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Overview of Pathogenesis and Risk Factors of Glaucoma; Treatment Approaches

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Abstract: **Current study was aimed to overview the Glaucoma from different medical aspects including pathogenesis and risk factors and with clinical aspects as the treatment options available for different types of glaucoma. A literature search was conducted using electronic databases such as MEDLINE, the Cochrane Library, and manuscript references for studies published in English up to March 2017 on the topics glaucoma and its pathogenesis and risk factors leading to this disorder with discussion its treatments options. Studies included in this review were limited to human subjects with English language. Recognizing glaucoma-associated genes will certainly also help elucidate the biochemical paths that create glaucoma. Knowing such pathways will certainly facilitate the advancement of novel medication treatments that can be customized to specific forms of glaucoma. New therapies could consist of agents based on the protein, enzymes, or RNA transcripts related to glaucoma. Due to the fact that the biochemical paths included in glaucoma can be particularly targeted, researchers can create more secure as well as more disease-specific treatments.**

Keywords: **Glaucoma, Retinal Ganglion Cells (RGC), risk factors.**

1. INTRODUCTION

Glaucoma, a leading source of irreversible aesthetic loss, is characterized by loss of retinal ganglion cells (RGC) and also their axons over a duration of years. Glaucomatous optic neuropathy is defined by adjustments in the optic disc as well as visual field issues [(1,2)]. The morphologic changes in the optic disc remain in the form of thinning of neuroretinal rim, pallor and also progressive cupping of the optic disc. The hemorrhage-associated retinal nerve fiber layer problems precede measurable adjustments of the optic disc arrangement [(3)]. The visual field flaws in glaucoma are frequently discovered just after 40% of the axons are shed [(4)].

Glaucoma impacts more than 70 million people globally with roughly 10% being bilaterally blind [(5)], making it the leading root cause of permanent loss of sight on the planet. Glaucoma can stay asymptomatic till it is extreme, causing a high probability that the number of damaged people is a lot greater than the number recognized to have it [(6,7)]. Population-level studies recommend that only 10% to 50% of individuals with glaucoma know they have it [(8,9)]. Glaucomas can be classified into 2 broad groups: open-angle glaucoma and also angle-closure glaucoma. In the United States, greater than 80% of cases are open-angle glaucoma; nevertheless, angle-closure glaucoma is accountable for a disproportionate variety of patients with extreme vision loss [(10)]. Both angle-closure and open-angle glaucoma can be primary diseases. Secondary glaucoma can arise from trauma, particular medications such as corticosteroids, inflammation, tumor, or problems such as pigment diffusion or pseudo-exfoliation [(10,11)].

Raised intraocular stress is a very regular risk factor for the presence of glaucoma, a number of population-based studies found intraocular pressure was lower than 22 mm Hg in 25% to 50% of individuals with glaucoma [(12)]. In spite of the solid organization between raised intraocular stress and glaucoma, considerable numbers of individuals with raised intraocular stress never ever develop glaucoma also during lengthy follow-up [(12)]. Glaucoma progresses without creating symptoms up until the disease is progressed with considerable quantities of neural damage. When signs do occur, the disease leads to vision loss with concomitant reduction in quality of life and also the capacity to carry out day-to-day activities, such as driving.

With retinal ganglion cell death and optic nerve fiber loss in glaucoma, characteristic adjustments in the look of the optic nerve head as well as retinal nerve fiber layer take place [12,13]. These modifications are the most vital aspect of a glaucoma diagnosis and can be determined during ophthalmoscopic evaluation of the optic nerve head (**Figure 1**) [13]. The relevance of conducting an ideal ophthalmologic exam of the eye cannot be overstated with respect to very early discovery of glaucoma. Retinal ganglion cell loss triggers modern wear and tear of visual fields, which normally begins in the midperiphery as well as could advance in a centripetal manner till there remains only a outer or central island of vision [13].

