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Review Article

Rethinking the Pathogenesis of Primary Open-Angle Glaucoma: An Optic Disc Axotomy

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Abstract

Primary open angle glaucoma (POAG), commonly known as glaucoma, is the leading cause of irreversible blindness in the world. The recognition of glaucoma as a separate entity dates back to the 1850s when ophthalmologists of the time observed the fundus of blind subjects with painless but firm eyes for the first time with the newly invented ophthalmoscope.

They observed that their optics discs were 'cupped' in glaucoma instead of the normal flat appearance. This observation led to the belief that the optics discs had become cupped as a result of the direct force of elevated intraocular pressure (IOP). The term 'cupping' was not seriously questioned at the time. However, this term gained acceptance which then gave birth to a cupping paradigm - a concept that persists to this day.

Within this paradigm, cupping of the optic disc implies that the pathology starts from the central part of the disc and extends concentrically to its peripheral part in glaucoma. Logically, this would suggest that the central vision nerve fibers (NF) should be destroyed first, and the peripheral vision NFs at the end stage, in accordance with the normal arrangement of nerve fibers in the optic disc. However, in actuality, the glaucomatous visual field defects show that the exact opposite field loss is occurring: the peripheral vision is destroyed first, while the central vision remains until the end stage, in an orderly sequence.

This fundamental contradiction challenges the credibility of the long-standing cupping paradigm introduced 170 years ago.

There are two established facts in the realm of glaucoma. Firstly, that elevated IOP, even as a stand-alone factor, is an established cause of glaucoma. Secondly, there is an orderly, peripheral-to-central loss of nerve fibers. This nerve fiber loss never occurs randomly. These two facts combined present a puzzling question: How does elevated IOP acting directly on the nerve fibers result in the orderly and systematic loss of nerve fibers in glaucoma?

The direct effect of elevated IOP, in a single action, cannot account for the orderly loss of nerve fibers in glaucoma. In fact, there is no known biological mechanism acting directly on the NFs which could result in their orderly loss. Thus, there must be some mechanical scenario which will first separate the densely packed NFs individually for their orderly one-by-one loss; even though that mechanism may have resulted from the biological effect of elevated IOP on some important component of the optic disc. Therefore, it is proposed that glaucoma may be a two-stage disease.

First stage: degeneration of the border tissue of Elschnig due to chronic ischemia induced by elevated IOP. This border tissue degeneration then results in the loosening of the lamina cribrosa. This is followed by the second stage: the sinking of the lamina cribrosa, leading to the stretching and severance (or axotomy) of nerve fibers from peripheral to central, in an orderly sequence, at the scleral edge. This progressive sinking of the lamina cribrosa and severance of nerve fibers will continue until the central-most

nerve fiber has moved to the scleral edge and is severed. The vasculature is also being severed along with the nerve fibers resulting in splinter hemorrhages at the disc margin.

The progressive sinking of the lamina cribrosa and the orderly, peripheral-to-central severance of nerve fibers corroborates with the observed visual field defects in glaucoma. The severance of nerve fibers can explain the orderly loss of nerve fibers in glaucoma. Glaucoma may not be an optic neuropathy, but an optic disc axotomy - a paradigm shift.

Keywords: *Pathogenesis; Primary Open-Angle Glaucoma; Optic Disc Axotomy; Intraocular Pressure (IOP); Nerve Fibers (NF)*

Introduction: Historical Evolution of the Cupping Paradigm

The invention of the ophthalmoscope by Herman Von Helmholtz in the early 1850s marked a pivotal period in ophthalmology, enabling a direct observation of the optic discs for the first time in individuals with primary open-angle glaucoma (POAG) [1]. Ophthalmologists of the time found that the optic discs as 'cupped' instead of being normally flat. Based on this observation, they believed that the discs had become cupped due to the direct force of elevated intraocular pressure (IOP) in glaucoma [2].

The validity of the term 'cupping' was not seriously questioned at the time. However, it became adopted which then gave birth to a cupping paradigm in glaucoma - that which has endured through time and is still accepted today. As this paradigm gained acceptance over time, incorrect parameters and anatomical terms were introduced in order to align and support the cupping paradigm.

