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Recent Research Progress in the Pathogenesis of Primary Angle-closure Glaucoma

Hainan Liu, Lingling He

Guangdong Medical University

Abstract: Primary angle-closure glaucoma(PACG) is a major subtype of glaucoma, caused by acute or chronic elevation of intraocular pressure due to angle closure, with or without changes in glaucoma optic disc characteristics and visual field damage. Angle closure is the basic pathological process of PACG, which is related to abnormalities of iris, lens, ciliary body and choroid. With the deepening of research, it has been found that emotional and psychological stress factors are also closely related to the occurrence and development of PACG. In recent years, with the development of molecular biology techniques in the study of glaucoma, many genes related to the pathogenesis of glaucoma and their mechanisms of action in the disease progression have been discovered. Therefore, this paper will elaborate on the pathogenesis of PACG from the perspectives of anatomical mechanism, psychological stress and gene.

Keywords: primary angle-closure glaucoma; angle closure; anatomical mechanism; physiological stress; gene

So far, there are approximately 67 million glaucoma patients worldwide, ranking second only to cataracts as a cause of blindness worldwide. It is estimated that there are about 9.4 million glaucoma patients in the population aged 40 and above in China, of which 5.2 million patients are single eyed blind, accounting for 55%, and 1.7 million patients are double eyed blind, accounting for 18.1%. Primary angle closure glaucoma (PACG) is a major subtype of glaucoma, and it is widely recognized internationally that angle closure is the basic pathological process of PACG. Acute or chronic intraocular pressure elevation is caused by angle closure, with or without changes in glaucoma disc characteristics and visual field damage.

With the continuous development of science and technology in recent years, anterior segment imaging technology has provided researchers with a deeper understanding of the mechanism of angle closure. Researchers believe that PACG patients have abnormal anatomical features such as short axial length, small cornea, shallow anterior chamber, thicker lens, and anterior lens position compared to normal individuals. Meanwhile, studies have shown that structural abnormalities in the iris, crystalline lens, ciliary body, and choroid are all associated with the onset of PACG[1]. However, the pathogenesis of PACG is closely related not only to abnormal ocular anatomical structures, but also to stress reactions and psychological factors; Clinical studies have shown that PACG patients are more prone to anxiety and depression than the general population[2]. In addition, with the development of molecular biology techniques, genes related to PACG pathogenesis and their mechanisms of action in the pathogenesis of glaucoma have been discovered. At present, it has been confirmed that there are three susceptible gene loci, namely rs11024102 in PLEKHA7 gene, rs3753841 in COL11A1 gene, and rs1015213 between ST18 gene and PCMTD1 gene located on the long arm of chromosome 8 . This article will focus on exploring the pathogenesis of PACG and briefly explain the treatment of PACG, as well as the impact of adjusting psychological status on the prognosis of PACG patients, in order to achieve the goal of improving vision.

1 Pupil obstruction

Pupil block is the most common pathogenic mechanism of PACG, which is mainly caused by the contact between the crystalline lens and the posterior surface of the iris, resulting

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in increased resistance to aqueous humor (AH) flowing from the posterior chamber to the anterior chamber [3]. AH is a transparent liquid secreted by the ciliary process located in the posterior chamber, flowing between the iris and the crystalline lens, entering the anterior chamber through the pupil, and then being expelled from the trabecular meshwork, ultimately flowing into the venous blood. When the relative position of the lens moves forward to a certain extent, the anterior surface of the lens covered by the iris exceeds the attachment point of the iris root, causing an increase in the force of the pupil opening muscle and sphincter towards the lens, thereby increasing the resistance of AH flowing through the pupil. Subsequently, the fluid pressure in the posterior chamber will gradually increase compared to the anterior chamber, causing the lens iris septum to move forward and tightly adhere to the iris, resulting in further obstruction of AH flow through the pupil and further forward movement of the iris, causing contact between the peripheral iris and the angle of the room, and even mechanical closure of the angle of the room[4].

1.1 Lens

Abnormal crystalline lens is the main cause of pupil obstruction and plays a crucial role in the pathogenesis of PACG. The thickness of the crystalline lens is positively correlated with the age of the patient. As age increases, the thickness of the crystalline lens increases by 19 μ m per year, and its volume also increases year by year. This change will lead to a continuous narrowing of the anterior segment spatial structure such as the angle and depth of the anterior chamber. Liu Xing et al. confirmed that the lens has a bidirectional effect on the anterior segment structure with age, causing the anterior chamber depth to become shallower when moving forward and expanding towards the vitreous cavity when moving backward. At the same time, it was found that the higher incidence of PACG in females is due to the fact that the growth of the male crystalline lens tends to expand towards the vitreous cavity, while the thickening of the female crystalline lens makes the anterior chamber depth shallower; Secondly, the suspensory ligaments of the crystalline lens gradually become relaxed as the volume of the lens increases, which will cause a change in the position of the lens[5]. Xiao Ping used ultrasound biomicroscopy (UBM) to diagnose PACG and found that the position of the crystalline lens in PACG patients was relatively forward, indicating that the relative position of the crystalline body plays an important role in the pathogenesis of PACG. However, with age, the thickness of the crystalline lens also increases in contact area with the iris, leading to increased resistance for AH to flow from the posterior chamber to the anterior chamber through the pupil, resulting in pupil obstruction[6]. Subsequently, the crystalline iris septum moves forward, the angle of the room narrows, the peripheral iris swells, and the iris and trabecular meshwork make positional contact and organic adhesion, leading to mechanical obstruction of the anterior chamber angle, obstruction of the AH outflow channel, and increased intraocular pressure, resulting in the occurrence of PACG. Therefore, it can be seen that crystalline and pupillary blocks often coexist.