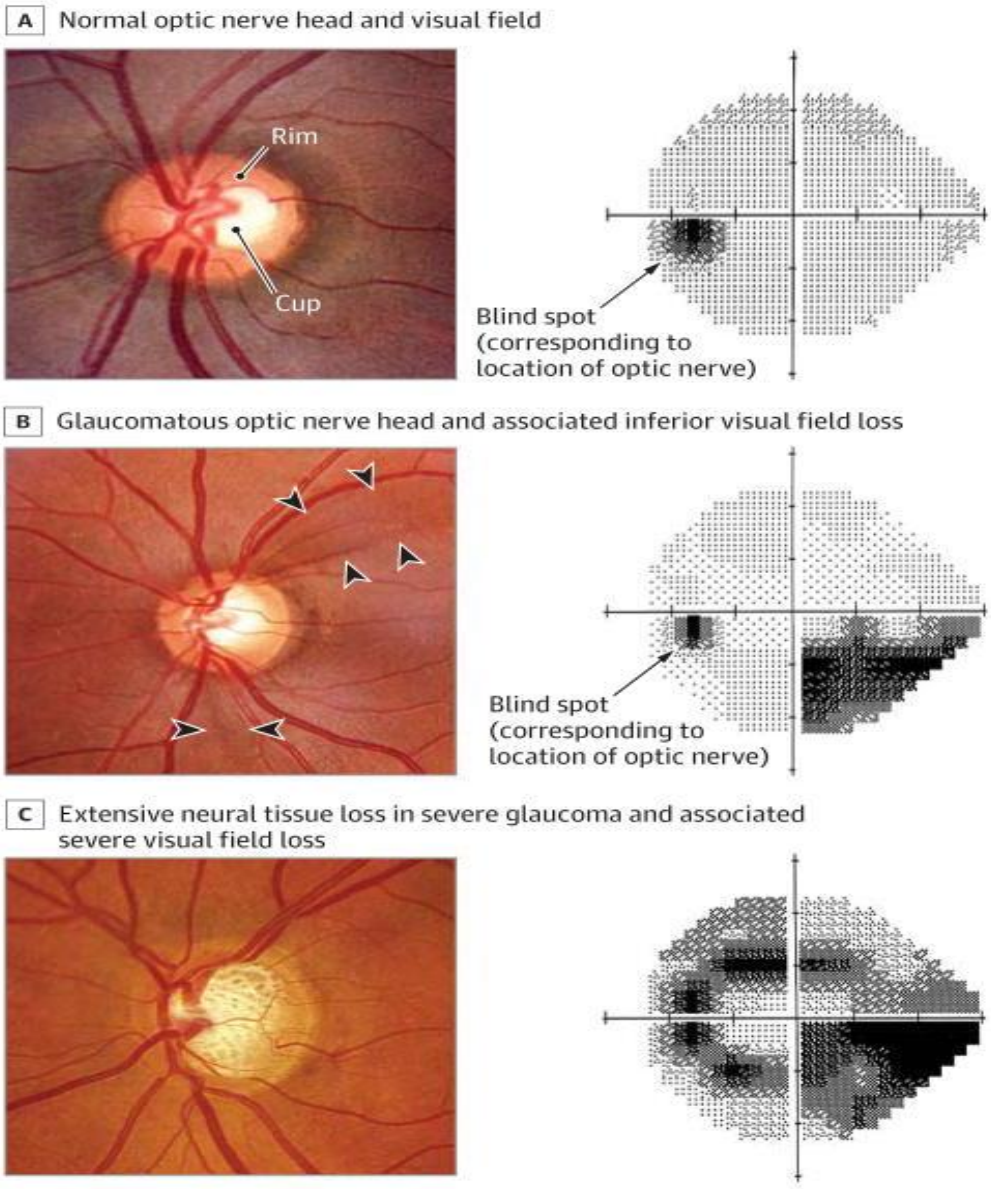

Figure1: Normal, Glaucomatous, and Severe Glaucomatous Optic Nerve Heads and Visual Field Test Results

Current study was aimed to overview the Glaucoma from different medical aspects including pathogenesis and risk factors and with clinical aspects as the treatment options available for different types of glaucoma.

2. METHODOLOGY

A literature search was conducted using electronic databases such as MEDLINE, the Cochrane Library, and manuscript references for studies published in English up to March 2017 on the topics glaucoma and its pathogenesis and risk factors leading to this disorder with discussion its treatments options. Studies included in this review were limited to human subjects with English language.