Approximately a century later, in the 1950s, instead of confirming the cupping theory, a parameter known as the cup-to-disc ratio was introduced [3]. This parameter inferred that the physiological (birth) cups begin concentrically enlarging as the disease progressed. However, these cups, ranging in size from 0.00 to 0.9, are actually the central meniscus of Kuhnt - fibrous remnants of Bergmeister's papilla - lying superficially on the nerve fiber layer of the optic disc [4]. Significantly, these terms are incorrectly applied and bear no relevance to glaucoma.

With this parameter, we began to refer to this meniscus as a 'cupped hole' devoid of nerve fibers and to the remaining uncovered area of the disc as the 'neuroretinal rim', containing the entire nerve fibers.

Hypothetically, if there is indeed a hole in the center of the optic disc, as suggested by the neuroretinal concept, then the entire force of elevated IOP would be dissipated into the hole, thus sparing the neuroretinal rim from damage; the larger the hole, the less likelihood of injury to the neuroretinal rim. However, this donut analogy of the optic disc is anatomically incorrect as histological illustrations in textbooks do not support this concept. All optic discs with or without original cups are densely packed with NFs all the way to the central part of the disc, even underneath this fibrous meniscus - without any empty space [4].

Furthermore, within the framework of the cupping paradigm, it has become generally accepted that the lamina cribrosa is bowing posteriorly [5]. According to this interpretation, the central vision fibers, situated at the apex of the bowed lamina cribrosa, should be destroyed first in glaucoma. However, in reality, glaucomatous field defects reveal an inverse pattern of field loss: the peripheral vision is destroyed first, while the central vision remains intact until the late stages of the disease.

Understanding primary open-angle glaucoma (POAG)

Primary open-angle glaucoma (POAG) stands as a prevalent form of glaucoma, characterized by its painless nature, gradually leading to blindness over time. Glaucoma, being a painless condition, often remains undetected and its diagnosis is usually made during routine eye examinations. POAG presents itself in two primary forms: high-tension glaucoma (HTG) and normal-tension glaucoma (NTG). In HTG, intraocular pressure (IOP) surpasses the normal range (10 - 21 mmHg), while in NTG, the IOP levels stay within the normal range.

Both HTG and NTG exhibit comparable pathological features in the optic disc and follow a parallel course of disease progression. The classification of NTG as a true glaucoma has been a subject of debate, mainly due to its normal IOP levels. However, it appears that NTG indeed represents a genuine form of glaucoma akin to HTG. Furthermore, in NTG, the normal IOP appears to be 'acting as elevated IOP' in individuals with compromised circulatory conditions, a concept we will discuss later in this article.

Arrangement of nerve fibers in the retina and optic disc

There are two main aspects in the arrangement of NFs in the retina and optic disc. Firstly, the central vision fibers originate closer to the optic disc, lie superficial (closer to the vitreous) and after making their 90-degree turn, they exit from the central part of the disc. Whereas, the peripheral vision fibers originate farthest from the optic disc, lie deeper (closer to the sclera), and after making their 90-degree turn, exit closer to the edge of the scleral opening [6] (Figure 1).

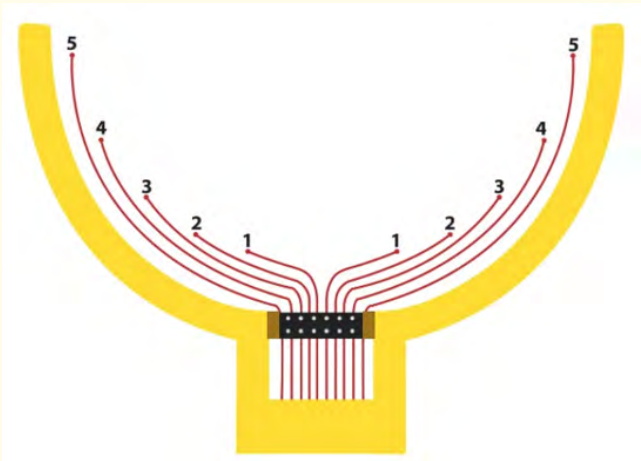

Figure 1: *Schematic diagram. Normal arrangement of nerve fibers in the retina and optic disc.*

The most peripheral nerve fibers [5] originate farthest from the optic disc, lie deepest (closest to the sclera) and exit nearest to the scleral edge. The most central fibers [1] originate closest to the disc, lie most superficial (closest to the vitreous) and exit from the most central part of the disc.

