using a customized pipeline (a set of programs) [7]. Histological: Sagittal sections, as well as serial transverse sections, were examined using the paraffin section method. Stained with hematoxylin-eosin. The studies were carried out jointly with A.A. Fedorov, Candidate of Medical Sciences, Head of the Laboratory of Fundamental Research in Ophthalmology of the Federal State Budgetary Scientific Institution "Research Institute of Eye Diseases" of the Ministry of Health [29]. Patients with concomitant ocular pathology (vitreomacular traction syndrome, secondary glaucoma, diabetic retinopathy, retinal detachment, chorioretinal dystrophy, etc.), imaging, as well as with concomitant diseases: diabetes mellitus, autoimmune thyroiditis. Visual acuity with appositional ROM visual acuity was initially higher than with CLSG and synechial ROM (Table 1). An acute attack of glaucoma was observed, as a rule, after 40 years. It has been proven that the genes responsible for glaucoma are expressed in the female reproductive organs. As a result, female sex hormones play a protective role in glaucoma. Thus, a congenital genetically determined disease manifests itself in middle age during hormonal dysfunction. Also, with age, there is an increase in the size of the lens, involutionary posterior vitreous detachment, which can also contribute to the predisposition of an acute attack of glaucoma [8].

In cases where gonioscopy was possible, 140 (72.7%) patients of the first group were found to have goniosynechia, a narrow angle of the anterior chamber (I degree of opening according to Van Beuningen). In patients of the control and comparison groups, the angle of the anterior chamber is of medium width with the 2nd-3rd degree of pigmentation (according to classification by A.P. Nesterov).

Type of glaucoma	Number of eyes	Visual acuity	
		0,01-0,3n (%)	0,4-1,0n (%)
PZUG with effective LIE	18	4 (25)	14 (75)
PZUG with inefficient LIE	12	6 (50)	6 (50)
ХЗУГ	16	14 (87,5)	2 (12,5)

Table 1: *Visual acuity in patients with PACG before laser iridectomy.*

Results and Discussion

According to the results of molecular genetic and clinical studies, the diagnosis of PACG was confirmed in patients, even without the presence of clinical signs of glaucoma. According to the established diagnosis, patients were consulted by a geneticist and given recommendations on the possibility of receiving effective targeted treatment in the future. Analysis of the results of the detected mutations in the 3rd group of patients with a clinical diagnosis of chronic angle-closure glaucoma revealed the polymorphisms listed in table 2.

Gene	Gene Description	SNP
IL-8 (interleukin-8)	Interleukin 8	rs4073
APEX1	Apurinic/apyrimidinic endodeoxyribo-nuclease1	rs1130409
Alpha 1 collagen type 11 chain - COL11A1	Collagen type XI alpha 1 chain	rs1676486
		rs12138977
		rs2126642
		rs2622848
		rs3753841
Alpha 1 collagen type 1 chain-COL1A1	Collagen type I alpha 1 chain	rs1107946 rs1800012
		rs2412298
		rs2586488
		rs72645331
		rs72656352
		rs72645365
		rs72667037
		rs72654802
5-hydroxytryptamine receptor 3C- HTR3C	5-Hydroxytryptamine Receptor 3C	rs7648564
		rs6808122
		rs6766410
Enzyme responsible for the synthesis of the neurotrans-mitter acetylcholine-CHAT	Choline O- Acetyltransferase	rs1258267
ABCC5 (ATP-binding complex protein - transporter)	ATP Binding Cassette Subfamily C Member 5	rs1401999
ADAMTS17	A disintegrin and metalloproteinase with thrombospondin Type 1 Motif 17 (Disinte-grin and metalloproteinase with thrombo-spondin type 1-17)	rs375971368

Table 2: *Pathogenetically significant polymorphisms in the examined patients with CLG from those described in the literature [9-19].*