3. RESULTS

- ***Pathophysiology:***

The pathogenesis of glaucoma is not completely comprehended; the level of intraocular stress is related to retinal ganglion cell fatality [4,6]. Glaucoma is a heterogeneous group of diseases and the pathophysiology of glaucoma is believed to be multifactorial. Several factors acting either on cell bodies or their axons are believed to bring about RGC death. Inning accordance with different concepts put forth, factors like elevated intraocular pressure (IOP) and vascular dysregulation primarily add to the preliminary disrespect during glaucomatous atrophy in the form of blockage to axoplasmic flow within the RGC axons at the lamina cribrosa, altered optic nerve microcirculation at the degree of lamina and also modifications in the laminar glial as well as connective tissue. The equilibrium in between secretion of liquid wit by the ciliary body as well as its drain through 2 independent paths the trabecular meshwork as well as uveoscleral discharge pathway figures out the intra-ocular pressure. In patients with open-angle glaucoma, there is enhanced resistance to aqueous outflow with the trabecular meshwork. In contrast, the access to the drainage pathways is blocked normally by their is in patients with angle-closure glaucoma (**Figure 2**) [13].

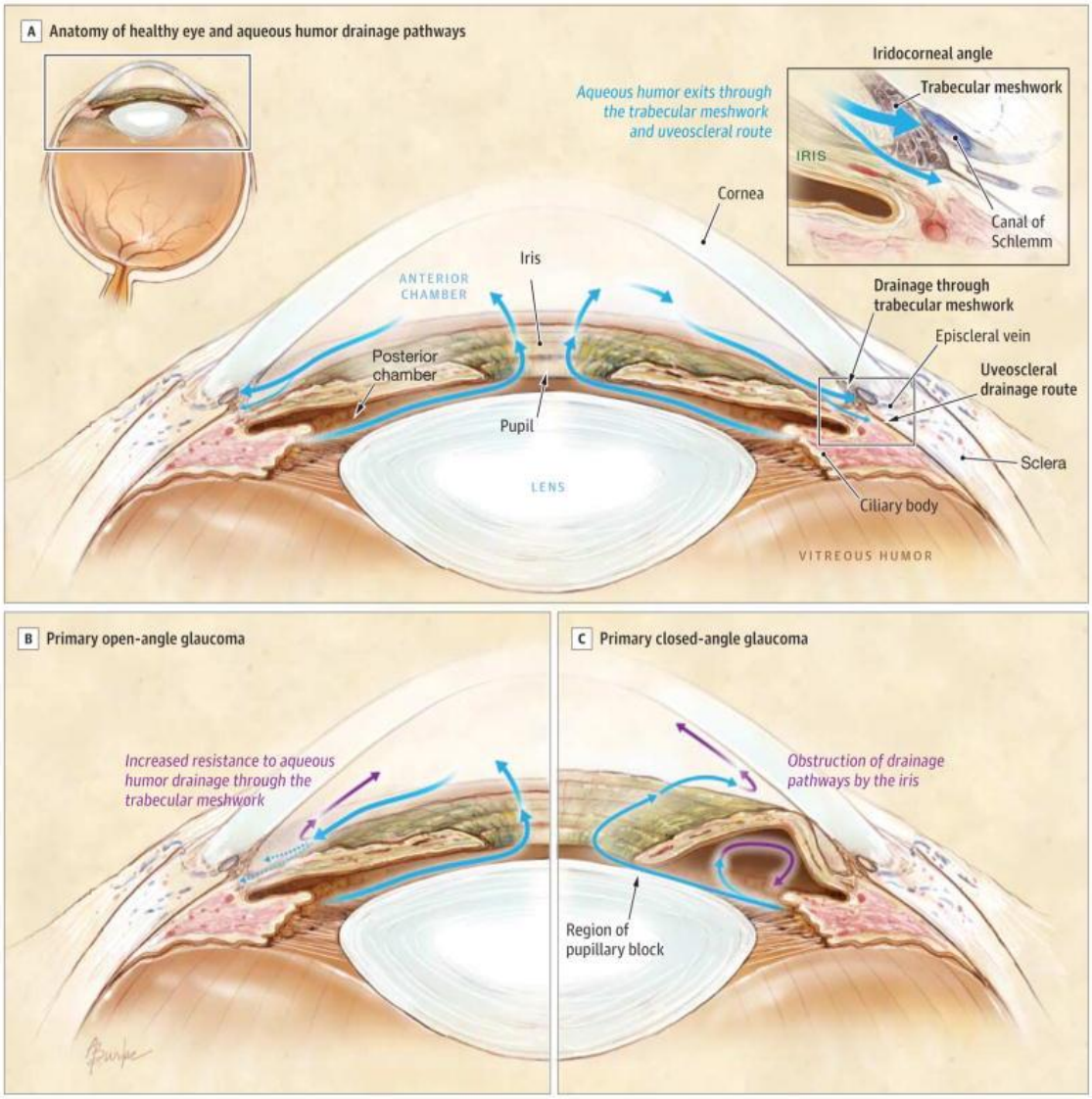

Figure 2: Aqueous Humor Drainage Pathways of Healthy and Glaucomatous Eyes

Intraocular pressure could create mechanical stress and anxiety as well as stress on the posterior structures of the eye, significantly the lamina cribrosa and surrounding tissues (**Figure 3**) [14]. The sclera is perforated at the lamina where the optic nerve fibers (retinal ganglion cell axons) exit the eye. The lamina is the weakest point in the wall of the pressurized eye. Intraocular pressure-- induced stress and also stress could lead to compression, deformation, and renovation of the

lamina cribrosa with subsequent mechanical axonal damage and disruption of axonal transportation [15,16] that disrupts backward delivery of essential trophic factors to retinal ganglion cells from their brainstem target (relay nerve cells of the side geniculate center). Studies including pet cats and monkeys with experimentally induced ocular hypertension have actually shown clog of both orthograde and also backward axonal transportation at the level of the lamina cribrosa [17]. Interrupted axonal transport happens early in the pathogenesis of glaucoma in experimental systems causing collections of vesicles as well as lack of organization of microtubules as well as neurofilaments in the prelaminar and postlaminar regions. Similar ultrastructural changes in optic nerve fibers are seen in postmortem human eyes that have glaucoma [14]. Since there additionally may be mitochondrial dysfunction in retinal ganglion cells and also astrocytes, high degrees of power demand could be difficult to fulfill during durations of intraocular pressure-- induced metabolic tension [18].