Secondly, the NFs originating from the nasal retina take a direct course to the nasal part of the optic disc.

The nasal macular NFs, recognized as the maculopapillary bundle, course to the temporal part of the optic disc. The temporal macular NFs, referred to as the arcuate bundles, originate from the horizontal temporal raphe.

These arcuate fibers arch above and below the maculopapillary bundle before entering the optic disc at the 11 and 7 o'clock positions, respectively. The NFs originating from the outermost temporal retina access the optic disc beyond the entry point of the arcuate fibers. This intricate assembly of nerve fibers are stratified in layers from superficial to deep in the retina (Figure 2).

Correlation of glaucomatous field defects with the arrangement of nerve fibers

Glaucomatous field defects provide a strong indication that the entire span of the deepest 360 degrees of retinal nerve fibers, encompassing both the maculopapillary and arcuate fibers, undergo simultaneous loss from day one in glaucoma. However, their initial

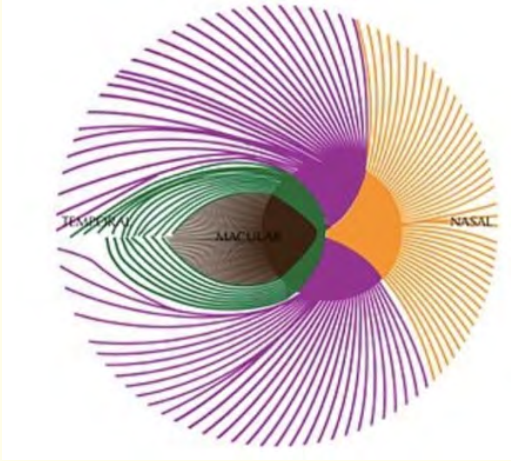

Figure 2: *Schematic diagram. Normal arrangement of nerve fibers in the retina and optic disc. The arcuate fibers (green) arch above and below the macular fibers to reach the poles of the optic disc.*

field loss is not recognizable and remains inconspicuous due to the abundance of nerve fibers. But the arcuate fibers, notable for their limited quantity and distinctive arcuate shape, emerge as a valuable diagnostic feature in glaucoma (Figure 3).

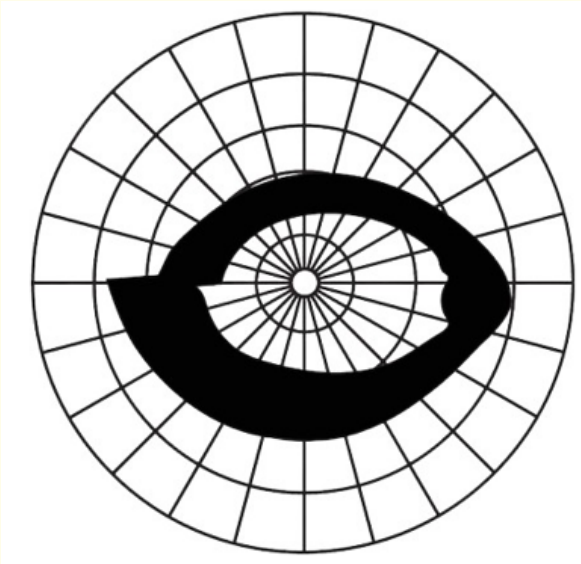

Figure 3: *Schematic diagram. The double arcuate field defect (Ring scotoma) in chronic glaucoma. The sharply-defined superior and inferior arcuate field defects with nasal step are salient features of glaucoma. Sharply-defined margins can only be produced by the depletion of the arcuate NFs, not by their atrophy.*

Furthermore, these glaucomatous field defects are horizontally-oriented and corroborate fully with the arrangement of the nerve fibers in the retina until they make their 90-degree turn in the optic disc. After making their 90-degree turn, they become vertically-oriented and thus their arcuate pattern is no longer present in the lamina cribrosa [7].

