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Review article

Controversies in the vascular theory of glaucomatous optic nerve degeneration

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ABSTRACT

An understanding of the pathogenesis of glaucoma is one of the foundations in glaucoma management. A number of theories have been presented to explain glaucomatous neural degeneration. The vascular theory attempts to explain the causation of glaucoma on the basis of vasogenic factors and altered hemodynamics in the body; however, this theory remains controversial. There are proponents for and against the role played by vascular factors in the development of glaucomatous optic nerve degeneration. This review aims to analyze the various studies performed to provide evidence for and against the vascular theory of glaucoma. It also affirms the need to undertake further studies regarding the pathogenesis of glaucoma and integrate them into our management strategies. The literature search for this systemic analysis was performed using search engines, such as PubMed, The Virtual Library of the Ministry of Health Malaysia, Google Scholar, and ClinicalKey.

1. Introduction

Glaucoma is a broadly used term signifying a neurodegenerative disorder of ocular tissues. It is characterized by structural damage to the cellular components of the retina and axonal elements in the optic nerve. These changes are correspondingly reflected in functional parameters, such as the visual fields, electroretinograms, and others. There is a plethora of knowledge regarding the structure–function changes and their management in glaucoma; however, the pathophysiologic mechanisms responsible for the development and progression of glaucoma remain unclear.[1,2]

A number of theories have been presented over the years to explain the causation of glaucoma. Initially, the mechanical theory was put forward to explain the pathogenesis of glaucomatous optic nerve degeneration (GOND). It was hypothesized that GOND occurred due to the raised intraocular pressure (IOP) forcing the lamina cribrosa backward and squeezing the nerve fibers within its meshes to disturb axoplasmic flow. However, this theory is unable to explain those patients whose IOP is above the normal range (21 mmHg), but who do not develop GOND (ocular hypertension). The Ocular Hypertension Treatment Study also reported that >90% of individuals with high IOP failed to progress to glaucoma when followed over a 5-year period.[3] Conversely, there is a sub-group of patients who develop changes characteristic of glaucoma, even though they have what is considered a statistically normal level of IOP (normal-tension glaucoma). It was also observed that some patients continue to progress, despite the lowering of IOP to an ideal target range.[3] Thus, the mechanical theory fails to entirely explain the pathophysiologic concepts of GOND.

Subsequently, a number of other theories have been presented to describe the etiopathogenesis of GOND. These include the vascular, genetic, and biochemical theories.[4] The vascular theory attempts to explain glaucoma causation on the basis of reduced perfusion pressure, faulty vascular autoregulation, or loss of neurovascular coupling.[5] While some researchers advocate the vascular theory as the cause of GOND, others provide evidence against this. Therefore, this article reviews the opposing perspectives in favor of and against the vascular theory of GOND.

The importance of studying the various mechanisms of glaucoma pathogenesis cannot be overemphasized. Only greater insight into these basic concepts can refine our current practice of glaucoma management.

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2. Evidence in favor of the vascular theory

2.1. History of the vascular theory

The earliest reference to a vascular etiology in the pathogenesis of glaucoma was attributed to von Jaeger in 1858, who argued that neuronal damage due to elevated IOP was mediated by ischemia and not compression of nerve fibers.[6]

Priestly Smith, Kummel, Magitot, Duke-Elder, and several others also contributed to the vascular theories of GOND.[7–11] In 1922, Felix Lagrange[12] claimed that glaucoma was just one manifestation of a deranged circulatory physiology affecting the entire body. He termed glaucomatous optic neuropathy a "sick eye in a sick body."

In 1948, Dienstbier et al[13] stated that, "the solution of the problem of pathogenesis of glaucoma has entered its final phase …. glaucoma is the expression of stasis in the venous system and the eye capillaries. It has its origin partly in organic vascular changes with a more or less marked spastic factor and partly in changes in function (vasoneurosis)."

In 1970, Hayreh[14] defined glaucoma as, "a disease wherein the normal balance between the IOP and blood pressure in the choroidal vessels, supplying the optic disc and retrolaminar part of the optic nerve is disturbed. This results in vascular insufficiency in the optic disc and retrolaminar part of the optic nerve and hence in visual field defects and pathological changes in the optic disc and optic nerve."