1.2 Iris

The iris plays an important role in the pathogenesis of PACG through mechanical and vascular mechanisms. During the AH drainage process in PACG patients, the structure and dynamic characteristics of the iris are mainly mechanically blocked.

The mechanical obstruction of the trabecular meshwork or adhesion between the iris tissue and the trabecular meshwork, leading to narrowing of the atrial angle, is an important mechanism for PACG atrial angle closure. Researchers believe that changes in type I collagen fibers in the iris stroma, the number of iris crypts, and iris tissues such as iris blood vessels are all related risk factors for the occurrence and development of PACG[7]. Yao Wen et al. demonstrated that type I collagen fibers in the iris stroma can cause thickening of the iris by affecting its hardness, ultimately leading to narrowing or even closure of the atrial angle. At the same time, the probability and area of contact between the thickened iris and the crystalline lens will also increase. According to literature reports, for every 1 mm dilation of the pupil, the volume of the iris increases by 1% to 3%[8]. The increase in iris volume leads to an increase in resistance when AH passes through the pupil, resulting in an increase in posterior chamber pressure. Optical coherence tomography (OCT) technology is used in the observation of eyes with angle stenosis. Iris patients with fewer crypts during pupil dilation are prone to sudden increase in intraocular pressure or acute primary angle closure (APAC). Eyes lacking iris crypts are more prone to APAC than those with iris crypts, and the risk of APAC decreases as the number of iris crypts increases. This may be due to the fact that the presence of iris crypts can improve fluid connectivity between the iris stroma and the anterior chamber, attributed to the fact that the more iris crypts there are, the larger the surface area of the iris, and the stronger the fluid flow on the surface of the iris. At the same time, the iris recess can improve the water permeability of the anterior surface of the iris, increasing its outflow from the uveosclera and trabecular pathways. In PACG, the pathogenesis of high pleated iris is the most typical feature, characterized anatomically by peripheral iris hypertrophy, short iris root, iris attachment point, and anterior position of ciliary body and process. Patients with

high pleated iris configuration may still experience angle closure and increased intraocular pressure due to spontaneous or dilated factors after peripheral iridotomy (excluding), which is called high pleated iris syndrome. The mechanism of angle closure can be divided into two situations: ① the anterior and thickened peripheral iris increases in volume after dilation, blocking the trabecular meshwork and leading to angle closure; ② The anterior ciliary process of the peripheral iris is pushed towards the angle of the room, causing mechanical closure of the angle of the room.

1.3 Ciliary body

The ciliary body is the middle part of the choroid, connected to the root of the iris at the front and moving along the choroid with a serrated edge at the back. It is adjacent to the iris on the outside and surrounds the equator of the lens on the inside, facing the posterior chamber and vitreous body. It mainly regulates intraocular pressure through the secretion of AH by the ciliary process and contraction of the ciliary muscle. The influence of changes in the morphology and position of the ciliary body on the pathogenesis of PACG has become a research hotspot. Related reports indicate that the anterior rotation and thickness of the ciliary body may push the iris root forward, leading to the closure of the atrial angle. In Asian people, even normal eyes show signs of ciliary body moving forward, while in patients with PACG, the ciliary process rotates forward more, which may be one of the factors contributing to the high incidence rate of PACG in Chinese people. Diseases leading to ciliary exudation and age factors are the causes of anterior rotation of the ciliary process. When the ciliary body rotates forward, on the one hand, it pushes the iris root towards the trabecular meshwork, causing wrinkles in the iris root and squeezing the angle of the room forward, causing it to narrow or even close, resulting in obstruction of AH outflow; On the other hand, pulling the lens and suspensory ligament forward causes pupil obstruction. During the acute phase of PACG, the ciliary body under high intraocular pressure may experience edema, leading to more anterior rotation and exacerbating the anterior displacement of the crystalline iris septum, ultimately resulting in more severe pupillary block. Therefore, during acute attacks of PACG, the ciliary body becomes congested and edematous, causing its thickness to increase and move forward, which further exacerbates pupil block and anterior chamber stenosis. In addition, as age increases, the ciliary process rotates forward due to atrophy and thinning of the ciliary body, the suspensory ligament becomes relaxed due to weakened contraction of the ciliary muscle, the lens thickness increases and its position shifts forward, leading to pupil obstruction and worsening of anterior chamber stenosis.