A multitude of isolated scotomas are produced within the paracentral 10 to 20 degrees area, indicating a gradual one-by-one destruction of nerve fibers in glaucoma. Over time, these minuscule scotomas coalesce to form a complete double arcuate/ring scotoma with Ronnie's nasal step. In the advanced stages of glaucoma, the peripheral and arcuate field loss join together, leaving a central vision of 5 to 10 degrees resulting in tunnel vision. The central vision remains intact until the disease's final stages due to the abundance of macular nerve fibers. However, the central vision is also eventually lost, leading to total blindness (Figure 4).

Two established facts in the realm of glaucoma

Within the domain of glaucoma, two fundamental principles emerge. First, there is an orderly and predictable loss of nerve fibers starting with the peripheral-most nerve fibers and ending with the central-most nerve fibers. Secondly, that elevated IOP, even acting independently, is a well-documented cause of glaucoma as exemplified by instances of unilateral traumatic glaucoma in healthy individuals. These two established facts raise the most puzzling question in glaucoma: How does the direct impact of elevated IOP on the nerve fibers within the densely packed optic disc invariably give rise to a systematic loss of nerve fibers that unfailingly progresses from the peripheral to the central region, defying randomness?

A myriad of glaucoma theories have been postulated, spanning the spectrum from the direct action of elevated IOP to the neurodegeneration of retinal ganglion cells (RGCs). Ironically, none of these prevailing theories encompass the systematic loss of nerve fibers - a pathognomonic feature of glaucoma. For any glaucoma theory to be valid, it must explain the orderly, peripheral-to-central loss of nerve fibers (Figure 4). Otherwise, it would be of no scientific value.

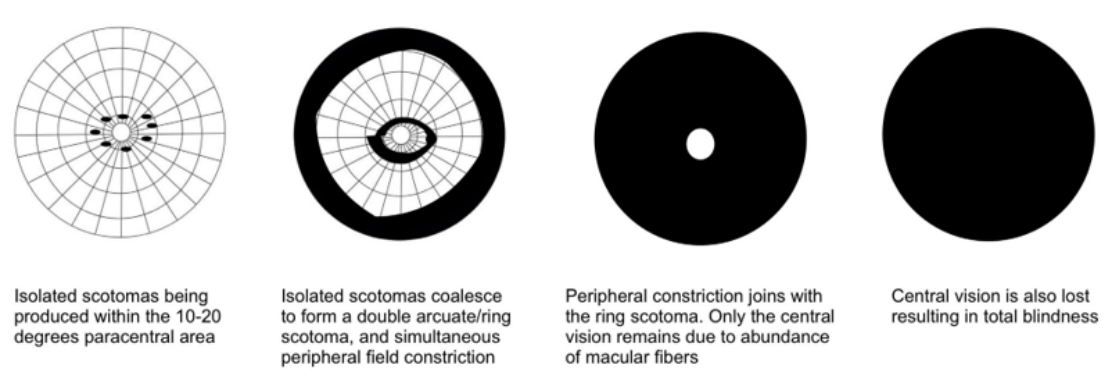

Figure 4: *Schematic diagram. The orderly, peripheral-to-central loss of the visual field in chronic glaucoma.*

Elevated IOP, whether it directly affects the retinal ganglion cells or their nerve fibers within the retina, or in the optic disc, cannot, by a single action, bring about the systematic loss of nerve fibers. In fact, there is no known biological mechanism acting directly on the NFs which could result in their orderly loss - only a mechanical scenario holds the potential to achieve this outcome.

How, then, does elevated IOP create the mechanical circumstances that lead to the systematic loss of nerve fibers in glaucoma? It is proposed that elevated IOP might be damaging a crucial component of the optic disc first, thereby setting in motion a mechanical scenario

that results in the systematic loss of nerve fibers from the periphery to the center. Thus the pathogenesis of chronic glaucoma may be a two-stage disease [8].

