

Arcuate Field Defects do not Validate the Lamina Cribrosa as the Primary Site of Injury in Chronic Glaucoma

Syed S Hasnain* and Aziz Hasnain

General Ophthalmology, Porterville, CA, USA

***Corresponding Author:** Syed S Hasnain, General Ophthalmology, Porterville, CA, USA.

Received: January 02, 2020; **Published:** January 23, 2020

Abstract

There is an abundance of glaucoma theories such as the direct effect of elevated intraocular pressure (IOP) on the nerve fibers (NF), posterior bowing of the lamina cribrosa (LC), the increased sensitivity of the NFs to IOP, apoptosis and neurodegeneration. However, none of these prevalent theories explain the production of the arcuate field defects which are the pathognomonic feature of chronic glaucoma. The arcuate field defects are produced in the paracentral area (10 to 20 degrees) of the visual field in the early stages of glaucoma. It is the basis for performing perimetry on patients with chronic glaucoma.

The main current hypothesis of glaucoma is that elevated IOP causes the lamina cribrosa to bow posteriorly (cupping) resulting in distortion of the laminar pores, thereby resulting in pinching of the NFs and death of retinal ganglion cells (RGCs). However, the LC can't be the primary site of injury because there is no arcuate arrangement of nerve fibers in the LC to produce the arcuate field defects. The arcuate arrangement of NFs while present in the retina is lost after the nerve fibers make their 90-degree turn in the optic nerve head (ONH) towards the LC. After becoming vertically oriented, the arcuate pattern disappears in the lamina cribrosa.

Similarly, the ganglion cells in the ganglion cell layer of the retina are not lying in an arcuate pattern. Thus, any direct injury or apoptosis of the ganglion cells couldn't produce arcuate field defects. Based on arcuate field defects, neither the ganglion cell layer of the retina nor the lamina cribrosa can be the primary site of injury in glaucoma.

Arcuate field defects correlate fully with the arcuate arrangement of nerve fibers while they are in the retina and up to the point they make their 90-degree turn in the ONH. Thus, arcuate field defects can only be produced if the injury to the NFs occurs somewhere between the nerve fiber layer and up to the point the NFs make their 90-degree turn, not afterwards. In fact, any injury elsewhere can't produce the arcuate field defects.

Normally, the NFs are firmly supported by the underlying lamina cribrosa. Further, the border tissue of Elschnig (BT) lies between the scleral edge and the LC and keeps it firmly in place like an 'O' ring seal. However, if the BT degenerates due to chronic ischemia induced by elevated IOP (normal range 10 to 21mmHg) or by normal range IOP 'acting as elevated IOP' in circulatory compromised subjects, then the lamina cribrosa will become loose and detach from the border tissue and start sinking in the scleral canal.

This would result in stretching and axotomy of the NFs at their 90-degree turn against the scleral edge starting with the most peripheral NFs being closest to the scleral edge and ending with the most central NFs in an orderly sequence. The degeneration of the BT and subsequent sinking of the LC is a prerequisite for the stretching and axotomy of nerve fibers.

It is hypothesized that the primary site of injury in chronic glaucoma is where the NFs make their 90-degree turn in the ONH. This being most vulnerable area in their journey towards the visual cortex. This article also discusses the causes of degeneration of the BT in both high-tension and normal-tension glaucoma. Chronic glaucoma may not be an optic neuropathy, but an optic axotomy.

Keywords: *Arcuate Field Defects; Lamina Cribrosa; Chronic Glaucoma*

Introduction and Discussion

The most characteristic feature of glaucoma is the orderly loss of nerve fibers. The one million or so densely packed NFs in the optic nerve head are being destroyed in an orderly tandem sequence, one-by-one, from peripheral to central. This never occurs randomly. Without answering the reasons for the orderly loss of nerve fibers, no glaucoma theory would be valid. In order to understand the orderly loss of nerve fibers, it is imperative to discuss the arrangement of NFs in the retina and in the optic nerve head (ONH). The arrangement of the nerve fibers is important in understanding the production of arcuate and other glaucomatous visual field defects.

In the retina, the nerve fibers are arranged in a characteristic way. The one million or so NFs are arranged in layers, superficial to deep. The NFs originating from the most peripheral retina lie deepest (closest to sclera) and exit closest to the edge of the scleral opening whereas the NFs originating closest to the optic disc lie most superficial (closest to vitreous) and exit from the most central part of the ONH [1] (Figure 1). The nasal NFs enter the nasal part of the disc and the NFs originating from the nasal macular area go directly to the temporal part of the ONH. The NFs originating from the temporal horizontal raphe arch above and below the macular area to reach the ONH. They are hence called the arcuate nerve fibers (Figure 2).