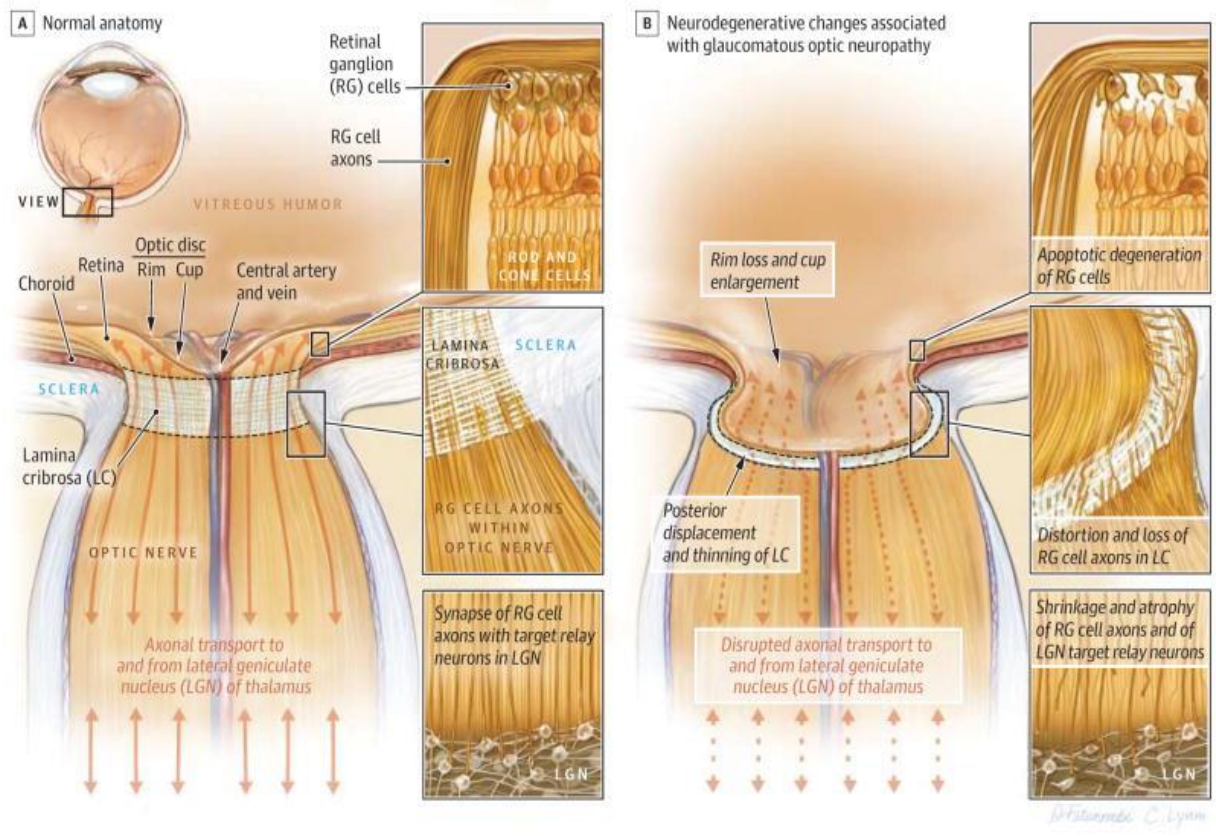

Figure 3: **Schematic Illustration of Normal Anatomy and Neurodegenerative Changes Associated With Glaucomatous Optic Neuropathy**

Glaucomatous optic neuropathy can happen in people with intraocular pressures within the normal variety. In such patients, there could be an extraordinarily reduced cerebrospinal liquid stress in the optic nerve subarachnoid space leading to a large stress slope throughout the lamina [19,20]. Impaired microcirculation, transformed immunity, excitotoxicity, and oxidative anxiety could also trigger glaucoma. Primary neural pathological procedures could create second neurodegeneration of other retinal nerve cells and cells in the main aesthetic path by changing their environment as well as enhancing vulnerability to damage [21].

Genetics background of glaucoma:

The most common form of glaucoma is primary open angle glaucoma (POAG), affecting over 33 million people worldwide [12,13]. This is a late-onset and complex problem that is related to raised intraocular pressures (IOPs) leading to axonal degeneration and visual field loss. The IOP boost in this problem seems to be owing to an "inefficiency" of the trabecular meshwork (TM) bring about decreased liquid discharge center. Its multifactorial etiology wased initially recommended in the year 1967 and it demonstrates a variable age of start and seriousness [22]. Most studies recommend an autosomal dominant inheritance with insufficient penetrance [23]. The inheritance pattern of this disorder appears to be multifactorial resulting from the communication of one or even more genes and/or environmental stimulations. To date, there have actually been over 20 genetic loci as well as 3 genes, MYOC (myocilin), OPTN (optineurin), and WDR36 that have actually been connected to POAG [13].

The very first reported locus for primary open-angle glaucoma was located on chromosome 1 (GLC1A). The pertinent genetics at the GLC1A locus is MYOC, which inscribes the protein myocilin. Disease-associated mutations of myocilin typically happen in the early or adolescent adult kind of primary open-angle glaucoma, typically identified by extremely