Pathogenesis of primary open-angle glaucoma: A two-stage disease

First (Biological) stage: Degeneration of the border tissue of Elschnig

The border tissue of Elschnig keeps the lamina cribrosa firmly in place, acting as an 'O' ring seal. This border tissue is supplied exclusively by the ciliary arteries, a low pressure circulatory system. Furthermore, this border tissue does not receive any contribution from the central retinal artery [9]. The ciliary circulatory system exerts a pressure of approximately 25 mmHg within the border tissue. This ciliary pressure supplying the border tissue is higher than 21 mmHg, the upper limit of normal range IOP.

Normally, the circulatory pressure of the border tissue should be higher than the IOP for its proper perfusion and healthy maintenance. However, if the IOP becomes higher than the circulatory pressure of the border tissue, say to 26 mmHg, it will begin compressing the border tissue circulation of 25 mmHg, resulting in chronic ischemia and its degeneration. This would be an example of high-tension glaucoma.

Conversely, when the circulatory pressure within the border tissue reduces, reaching a level like 15 mmHg, which can occur in individuals with chronic hypotension, then even a normal IOP of 16 mmHg can 'act as elevated IOP' in these subjects. In this scenario, the normal IOP of 16mmHg would compress the reduced border tissue circulation of 15 mmHg, resulting in chronic ischemia and its degeneration - an example of normal-tension glaucoma.

In both HTG and NTG, a common mechanism prevails: when the IOP exceeds the pressure of the ciliary circulation, it leads to chronic ischemia, and the subsequent degeneration of the border tissue (Figure 5).

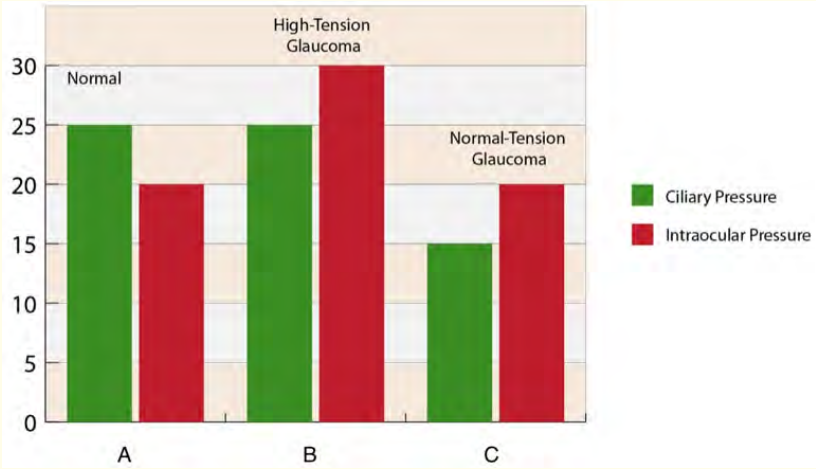

Figure 5: *Graphic diagram. The relationship between ciliary pressure and IOP.*

Normally, the ciliary pressure supplying the border tissue should be higher than IOP for its proper perfusion and healthy maintenance as in column (A). In column (B) the IOP is increased to 30 mmHg due to an ocular problem whereas the ciliary pressure is still the same at 25 mmHg, resulting in high-tension glaucoma. In column (C), due to decrease of the ciliary pressure to 15 mmHg resulting from systemic problems such as hypotension, the normal IOP at 20 mmHg is now 'acting as elevated IOP', resulting in normal-tension glaucoma.

The ciliary circulatory pressure of the border tissue, being higher than IOP, is important for its healthy maintenance. The degeneration of the border tissue appears to be the common ground in both HTG and NTG.

Second (Mechanical) stage: Sinking of the lamina cribrosa and the orderly axotomy of nerve fibers

The degeneration of the border tissue will cause the lamina cribrosa (LC) to become loose and to begin sinking in the scleral canal. The early stages of glaucoma have been observed to involve the posterior migration of the lamina cribrosa, a noticeable process that can be likened to the lamina cribrosa sinking [10]. Due to sinking of the LC, the entire 360 degrees of the deepest (peripheral) nerve fibers, being closest to the scleral edge [11], including the arcuate and maculopapillary NFs would be stretched and severed (axotomized) first at the scleral edge.

