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The Pathophysiology, Diagnosis, and Possible Treatments of Glaucoma

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Abstract

Glaucoma is a disease related to the eyes. The intraocular pressure is said to be the cause of it, although there are many cases that can't be explained by the rise in eye pressure. Therefore, diagnosis and treatments involved with glaucoma are not fully developed due to this unclear pathophysiology. Patients with glaucomatous eyes experience exacerbation of vision, and permanent blindness eventually appears in some. This literature review is a compilation of many studies, research, and sources that contain information related to the disease glaucoma. The aim is to introduce the types of glaucoma, pathophysiology, genetic aspects, diagnosis, and possible treatments.

Keywords- Glaucoma, Intraocular Pressure, Rho-kinase, Primary open-glaucoma, Laser Treatment, Eye surgery

I. INTRODUCTION

Glaucoma is a leading cause of today's irreversible blindness, with a population of 70 million people diagnosed. The pathophysiology of the disease is not yet fully understood; as a result, the technology involved with its treatment is also not yet fully developed compared to other optical diseases due to the difficulty in targeting the cause of it. [1]

Symptoms of glaucoma patients are not clearly shown in the first stage. Thus, patients are not aware of the disease until it gets severe, and diagnosis often takes place when it has already been in the late stage of glaucoma. When the symptoms slowly appear, peripheral vision is affected and blurred. Patients may also experience seeing "halos," which are rainbow circles around bright lights. Glaucomatous eyes may feel extreme pain as well as redness. In addition to optical symptoms, sudden headaches, nausea, and vomiting may happen. It is worth noting that glaucoma in both eyes may not be at the same level in terms of severity. [2]

The following are factors contributing to being in the risk group of glaucoma: age, race, family history, and medical complications. Glaucoma is frequently found in people as they age. The ethnicities that are often associated with it are Africans, Caribbeans, and Asians. Individuals with nearsightedness or farsightedness are in the risk group, and several diseases including diabetes and hypertension can also lead to having glaucoma. A study by Patil et al. [3] has concluded that children with hypertension should constantly check their blood pressure and intraocular pressure to prevent getting glaucoma. Furthermore, usage of steroids is also a factor. [4]

The cause of most types of glaucoma is known to be the raised intraocular pressure (IOP). However, there are certain types of glaucoma that are not due to this reason. New research and studies have suggested new possibilities of the pathophysiology of glaucoma, leading to newly developed techniques to test glaucoma and cure it.

II. PATHOPHYSIOLOGY

The accumulation of aqueous humor in the eye increases the IOP. In primary open-angle glaucoma, this accumulation is caused by the blockage of the trabecular meshwork, the main drainage pathway for the aqueous humor. The raised IOP then compresses the optic nerve which eventually leads to the death of retinal ganglion cells (RGC). After the optic nerve has been deteriorated, visual information cannot be carried to the brain, thus hindering vision.

A study in mice conducted by Guttenplan et al. [5] concluded that the death of RGCs are specifically caused by reactive astrocytes. After the RGCs are damaged by the increase in IOP, astrocytes, a type of glial cell in the central nervous system, secretes a toxin that kills the RGCs. In the study, the number of RGCs were maintained when astrocytes were inhibited from taking action. In addition, although the structure of RGCs were changed, they were still able to

function, as observed through electrophysiological and morphological analysis.

Another study done on donated glaucomatous eyes by Overby et al. [6] suggested that the resistance of the flow of aqueous humor is caused by the altered gene expression in cells of the Schlemm canal which contains the trabecular meshwork. The change induces the cytoskeleton to become hard and therefore decreases the pore formation of the cells.

It is shown in Cooper's et al. research study [7] that there is a possibility that glaucoma in an eye can be induced by the opposite glaucomatous eye. When there is a rise in IOP of one eye, metabolic resources from the opposite eyes are passed to the glaucomatous eye through gap junctions of astrocytes. This causes degeneration of cells in the healthier eyes. It also aligns with Weinreb et al.'s literature review [1] about the inability to function of mitochondria in glaucomatous eyes when IOP is increased.

There are some cases in which glaucoma is not caused by the increase in IOP. An alternative explanation is the "CSFP hypothesis," an effect of cerebrospinal fluid pressure (CSFP). CSF is the fluid that is contained in the ventricles of the brain and surrounds the central nervous system. CSF can place pressure on the optic nerve in a similar pattern to IOP. The CSFP hypothesis is based on the idea that the difference between IOP and CSFP damages the RGCs. This means that high IOP and low CSFP can be largely detrimental to the RGCs. In addition, high CSFP can also countervail with high IOP, making it a supporting explanation of cases in which patients with hypertension do not experience glaucoma. Although the CSFP hypothesis has not been justified through clinical processes, experiments done in animals by Ficarrotta et al. [8] has shown that reducing the CSFP can lead to signs of glaucoma.