The entire 360 degrees of retinal NFs converge on the ONH as a superficial nerve fiber layer and are arranged on the anterior surface of the ONH in the same way as in the retina. After making their 90-degree turn, the NFs change to become vertically oriented. Thus, the arcuate pattern of nerve fibers disappears along with the temporal horizontal raphe.

After their 90_degree turn, the loose prelaminar NFs begin to arrange in bundles and the macular NFs start shifting to occupy the central position. In the lamina cribrosa, the bundles of NFs become fastened in its pores. Thus, the arrangement of NFs becomes completely different in the LC compared to while the NFs were in the retina (Figure 3).

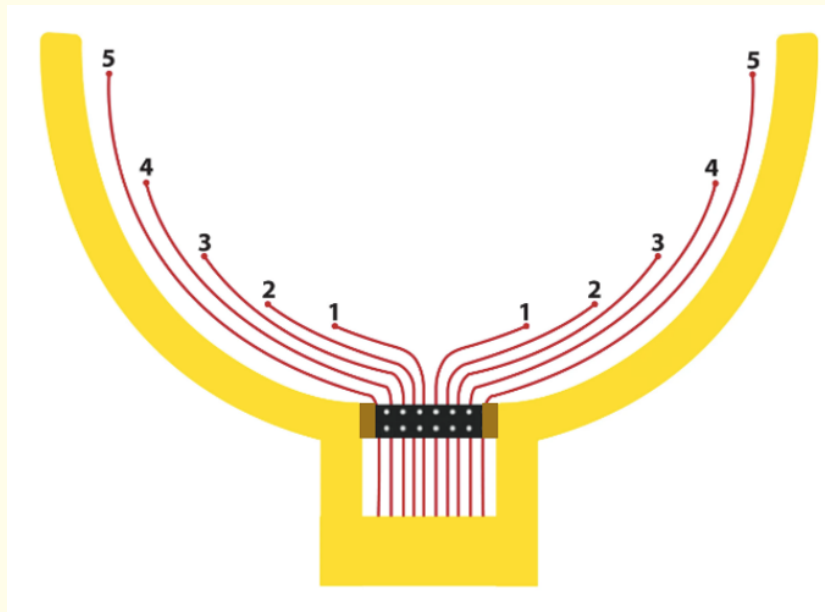


Figure 1: Schematic diagram: The Arrangement of Nerve Fibers in the Retina and Optic Disc. The most peripheral fibers (5) originate farthest from the optic disc, lie deepest (closest to sclera) and exit closest to the scleral edge. The most central fibers (1) originate closest to the disc, lie most superficial (closest to vitreous) and exit from the most central part of the disc.

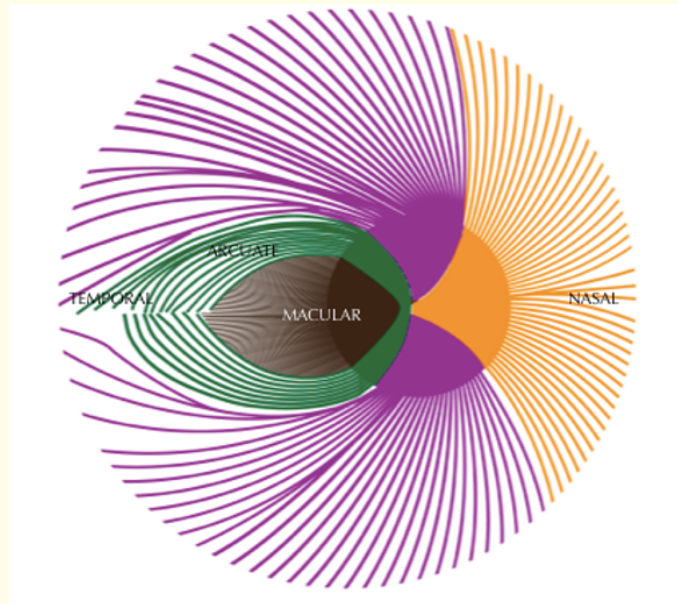


Figure 2: Schematic diagram: The Arrangement of Nerve Fibers in the Retina. The arcuate fibers arch above and below the macular fibers to reach the poles of the optic disc.