1.4 Choroidal membrane

The choroid is located between the retina and sclera, rich in vascular beds, connective tissue, and melanin. The 2020 Glaucoma Guidelines in China suggest that choroidal dilation is one of the main types of angle closure mechanisms. With the improvement of medical imaging technology, studies have found that the choroid of PACG is thicker than that of primary open angle glaucoma (POAG) and normal subjects, which may be another risk factor for PACG. Subsequently, some scholars proposed the theory of choroidal dilation, which suggests that in anatomically susceptible eyes, when the choroid rich in vascular beds dilates, with fluctuations in choroidal blood volume, the position of the iris lens diaphragm plane may move forward due to the toughness and resistance of the sclera and cornea, leading to pupil obstruction and angle closure, thereby inducing glaucoma . In addition to self-regulation and self-regulation, external factors such as temperature, medication, and hormones can also affect the choroid and cause changes in its thickness.

2 Psychological stress

There is a significant correlation between anxiety or depression and the risk of PACG, and intraocular pressure is influenced by emotional states. When emotions are tense and excited, the pupil opening muscle controlled by the sympathetic nervous system is excited, causing the pupil to enlarge, the surrounding iris to swell, the angle of the room to close, the AH circulation to be obstructed, and the intraocular pressure to increase. Under stress, the hypothalamic pituitary adrenal axis is activated, sympathetic nervous system activity increases, and more plasma catecholamines and cortisol are released. A large amount of adrenaline can excite the pupil opening muscle, causing the pupil to dilate and the AH circulation to be blocked, thereby causing an increase in intraocular pressure. In addition, psychological stress disrupts the central regulation of blood vessels and nerves, leading to increased vascular permeability after capillary dilation, resulting in anterior ciliary edema, narrowing or even obstruction of the atrial angle, and increased intraocular pressure. This also indicates that personality type, emotional and social background are risk factors that need to be considered in the study of PACG pathogenesis. Therefore, in future research, we may need to consider PACG as a systemic disease rather than just focusing on the eyeball.

3 Genes

With the study of susceptibility genes related to the pathogenesis of PACG, it has been confirmed that rs11024102 in the PLEKHA7 gene, rs3753841 in the COL11A1 gene, and rs1015213 between the ST18 gene and PCMTD1 gene located

on the long arm of chromosome 8 are genes associated with PACG pathogenesis. PLEKHA7 is located on chromosome 11 and belongs to the protein family containing the pleckstrin homologous 70 domain. Sluysmans et al. and Lee et al. found that PLEKHA7 is mainly expressed in the iris ciliary body and choroidal tissue of PACG patients, and the C-terminal and coiled coil regions of this gene can promote their localization at cellular AJ (E-337 cadherin and - catenin) and TJ (ZO-1). However, AJ and TJ play an important role in maintaining intercellular adhesion and paracellular fluid transport, maintaining tissue stability and regulating fluid dynamics. The COL11A1 gene encodes two alpha-1 chains of Xl type collagen, which is a member of the collagen family and a major component of the extracellular matrix (ECM). Most of the outflow resistance experienced in the AH outflow pathway is generated by the extracellular matrix in the proximal tubular region, so mutations in this gene will increase AH flow resistance and intraocular pressure. Rs1015213 is located on chromosome 8 between the PCMTD1 gene and ST18 gene, and PCMTD1 encodes a protein containing the protein-L-aspartate methyltransferase domain. Research has shown that ST18 is expressed in the iris and trabecular meshwork, and the rs1015213 polymorphism is associated with the shallow anterior chamber of PACG, indicating a high potential risk for this gene.

4 Conclusion

The main mechanism of PACG is the obstruction of AH cycle caused by the closure of the atrial angle. Understanding the mechanism of atrial angle closure is of great significance for the prevention and treatment of PACG. Different mechanisms guide the application of corresponding treatment methods, such as peripheral iridectomy to treat angle closure caused by pupil block, miotic agents or peripheral iridoplasty to solve angle closure caused by high pleated iris, lens block requiring lens extraction, and mydriatic agents to alleviate high intraocular pressure caused by ciliary ring block. At the same time, psychological stress and negative emotions are risk factors for the onset of PACG. Although they cannot replace surgery and medication treatment, guiding glaucoma patients to stabilize their emotions and implementing reasonable psychological interventions can alleviate their anxiety and depression, which is crucial for controlling eye pressure fluctuations and preventing the occurrence and development of PACG.

In addition, research on pathogenic genes is still in its early stages, and there are still many new glaucoma related gene mutations that have not been discovered. Therefore, research on the PACG gene level remains challenging. Meanwhile, due to the lack of detailed functional research on the pathogenic genes of glaucoma, gene therapy for glaucoma is still in its early stages, and its effectiveness has not yet reached the expected results, with certain risks involved. Therefore, further research on the occurrence and development of glaucoma at the genetic level is needed to lay the foundation for screening and diagnosis of glaucoma, and to make gene therapy an emerging intervention or treatment for glaucoma. Therefore, studying PACG related genes also has important clinical significance and prospects.

Author Introduction

Hainan Liu, Master's degree, Research direction: Glaucoma

Lingling He, Master's degree, Research direction: ophthalmic related diseases

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