high degrees of intraocular pressure. In populations of adults with primary open-angle glaucoma, the prevalence of myocilin anomalies varies from 3% to 5% [24]. Providers of disease-associated anomalies establish the glaucoma phenotype in an estimated 90% of the situations. The device of myocilin-related glaucoma has not been completely elucidated. It appears that anomalies change the myocilin healthy protein in a way that disrupts typical policy of intraocular stress. Disease-associated forms of myocilin hinder healthy protein trafficking and also lead to intracellular accumulation of misfolded protein. Failure to sufficiently produce the protein is believed to in some way trigger the intraocular stress to increase [24].

In comparison to people with the MYOC genetics, those with the OPTN gene have normal levels of intraocular pressure. Although the device connecting the OPTN genetics variants to glaucoma have actually not been illuminated, there is evidence recommending that optineurin could have a neuroprotective role by reducing the vulnerability of retinal ganglion cells to apoptotic stimulations [24,25]. A growing number of researches utilize genome-wide scans to search for glaucoma vulnerability loci. The CAV1/CAV2 (HGNC:1527/ HGNC: 1528) locus on 7q34 might be connected with primary open-angle glaucoma in European-derived populations. This searching for has actually been duplicated by independent researches [25]. These genes inscribe proteins (caveolins) associated with the generation and function of caveola, which are invaginations of the cell membrane layer associated with cell signaling and also endocytosis. The CDKN2BAS (HGNC:34341) locus on 9p21 was shown to be associated with glaucoma risk in several friends [26]. The system through which these genetics could contribute to primary open-angle glaucoma is not clear, but they may engage with changing development factor β, a molecule regulating cell development and also survival throughout the body. Regardless of appealing outcomes, sensitivity genes that have actually been recognized to date for primary open-angle glaucoma only have a modest result size in describing glaucoma risk.