As a clinical example, we present a patient with pathogenetically significant polymorphism in the ADAMTS17 metalloproteinase gene (disintegrin and metalloproteinase with thrombospondin Type 1 Motif 17). A 41-year-old female patient with an attack of glaucoma (vitreocrystalline block) was found to have a heterozygous variant (rs375971368) in the 17th exon (out of 22) in the ADAMTS17 gene, which has not been previously described in the literature (rs375971368). the development of Weill-Marquezani syndrome type 4 [20] is a hereditary connective tissue disease characterized by destabilization of the ligamentous apparatus of the lens and spherophakia. At In this patient, the mutation manifested itself in the development of PACG. There were no other clinical manifestations of the syndrome in the patient. Our data are consistent with those of other authors [18,19], who studied the levels of MMP-9 (gelatinase B) and TIMP-1 (tissue inhibitor of metalloproteinase-1) in tears [21]. When analyzing the ratio of MMP-9/TIMR-1 in tears, an increase in its level was found in glaucoma.

Mutations in the collagen gene COL11A1, ADAMTS17 (a disintegrin and metalloproteinase with thrombospondin Type 1 Motif 17) occur in CLSG, which explain synechiogenesis in CPC [6]. Violation of the activity of matrix metalloproteinases and their specific inhibitors leads to an imbalance in the biosynthesis and degradation of extracellular matrix components in the trabecular meshwork with its further damage by decay products and plays a role in the development of glaucoma degeneration of retinal ganglion cells [18,19,24].

The thin and flexible iris in CLSG with reduced expression of the COL1A1 gene and with pathogenetically significant polymorphisms in the metalloproteinase gene undergoes changes in position caused by water flows, and, in combination with genetic polymorphisms responsible for proliferation, exacerbates pupillary block due to synechia closure [11, 12.18].

Gene	Description	SNP
Membrane coil-associated protein -MFRP	Membrane Frizzled-Related	rs2510143
		rs36015759
		rs3814762
Enzyme responsible for neurotransmitter synthesis acetylcholine-CHAT	Protein Choline O- Acetyltransferase	rs1258267
ABCC5 (ATP-binding complex protein - transporter)	ATP Binding Cassette Subfamily C Member 5	rs1401999
Alpha 1 collagen type 11 chain - COL11A1	Collagen type XI alpha 1 chain	rs1676486
		rs12138977
		rs2126642
		rs2622848
		rs3753841
Alpha 1 collagen type 1 chain - COL1A1	Collagen type I alpha 1 chain	rs1107946
		rs1800012
		rs2412298
		rs2586488
		rs72645331
		rs72656352
		rs72645365
		rs72667037
		rs72654802
PLEKHA7	Pleckstin homology domain containing family A member 7 (plextrin homology domain, containing 7 family member A)	rs216489
		rs1027617
		rs366590
		rs11024060
		rs6486330
		rs11024097

Table 3: *Identified single nucleotide polymorphisms (SNPs) in the synechial ROM group, including those found in the world literature, with a description of genes [9-19].*

PACG reveals mutations in the Col1A1 gene, which encodes the pro-α1(I) chain component of type I collagen. Moreover, the density of type I collagen was higher in the iris of eyes with an acute attack of glaucoma than in primary open-angle glaucoma, primary closure of the anterior chamber angle, and in healthy eyes [11,12]. With an increase in sympathetic regulation, a thicker iris contributes to the development of pupillary block [26]. In order to study the effectiveness of retrospective prophylactic laser iridectomy in APC with PACG, morphological studies were carried out on 3 enucleated eyes of patients with terminal PACG of the 2nd and 3rd groups.

Increased synechiogenesis was found after prophylactic LIE in the 2nd and 3rd groups of patients (Figure 1). As shown by a retrospective analysis, due to the stimulation of synechiogenesis, LIE was ineffective in the 2nd and 3rd groups of the patient. Due to inefficiency in 80% of cases, phacoemulsification was required at various times after LIE in groups 2 and 3.