As the sinking of the LC progresses, the next-in-line nerve fiber would move to the periphery to occupy the space vacated by the preceding severed NF, and also gets severed. This cascade of progressive sinking of the LC and severance of NFs will continue until the central-most NF has moved to the scleral edge and is severed (Figure 6). The vasculature is also being severed simultaneously, resulting in the splinter hemorrhages [12] and blanching (whiteness) of the glaucomatous optic disc. Furthermore, the severance of NFs fibers is producing excavation (empty spaces) in the pre-laminar area. The end-stage glaucomatous disc is an empty crater left over after severance of NFs and vasculature, not a 100% cupped lamina cribrosa (Figure 7).

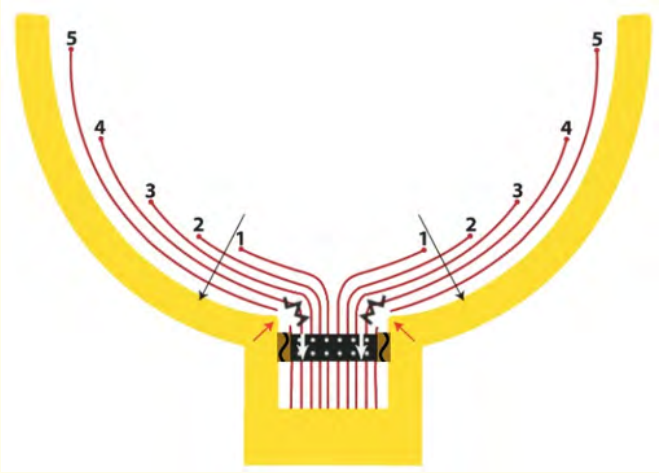

Figure 6: *Schematic diagram. Sinking of the lamina cribrosa and severance (Axotomy) of nerve Fibers. Due to sinking of the LC, the most peripheral and deepest prelaminar nerve fibers [5] are stretched and severed against the scleral edge (red arrows). As the LC continues sinking, the next-in-line fibers [4] will then move towards the scleral edge to occupy the space vacated by the preceding severed fiber and will also get stretched and severed. As sinking of the LC progresses, this process will continue until the central-most nerve fiber [1] moves to the scleral edge and is severed. Note: the degeneration of the border tissue (brown) and sinking LC.*

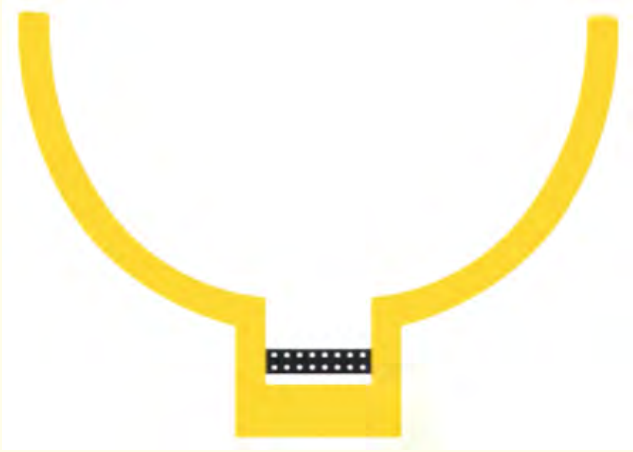

Figure 7: *Schematic diagram. End-stage glaucomatous disc.*

At the end stage, the lamina cribrosa is empty of nerve fibers and its vasculature, lying at the bottom of the crater.

Numerous studies have reported the posterior migration of the lamina cribrosa in the early stages of glaucoma [13]. The posterior migration of the LC contradicts the prevailing cupping theory in glaucoma. It is challenging to explain how a loosened, rigid, and multi-layered lamina cribrosa migrating posteriorly would also become bowed posteriorly (i.e. cupped) due to elevated IOP.

The entire temporal fibers consisting of the macular, superior, and inferior arcuate fibers are being severed simultaneously in glaucoma. However, the arcuate fibers being fewer in number compared to the rest of the NFs, are depleted earlier resulting in production of the sharply-defined arcuate scotoma. These sharply- defined arcuate field defects can only be produced by the severance and depletion of nerve fibers. The production of the arcuate scotomas are not due to the increased sensitivity of arcuate fibers to elevated IOP, as commonly believed.