- **Risk factors:**

The factors leading to secondary insult consist of excitotoxic damages caused by glutamate or glycine released from damaged neurons and oxidative damage triggered by over-production of nitric oxide (NO) and various other reactive oxygen varieties. Whatever may be the additional and also primary factors, the end result in glaucomatous eyes is the dysfunction and fatality of RGCs bring about permanent visual loss, as a result of a complicated interaction of several factors as opposed to any type of among them functioning independently [27].

A. Neuronal loss as first risk for glaucoma:

The characteristic change in the optic nerve head in glaucoma is a “cupping” of the optic disc where ganglion cell axons have been lost. The death of the axons is associated with a loss of ganglion cell bodies in the retina and ganglion cell axon terminals in the dorsal lateral geniculate body. Death of RGCs in glaucomatous human eyes and experimental animal models of glaucoma takes place by apoptosis, which is also the means of eliminating 50% of the RGCs during normal developmental organization of the visual pathway [28,29]. Apoptosis is a process of programmed cell death in the absence of inflammation, characterized by DNA fragmentation, chromosome clumping, cell shrinkage and membrane blebbing [30]. Nuclear damage is followed by breaking down of the cell into multiple membrane-bound vesicles which are engulfed by neighboring cells. Some researchers have suggested preferential loss of larger ganglion cells in the retina belonging to parasol and midget cell classes but this issue still remains debatable [31,32]. Although there are compelling evidences showing apoptosis as the primary and early mechanism of ganglion cell death in glaucoma, necrosis is also a contributory mechanism in the late phase, evidence to which was observed in rats subjected to optic nerve transection [33,34].

B. Vascular insufficiency:

Plainly, elevated IOP plays a major function in RGC damage in glaucomatous eyes yet restorative control of IOP in many patients is not sufficient to enhance the visual functions and also apprehend the development of the disease procedure [35]. Glaucomatous modifications have actually been observed in people with normal IOP. This recommends a vital role of other consider the initiation as well as development of glaucomatous changes.

A variety of circumstantial evidences direct to an organization between vascular deficiency and glaucoma. A favorable organization of glaucoma has been observed with migraine as well as outer vascular irregularities that involve dysregulation of outer and also cerebral vasculature specifically. Boosted level of sensitivity to endothelin-1-mediated

vasoconstriction is implicated in these vascular irregularities [36,37]. The possible role of this vasoconstrictor is likewise suspected in the pathogenesis of glaucoma as boosted degrees of endothelin-1 have actually been discovered in the aqueous humor and also plasma of glaucoma patients [38].

The molecular mechanisms bring about RGC fatality due to vascular dysregulation are not clearly comprehended. The vascular lack could straight create and also harm RGC apoptosis. Upregulation of MMP-9 expression in circulating leucocytes has been observed in patients with vasospastic NTG (39). The upregulation of MMP can be a direct action to ischemic injury or it can be a secondary response to raised levels of endothelin and TNF-A. The MMP produced by the flowing leukocytes of these patients could be associated with the partial barrier failure and RGC damage (**Figure 4**) [40].

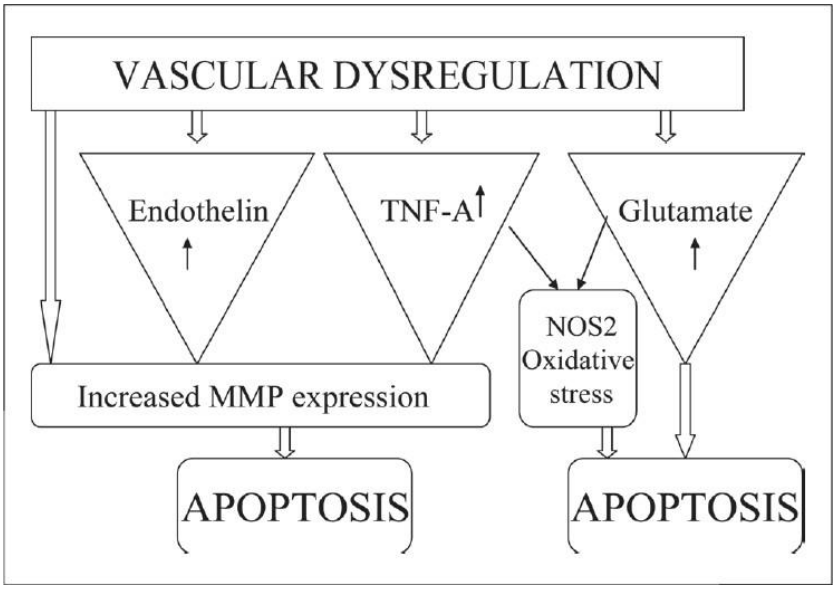

Figure 4: Mechanisms involved in glaucomatous RGC apoptosis secondary to vascular dysregulation.