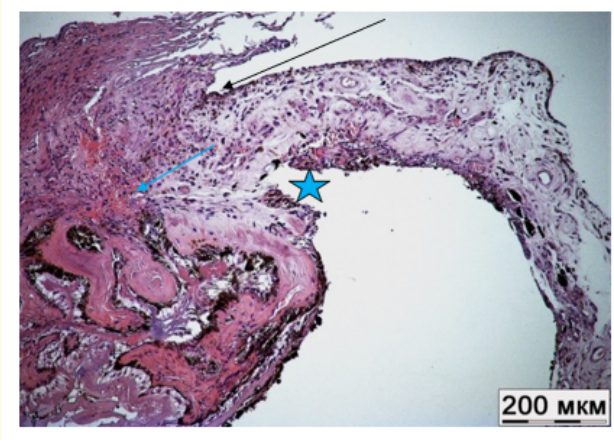

Figure 1: *Closure of the APC as a result of adhesion of the iris root to the cornea (black arrow). At the site of adhesion inflammatory infiltrate. Edema and hyperemia of the ciliary body (blue arrow). The iris is devoid of pigment sheet at the site of attempted laser iridectomy (asterisk). Hematoxylin-eosin staining.*

As a result of prophylactic LIE in patients of the 1st group, 5 - 15 years after the operation, there was no enhanced synechiogenesis, no glaucomatous optic neuropathy was detected. In patients of the 2nd and 3rd groups, progression of glaucomatous neuropathy and snechiogenesis occurred. As a result, they received antihypertensive therapy and were taken for phacoemulsification with 2-3 stages of glaucoma due to the ineffectiveness of iridectomy 3-7 years after it (Table 4). This is due not only to the cataractogenic effect of LIE, but also to progressive glaucoma neuropathy, as evidenced by the deterioration of computer perimetry and deepening of the E/OND during ophthalmoscopy (Table 4). Perimetry indicators in this case are less informative due to the development of cataracts in most patients. But immature cataract was not an obstacle to ophthalmoscopy.

Type of glaucoma	Number of eyes	Visual acuity		E/DZN	
		0,01-0,3n (%)	0,4-1,0n (%)	0,6-1,0n (%)	0,1-0,5n (%)
PZUG with effective LIE	18	4 (25)	14 (75)	0	18 (100)
PZUG with inefficient LIE	12	10 (83,3)	2 (16,7)	6 (50)	6 (50)
ХЗУГ	16	15 (93,75)	1 (6,25)	16 (100)	0

Table 4: *Status of visual acuity and visual field in patients with PACG after laser iridectomy before phacoemulsification.*

Of all patients of group I (100%) with effective LIE, 5 - 15 years after surgery, there was no glaucomatous optic neuropathy, the state of the optic nerve was normal. In 6 patients of the 2nd group (50%), after 3 - 15 years, the disease began to correspond to the advanced stage, in 50% - to the advanced stage, in 16 patients with CGD (100%) - to the advanced or advanced stage.

PZUG classification in our opinion, ROM can be attributed to the period during glaucomatous optic neuropathy, preceding the death of axons, and then the GCS itself - "critical period of dysfunction" or "plastic" period. This concept was introduced in Russia by Zueva M.V. (2016). During this period, according to the ERG pattern, the activity of retinal ganglion cells (RGCs) changes long before the thickness of the retinal nerve fiber layer (RNFL) decreases [25]. This issue needs further study. In our opinion, given all the features of predisposition to angle-closure glaucoma, including genetic, this form of glaucoma may be congenital, despite the clinical manifestation after 40 years. Based on the clinical and genetic data described in this paper, the classification of PACG would be as follows: congenital appositional iridotrabecular contact and congenital synechial iridotrabecular contact (CSCG). With congenital appositional iridotrabecular contact, prophylactic laser iridectomy can be done, because. it will not stimulate the formation of synechiae. If there is a congenital predisposition to synechia (polymorphisms in CZUG), then in adulthood they are necessarily formed. Moreover, in patients predisposed to this pathological process, laser iridectomy can stimulate reparative processes with the formation of synechiae. We propose the term "congenital genetically determined primary angle-closure glaucoma", because all the mechanisms predisposing to it - both the biomicroscopic structure of the eye and the tendency to form synechiae - are laid down at birth. But it manifests itself in middle age, with the onset of hormonal dysregulation. So, we noted that an acute attack of glaucoma was observed, as a rule, after 40 years. Congenital genetically determined primary angle-closure glaucoma, if laser iridectomy was performed, but for some reason did not give an effect, we suggest leaving it in the group of laser-operated PACG.