III. TYPES

In general, the 2 most known types of glaucoma are open-angle glaucoma and angle-closure glaucoma. Other types include normal-tension, congenital, pigmentary, and exfoliative glaucoma. [9]

Primary open-angle glaucoma is the most common, and it rises with age. Blockage of the drainage outlets such as the trabecular meshwork could lead to it, although there are no visible symptoms. In contrast, secondary open-angle glaucoma is induced by eye injuries or inflammation.

Angle-closure glaucoma, although quite rare, results in the most cases of blindness. The cause of it is the narrowing of the angle through which the aqueous humor exits. This type of glaucoma is more commonly found in Asians than Westerners because of their small eyes, making their drainage angles narrow and prone to the disease.

Normal-tension glaucoma has symptoms of primary-open angle glaucoma, although the patient has IOP within the normal range or below normal.

Congenital glaucoma occurs in infants without complete development of the drainage channel. Their eyes are larger than mediocre because of the raised IOP.

Pigmentary glaucoma is found in younger males. The granules withdraw from the iris and block the trabecular meshwork, which then raises the IOP.

Exfoliative glaucoma is caused from the build-up of flaky substances on the lens, especially in old people and Scandinavians. It is also said to be related to auditory issues in elder people.

IV. GENETICS

The following are examples of genes that are related to an autosomal dominant trait controlled by a single gene: Myocilin, optineurin, GLC1G. Although they are said to be genes that contribute to the cause of glaucoma, it is worth noting that less than 10% of glaucoma cases are due to them. The gene on the GLC1A locus that synthesizes the protein myocilin is mutated; carriers of this mutation account for approximately 90% of the glaucoma cases. The pathophysiology of the mutation's influence on the disease is not yet fully understood, but it is suggested that the inability to secrete protein causes a build-up of misfolded protein and thus leads to the raised IOP.

In opposition to the gene associated with myocilin, patients with the OPTN gene have IOP within the normal range. Studies suggest that optineurin may act by decreasing the chance in which the RGCs experience apoptotic stimuli. [9]

V. DIAGNOSIS

Due to the incomplete understanding of the pathophysiology of glaucoma, there is no clear diagnosis for it. In addition, because its symptoms do not become visible until it is severe, this adds on to the difficulty. A common sign that appears in diagnosis is "cupping." Cupping refers to

the condition in which the center of the optic disc gets enlarged compared to the entire optic disc. [10] Thus, cupping is often expected in diagnosis of glaucomatous eyes. Several techniques that are used today are optical coherence tomography (OCT), dilated eye exam, gonioscopy, ophthalmoscopy, slit-lamp exam, tonometry, pachymetry, and visual tests.

Optical coherence tomography is a type of imaging technique that measures the thickness of the nerve fiber layer in the retina. It also measures the intensity of the cupping. The observation is done through rays of light, which causes no pain to the patients. [11]

Dilated eye exam, a common way for opthamologists to check on visual diseases, is often used to test glaucoma. The doctor applies eye drops on the patients that would keep the pupils to stay dilated. Then, the doctor would examine the optic nerve. [12]

Gonioscopy can also be implemented to observe the area where the iris and cornea coincide. This area is the angle at which the aqueous humor is drained out of. The process involves using contact lens, eye drops, and light to see this angle. [13]

Ophthalmoscopy is a technique that is done with the usage of a handheld device, a head-mounted device, and a particular special lens to look through the pupil; the optic nerve is then observed. [9]. A similar test to this one is the slit-lamp exam, but a microscope called a "slit lamp" is used instead.

Because many cases of glaucoma are due to the rise in IOP, the pressure in the eye is often observed as well. Tonometry is an examination that measures the IOP. [9] Another method that is done along with tonometry is pachymetry. Pachymetry measures the cornea thickness, which is a factor that may affect the accuracy of IOP.