In glaucoma, the degeneration of retinal ganglion cells and neurons in the lateral geniculate nucleus may not be due to primary neurodegeneration. The RGCs may be dying due to retrograde degeneration, while lateral geniculate nucleus neurons may be perishing due to anterograde degeneration. Both of these manifestations may be a result of nerve fiber axotomy at the scleral edge in glaucoma.

Furthermore, although elevated IOP is the primary risk factor in both high and normal-tension glaucoma, additional secondary factors such as inherently weak border tissue (e.g. high myopia) will accelerate the degeneration of the border tissue. Systemic factors including poor oxygen saturation of blood (e.g. COPD, long-term smoking) will also accelerate the degeneration of the border tissue. The more risk factors that are present, the faster the rate of border tissue degeneration and the development of glaucoma.

Conclusion

The most salient feature of glaucoma is the orderly, peripheral-to-central loss of nerve fibers. Prevalent glaucoma theories do not explain the etiology of the orderly loss of nerve fibers. Furthermore, there is no biological mechanism which could result in the orderly loss of NFs in glaucoma - only a mechanical scenario can achieve this goal.

Glaucoma may be a two-stage disease. In the first stage, elevated IOP (e.g. HTG) or normal IOP 'acting as elevated IOP' (e.g. NTG), compresses the circulation of the border tissue of Elschnig resulting in chronic ischemia and its degeneration. This border tissue degeneration results in the loosening and sinking of the lamina cribrosa.

In the second stage, the sinking of the lamina cribrosa initiates a mechanical process, or perimetric glaucoma: stretching and the orderly severance of nerve fibers at the scleral edge. Sinking of the optic disc would affect the deepest, peripheral-most NFs, being closest to the scleral edge, and ending with the superficial, central-most NFs, closest to the vitreous, in an orderly sequence. This process will continue until the central-most NF has moved to the scleral edge and is severed along with the vasculature. The disc area which once housed the optic disc becomes an empty crater left over after severance and depletion of NFs and its vasculature.

Glaucomatous field defects are horizontally-oriented and corroborate fully with the arrangement of the nerve fibers in the retina until they make their 90-degree turn in the optic disc and become vertically-oriented prior to entering into the lamina cribrosa. Therefore, based on the glaucomatous field defects, neither the retinal ganglion cells nor the lamina cribrosa can be the primary site of injury in glaucoma. Retinal ganglion cells are not lying in the glaucomatous field defect pattern; thus primary neurodegeneration of the retinal ganglion cells can't be the cause of glaucoma.

The lamina cribrosa also can't be the primary site of injury in glaucoma since after their 90-degree turn in the optic disc, the NFs become vertically-oriented in the lamina cribrosa, and thus can't produce horizontally- oriented glaucomatous field defects. After making their 90-degree turn, the arcuate pattern of NFs disappears and is no longer present in the lamina cribrosa. The most probable site of injury appears to be where the nerve fibers make their 90-degree turn in the optic disc, where it can still produce horizontally-oriented glaucomatous field defects, but not after they have become vertically-oriented after their 90-degree turn [14].

The degeneration of the border tissue of Elschnig is able to explain the prevalence of glaucoma in subjects with high myopia due to their inherently weak border tissue. Furthermore, it can also explain NTG in subjects with chronic hypotension and other systemic circulatory problems due to their compromised circulation of the border tissue. Thus, HTG may be an ocular disease and NTG may be more appropriately described as a systemic disease. However, the degeneration of the border tissue appears to be the common ground in the pathogenesis of both HTG and NTG.

In summary, the cupping paradigm falls short in explaining the orderly, peripheral-to-central loss of nerve fibers in glaucoma. This systematic loss of nerve fibers and glaucomatous field defects can be explained by the sinking of the lamina cribrosa leading to the subsequent severance of nerve fibers at the scleral edge.

Glaucoma may not be an optic neuropathy, but an optic disc axotomy - a paradigm shift [15].

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