With regard to an acute attack of glaucoma with a configuration of the iris plateau, with pupillary block, with the syndrome of improper intraocular fluid flow (vitreocrystalline block), the classification remains the same. Previously, we described the influence of the autonomic nervous system on the formation of an acute attack of glaucoma [26]. We propose to adhere to the concept of "mixed" glaucoma in two cases, as in the classification of Nesterov A.P. [27]: CPC is closed only in one segment and open in other departments; - The CPC is open, but it is very narrow, slit-like. In this form of glaucoma, the mechanisms of disturbance of regional blood circulation in the vessels of the ONH, which are characteristic of PACG, prevail [26]. Combined glaucoma (according to Ryabtseva A.A.) includes glaucoma, including a combination of signs of primary glaucoma with changes in the eyeball of secondary origin: post-inflammatory changes in the area of the APC, iridolenticular diaphragm of the eye and other post-surgical changes, as well as a combination of primary glaucoma with cataracts and postoperative aphakia [28]. Thus, we present the classification of PACG, taking into account pathogenetic features: congenital appositional iridotrabecular contact (possible prophylactic LIE); congenital synechial iridotrabecular contact (CZUG); congenital genetically determined primary angle-closure glaucoma; congenital genetically determined primary angle-closure glaucoma operated on with a laser; glaucoma attack: acute and subacute (with pupillary block, with vitreocrystalline block or with a flat iris). Mixed and combined glaucoma are separated separately. Thus, a classification of primary angle-closure glaucoma based on pathogenetically significant genetic polymorphisms has been proposed. Genetic and bioinformatic research methods provide more complete information about the hereditary predisposition to PACG with clinical manifestations after 40 years.

Conclusion

1. Pathogenetically significant genetic polymorphisms responsible for synechiogenesis in CLSG have been found. 2. A pathogenetic classification of PACG has been proposed. 3. To be able to clarify the prognosis of the course and severity of the process in patients with PACG, to select the optimal pathogenetic-oriented targeted therapy, it is necessary to conduct a specialized molecular genetic test in the presence of a biometric predisposition to PACG. 4. Patients with a genetic predisposition to synechiogenesis are recommended to undergo phacoemulsification without prior iridectomy.

Author's Contribution

N. A. Bakunina - Concept and design of the study, collection of the data and their interpretation, writing the article, final preparation, L. M. Balashova - Concept and design of the study; A.A. Fedorov - Conducting morphological studies; M.E. Viner - Conducting a genetic study.

Conflict of Interest

None.

Transparency of Financial Activities

The project was partially funded from Bakunina N.A.'s own funds, the rest of the authors declare no conflict of interest.

Bibliography

1. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 2: Classification and Terminology Supported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 2 Classification and Terminology *British Journal of Ophthalmology* 101.5 (2017): 73-127.
2. Foster PJ., *et al*. "The definition and classification of glaucoma in prevalence surveys". *British Journal of Ophthalmology* 86.2 (2002): 238-242.
3. Do T., *et al*. "Ultrasound Biomicroscopic Diagnosis of Angle- closure Mechanisms in Vietnamese Subjects with Unilateral Angle-closure Glaucoma". *Journal of Glaucoma* 27.2 (2018): 115-120.
4. Nesterov AP. "Glaucoma". Moscow: Medical information Agency (2008).
5. Ritch R. "Exfoliation syndrome and occludable angles". *Transactions of the American Ophthalmological Society* 92 (1994): 845-944.
6. Weener ME., *et al*. "Genetic testing of ocular manifestations of proliferative syndrome to provide pathophysiology-oriented treatment". *Russian Journal of Clinical Ophthalmology* 22.1 (2022): 16-22.
7. Lee S., *et al*. "NGSCheckMate: software for validating sample identity in next-generation sequencing studies within and across data types". *Nucleic Acids Research* 45.11 (2017): 103.
8. Ermolaev AP. "On the connection of the primary manifestations of angle-closure glaucoma with the appearance of posterior vitreous detachment". *Bulletin of Ophthalmology* 129.2 (2013): 23-27.
9. Nongpiur ME., *et al*. "ABCC5, a gene that influences the anterior chamber depth, is associated with primary angle closure glaucoma". *PLOS Genetics* 10.3 (2014): e1004089.
10. Awadalla MS., *et al*. "Association of genetic variants with primary angle closure glaucoma in two different populations". *PLOS ONE* 8 (2013): 67903.
11. Chung C., *et al*. "Correlation of iris collagen and in-vivo anterior segment structures in patients in different stages of chronic primary angle-closure in both eyes". *Indian Journal of Ophthalmology* 67.10 (2019): 1638-1644.
12. Seet LF., *et al*. "Distinct iris gene expression profiles of primary angle closure glaucoma and primary open angle glaucoma and their interaction with ocular biometric parameters". *Clinical and Experimental Ophthalmology* 44 (2016): 684-692.
13. Haer-Wigman L., *et al*. "Diagnostic exome sequencing in 266 Dutch patients with visual impairment". *European Journal of Human Genetics* 25 (2017): 591-599.