Lastly, visual field tests, also known as "perimeter," is a method in which the peripheral vision of an individual is checked. Different levels of lights are shown, while the person's role is to push a button when they are able to see the light. A computer then outlines the framework of the visual field. There are certain points of visual fields that a doctor would look for in glaucomatous patients. [9]

VI. TREATMENTS

There is no complete cure to glaucoma, but the goal is to reduce the damage caused by it and slow down the effects. In most treatments, the common target is reducing the IOP; examples of common treatments include usage of eye drops, laser treatments, and surgeries."The Ocular Hypertension Treatment Study," a 5-year study conducted by Kass et al. has shown the importance in reducing IOP. A participant sample group that was not initially diagnosed with glaucoma was separated into two groups. 4.4% of the experimental group who had been treated to reduce eye pressure treatment developed glaucoma symptoms, whereas 9.5% of the control group did. [1]. Many new studies have also been done to find a new target to mitigate the condition. [9]

Eye drops are prescribed to patients in order to reduce the IOP, and they are considered the first-line of treatment. The first class of drugs is called "beta-Andre hernia antagonists." These drugs act by restricting the secretion of the aqueous humor. Although they used to be known as the most effective, the side effects include the aggravation of respiratory diseases and low blood pressure. In the present, another class of drugs called "prostaglandin analogs" is the most common. This type of drug increases the drainage of aqueous humor. The side effects are less compared to beta-blockers, but it can still cause redness, inflammation and change of the iris's color. [9] A recent development of 2 new type of eye drops, "Latanoprostene bunod ophthalmic (Vyzulta)," and "Netarsudil (Rhopressa)," have been approved in 2017 by FDA. These 2 types of drugs are more effective than prostaglandin analogs; prostaglandin works mainly on the uveoscleral pathway, where the minority of the aqueous humor flows out of and less on the trabecular meshwork. In contrast, Vyzulta and Rhopressa work mainly on the trabecular meshwork, with less side effects. [14] Vyultza works through a nitric oxide intermediate. A study in monkeys conducted by Heyne et al. [15] has shown that nitrovasodilators tend to relax the trabecular meshwork; they concluded that increasing the concentration of NO may help reduce IOP, which is the mechanism that Vyultza relies on. Rhopressa, on the other hand, is in the group called rho kinase inhibitors. Rho kinase is an enzyme that triggers contraction in cells. Epstein et al. [16] conducted a research study that shows that inhibition of this enzyme seems to contribute to the relaxation of trabecular meshwork and helps in the facilitation of aqueous humor outflow. [17]

Surgeries may be performed to treat glaucoma. Trabeculectomy, a type of conventional surgery, is the most

common among all. This surgery requires a process of removing a small part of the trabecular meshwork in order to increase the space for aqueous humor to flow out. Although considered the most effective, there are complications involved, thus causing the suggestion of alternatives. Another type of surgery called "Minimally Invasive Glaucoma Surgery (MIGS)" is done by inserting a microscopic device into the eye to lower the IOP. [9]

Laser treatments are also available in order to enhance the drainage of the aqueous humor. Selective Laser Trabeculoplasty (SLT) opens up the drainage channels, which then lets the aqueous humor flow out more, thus reducing the IOP. [18] Laser Peripheral Iridotomy (LPI) works by making holes in the iris in order to create more drainage channels. Another type of treatment called Cyclodiode Laser is based on the mechanism of deterioration of cells that produce the aqueous humor so that less fluid is secreted. Lastly, argon laser treatment is the most common for open-angle glaucoma, which works by opening up the drainage channels. [19]

A recent study by researchers from NYU Grossman school of Medicine was performed in rats [20]. It was concluded that citicoline, a chemical associated with the building blocks in membranes that surround nerve cells and improve communication, reinstates the signals between the brain and the eyes without the reduction in IOP. The destruction of nerve structure and vision was slowed down by 74% in rats in the treatment group that consumed this chemical.

Another study in aged mice by Williams et al. [21] suggested that vitamin B3 ingestion helps with mitochondrial health and its metabolism. Thus, it was concluded that consuming vitamin B3 may help reduce the possibility of getting glaucoma.

As the modern technology of stem cells is involved in many treatments, it has also been associated with glaucoma. A study by Mead et al. [22] has shown that exosomes grown in stem cells can lower the deaths of RGCs. Exosome is a tiny membrane-enclosed package that comes from inside cells before getting exported; its role is facilitating cell-to-cell interaction and signaling. In the treatment group of mice, ⅓ of the RGCs died, whereas 90% of the untreated group died.

VII. CONCLUSION

The pathophysiology of glaucoma is still not fully elucidated by scientists. Thus, the diagnosis and treatments for it are affected and are still being developed by researchers all over the world. Despite the fact that glaucoma cannot be cured but can only be slowed down and mitigated, the continuous advancements in technology and scientific fields today are still largely contributing to the diagnosis and treatment for it.

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