2.2. Ocular blood flow

One of the foundations of the vascular theory is ocular blood flow (OBF). It is theorized that faulty blood flow is an important contributor to GOND. Indeed, ocular circulation is an intricate system that supplies essential nutrients to a diverse group of ocular structures, such as the optic nerve, retina, and choroid. Concurrently, this vascular system is required to perform functions without interfering with image formation and transmission in the visual pathway. Therefore, OBF requires meticulous regulation and adapts to ever-changing metabolic requirements as stipulated by the varying visual functions. Additionally, OBF compensates for fluctuating perfusion pressures and maintains an optimal temperature around the eye. However, ocular circulation is not uniform, and considerable individual variation exists in the distribution of vascular flow in this region.[15]

Some researchers suggested that the decrease in OBF intrinsically does not lead to glaucoma. Instead, other characteristics, such as an alteration in the quality of blood supply to the optic nerve head (ONH) are implicated in GOND.[16] Flammer et al[17] suggested that an unstable, fluctuating OBF is the likely mechanism of glaucomatous damage. Fluctuating OBF leads to unstable oxygen supply, which, in turn, triggers oxidative stress. Deokule et al[18] studied the correlation of blood flow with perimetric changes and reported that retrobulbar blood-flow velocities are reduced in advanced disease and correlate with standard automated perimetry (SAP) global indices in glaucoma patients. Changes in neuroretinal rim blood flow in primary open-angle glaucoma (POAG) patients also correlate positively with mean deviation (MD) on SAP.[18] Additionally, increasing parapapillary atrophy was reported in eyes with progressive glaucomatous changes, and is assumed to be related to hypoperfusion of the ONH.[19]

2.3. Ocular perfusion pressure

Ocular circulation is dependent upon a net pressure gradient that causes blood flow to the eye and is known as ocular perfusion pressure (OPP). This factor represents a relationship between two key dynamic biological parameters: blood pressure (BP) and IOP. In simplistic terms, OPP is defined by:

$$\mathrm{OPP} = \mathrm{BP} - \mathrm{IOP} \quad (1)$$

From Eq. (1), a higher BP or a lower IOP results in a better OPP. Studies showed that low OPP is a risk factor for the prevalence, incidence, and progression of glaucoma.[20] According to Flammer et al,[17] the best predictor of progression of glaucomatous damage is fluctuation in OPP; however, underlying factors relating OPP and glaucoma have not been identified. It is yet to be determined whether low OPP is independent of the sum of the two risk factors, i.e., low BP/mean arterial pressure and high IOP.[21,22]

Increased systemic BP will correspondingly increase pressure in the anterior ciliary artery. This, in turn, leads to an increased ultrafiltration and, therefore, increased IOP. However, as per Eq. (1), a rise in BP should cause an increase in OPP. Epidemiological studies, quoted by He et al[1] also suggested that systemic hypertension is a protective factor in glaucoma; however, glaucoma is frequently reported in both hypo- and hypertensive patients. Moreover, normal tension glaucoma (NTG) was commonly reported in patients with low BP. The Barbados Eye Study, the Proyecto VER Study, and the Egna-Neumarkt Study showed that low diastolic perfusion pressure (45–50 mmHg) is associated with a higher risk of developing glaucoma.[23–25] The Los Angeles Latino Eye Study concluded that both low diastolic pressure and high systolic pressure are associated with an increased prevalence of open-angle glaucoma.[26] Glaucoma is also seen in individuals who have large nocturnal dips in BP. Interestingly, the Baltimore Eye Survey demonstrated that systemic hypertension is protective against glaucoma in younger patients, but poses an increased risk in elderly patients.[27] It is theorized that vascular sclerosis in old age reduces OBF, even in hypertensive patients, thereby increasing the risk of GOND.[2]

Studies have showed that alterations in ocular hemodynamics may play a significant role in the POAG pathogenesis. It was suggested that in glaucomatous eyes, OBF decreases, because apoptotic retinal ganglion cells (RGCs) require less oxygen and nutrients. Therefore, reduced OBF is assumed to be a secondary phenomenon resulting from the loss of RGCs. There are conflicting schools of thought, however, which infer a reduced OBF as the primary event that subsequently leads to ischemic death of RGCs. This process most likely involves some vascular factors.[18,28,29]

2.4. Biochemical factors and ocular blood flow

Ocular blood flow can be affected by a number of biochemical factors. The retina and ONH of glaucoma patients exhibit increased levels of hypoxia inducible factor 1α.[17] This oxygen-regulated transcriptional activator can increase oxygen delivery or facilitate metabolic adaptation to hypoxia.[30] Some of the circulating molecules that diffuse from the choroid into the ONH and retina include endothelins (ET), vascular endothelial growth factor, and matrix metalloproteinases (MMPs). These molecules weaken the blood-retina barrier and allow erythrocytes to escape from vessels, clinically appearing as splinter hemorrhages at the optic disc margin.[5] Elevated ET-1 levels in glaucomatous patients are associated with oxidative stress as a causative factor. ET-1 reduces blood flow in posterior ciliary arteries, and high ET-1 levels are also associated with disease progression.[3,31,32] Similarly, MMP-2 and MMP-9 are upregulated in the ONH of glaucoma patients, contributing to apoptosis.[33]

Ischemia causes oxidative stress, which is mediated by a group of cytotoxic byproducts known as reactive oxygen species (ROS), such as free radicals, superoxide, and lipid peroxides. ROS are constantly produced as a result of normal cellular metabolism and

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