14. Y Chen., *et al*. "Extended association study of PLEKHA7 and COL11A1 with primary angle closure glaucoma in a han chinese population". *Investigative Ophthalmology and Visual Science* 55 (2014): 3797-3802.

15. Zhong Y., *et al*. "Flat Anterior Chamber after Trabeculectomy in Secondary Angle-Closure Glaucoma with BEST1 Gene Mutation: Case Series". *PLoS ONE* 12.1 (2017): e0169395.

16. Vithana EN., *et al*. "Genome-wide association Analyses identify three new susceptibility loci for primary angle closure glaucoma". *Nature Genetics* 44 (2012): 1142-1146.

17. Zhuang W., *et al*. "Genotype-ocular biometry correlation analysis of eight primary angle closure glaucoma susceptibility loci in a cohort from Northern China". *PLoS ONE* 13.11(2018): e0206935.

18. MS Awadalla., *et al*. "Matrix metalloproteinase-9 genetic variation and primary angle closure glaucoma in a Caucasian population". *Molecular Vision* 17 (2011): 1420-1424.

19. Micheal S., *et al*. "Polymorphisms in matrix metalloproteinases MMP1 and MMP9 are associated with primary open angle and angle closure glaucoma in a Pakistani population". *Molecular Vision* 19 (2013): 441-447.

20. Evans DR., *et al*. "A novel pathogenic missense ADAMTS17 variant that impairs secretion causes Weill-Marchesani Syndrome with variably dysmorphic hand features". *Scientific Reports* 10.1 (2020): 10827.

21. AS Khokhlova., *et al*. "The role of the matrix metalloproteinase system in the progression of primary open-angle glaucoma". *Pacific Medical Journal* 2 (2017): 32-34.

22. Sundin OH., *et al*. "Extreme hyperopia is the result of null mutations in MFRP, which encodes a Frizzled-related protein". *Proceedings of the National Academy of Sciences of the United States of America* 102.27 (2005): 9553-9558.

23. Pauer GJ., *et al*. "Mutation screen of the membrane- type frizzled-related protein (MFRP) gene in patients with inherited retinal degenerations". *Ophthalmic Genetics* 26.4 (2005): 157-161.

24. Beletskaya IS and Astakhov SYu. "The role of matrix metalloproteinases in glaucoma pathogenesis". *Oftal'mologicheskie Vedomosti* 8.3 (2015): 28-43.

25. Zueva MV. "Dynamics of retinal ganglion cell death in glaucoma and its functional markers". *National Journal Glaucoma* 15.1 (2016): 70-85.

26. Bakunina NA., *et al*. "Vascular and vegetative factors of glaucoma attack". *Russian Ophthalmological Journal* 14.4 (2021): 22-30.

27. Nesterov AP. "Glaukoma". M.: Medicine (2014).

28. Chencova OB., *et al*. "Optimization of diagnosis and treatment of primary and secondary glaucoma". *Al'manah Klinicheskoj Mediciny* 3 (2000): 109-114.

29. Bakunina NA., *et al*. "A method for reducing the formation of scar tissue after non-penetrating deep sclerectomy". *Glaucoma* 1 (2009): 3-6.

Volume 14 Issue 6 June 2023