C. Role of nitric oxide in glaucoma:

In regular human eyes the visibility of NOS-1 has actually been identified in scattered astrocytes throughout the optic nerve head suggesting that the NOS-1 is an integral enzyme in particular glia and also NO offers features as a physiological arbitrator between astrocytes or between axons as well as astrocytes. In patients with glaucoma a multitude of cells show NOS-1 positivity on vitreal surface, in the remnant glial cells and also in the cells in lamina cribrosa within glaucomatous cells. Enhanced gene expression of the mRNA as well as most likely afresh synthesis of the NOS-1 isoform in astrocytes of the lamina cribrosa have also been observed. NOS-3 is likewise a constitutive enzyme existing in the vascular endothelial cells in the prelaminar region of the optic nerve head in normal eyes and features as a vasodilator. In glaucomatous eyes by creating vasodilation and boosting the blood flow NOS-3 induction could give neuroprotective results. The function of NOS-3 existing in the astrocytes of glaucomatous optic nerve heads is not plainly recognized [41,42].

Treatment approached:

Glaucomatous optic neuropathy is a chronic procedure, which progresses over several years. Till lately, inflection of elevated IOP was the only setting of restorative intervention. As the glaucomatous modifications continue to advance regardless of well-controlled IOP, growth of pressure-independent and preferentially neuroprotective therapy approaches is extremely crucial. As the understanding of pathophysiological mechanisms associated with glaucomatous optic neuropathy has actually advanced tremendously, an enormous quantity of study has actually been promoted for the growth of effective neuroprotective strategies [43].

Because of this a selection of restorative choices have revealed efficacy as neuroprotective agents in experimental researches. Eye hypotensive agents the ocular blood circulation enhancers such as calcium network blockers were recommended to supply neuroprotection by boosting the optic nerve head blood circulation. However there were issues as these agents lower the systemic high blood pressure and also might get worse the optic nerve head ischemia by reducing the perfusion stress. Carbonic anhydrase preventions are additionally suggested to enhance the optic nerve head blood circulation [44].

A range of agents with antiapoptotic task have been reviewed for neuroprotective effects in experimental animal versions. Both the irreparable as well as relatively easy to fix caspase preventions were discovered to secure RGCs in axotomised rats. Erythropoietin, which advertises expansion as well as distinction of bone marrow precursor cells by hindering apoptosis, when given by intravitreal shot in an episcleral vessel cautery-induced rat model of glaucoma was located to boost RGC feasibility [45,46,47]. Nevertheless, using these representatives, which act by stopping the apoptosis, is actually the treatment of the outcome rather than the degenerative procedure itself.

Restorative treatments to modify the procedure of RGC deterioration have also been examined thoroughly. A variety of neurotrophic factors (BDNF, nerve development factor), an antioxidant (N-ace-tyl-L-cysteine), as well as a NOS inhibitor (L-NAME, aminoguinidine) have actually shown appealing neuroprotective effects by regulating the procedure of RGC degeneration in experimental animals. The NMDA villains particularly appear to hold guarantee in glaucoma neuroprotection. NMDA receptor villains have largely fallen short the clinical trials as they act by virtually obstructing all the NMDA receptors, and physiological NMDA activity is necessary for typical neuronal features. Memantine, an adamantine derivative, has revealed encouraging results as it selectively blocks the excessive receptor activation without impacting the typical receptor task. Memantine is a noncompetitive, low-affinity, open channel blocker as well as blocks the receptor-associated ion network when it is excessively open. As its off-rate is really high it does not collect substantially within the channel to disrupt the normal neuronal features. Memantine is therefore well endured and also has actually been approved for use in Alzheimer's disease [47].

4. CONCLUSION

Recognizing glaucoma-associated genes will certainly also help elucidate the biochemical paths that create glaucoma. Knowing such pathways will certainly facilitate the advancement of novel medication treatments that can be customized to specific forms of glaucoma. New therapies could consist of agents based on the protein, enzymes, or RNA transcripts related to glaucoma. Due to the fact that the biochemical paths included in glaucoma can be particularly targeted, researchers can create more secure as well as more disease-specific treatments.

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