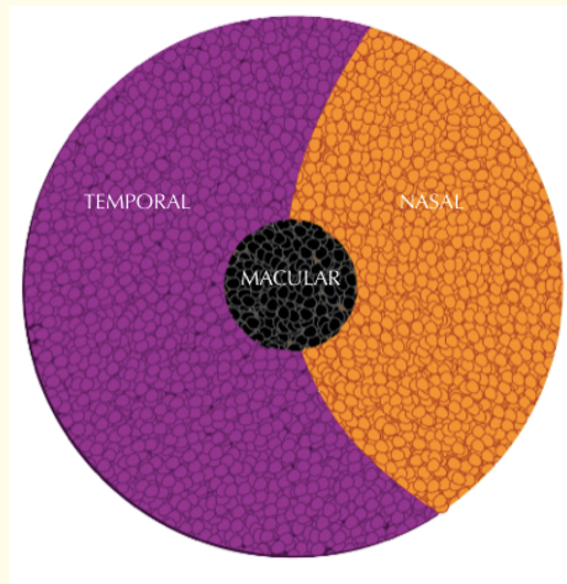


Figure 3: Schematic Diagram: Cross-Section of Nerve Fibers in the Lamina Cribrosa. A substantial change in the arrangement of NFs compared to while they were in the retina. Due to the vertical orientation of the NFs, the arcuate pattern and temporal raphe disappear in the LC. Therefore, any injury to nerve fibers in the LC can't produce arcuate scotomas.

The production of arcuate and other glaucomatous field defects

Glaucomatous field defects are produced in an orderly and predictable sequence which is the basis for performing perimetry in glaucoma. In glaucoma, the peripheral NFs are destroyed first resulting in peripheral visual field loss. In the early stages of glaucoma, along with peripheral field constriction, isolated scotomas begin to appear in both superior and inferior paracentral areas (10 to 20 degrees) which are diagnostic of glaucoma [2]. As glaucoma progresses, these isolated scotomas become more frequent and ultimately coalesce to form single and double arcuate scotomas with sharply-defined margins (Figure 4).

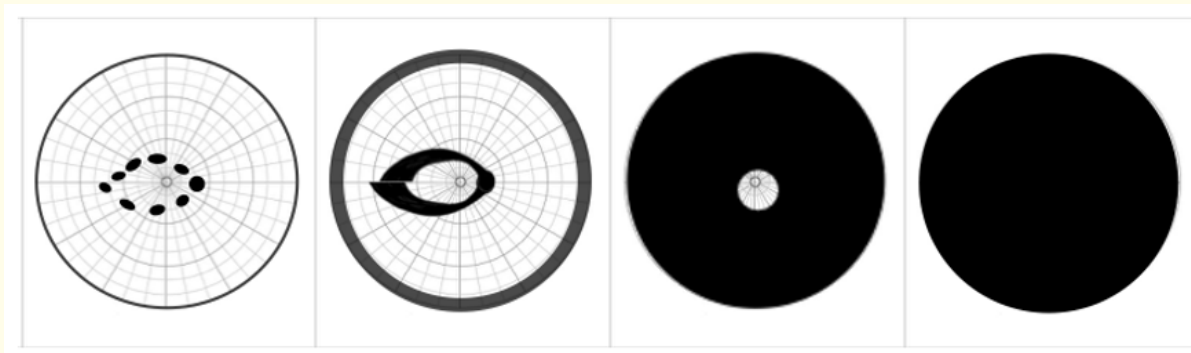


Figure 4: Schematic diagram: The Orderly Loss of the Visual Field in Chronic Glaucoma. Initially, there is peripheral field loss followed by isolated scotomas in the paracentral area which coalesce to form double arcuate scotomas. Central vision is retained until the end.

The superior arcuate scotoma usually appears first in glaucoma. Although both superior and inferior arcuate scotomas start from the blind spot, they end sharply at different levels at the horizontal raphe giving rise to Ronnie’s nasal step. This corresponds with the arrangement of superior and inferior arcuate NFs in the temporal horizontal raphe. Meanwhile, the peripheral field loss is also progressing towards the center and ultimately joins the double arcuate scotomas. As this occurs, only about 10 degrees of central vision remains, which is ultimately also lost and a subject becomes 100% blind.

Important questions

Can arcuate field defects be produced if the lamina cribrosa is the primary site of injury in glaucoma?

Unlikely. Although the lamina cribrosa is widely believed to be the primary site of injury in glaucoma, the arcuate field defects do not validate the LC as the primary site of injury. It is theorized that elevated IOP causes posterior bowing of the LC (cupping) resulting in distortion and misalignment of its pores, thereby impeding the axoplasmic transport leading to death of RGCs.

However, this theory can’t be valid in context of the arcuate field defects in glaucoma. The arcuate field defects correspond fully with the horizontal arrangement of NFs while in the retina or in the ONH prior to their 90-degree turn. After the nerve fibers make the 90-degree turn, they become vertically oriented and lose their arcuate pattern. The arcuate pattern of the NFs and the temporal horizontal raphe disappear in the lamellar region and beyond.

Due to vertical orientation of NFs in the lamina cribrosa, the sharply-defined arcuate defects and Ronnie’s nasal step can’t be produced if the LC is the primary site of injury. Therefore, the lamina cribrosa can’t be the primary site of injury in glaucoma.

Can arcuate field defects be produced if the ganglion cell layer is the primary site of injury in glaucoma?

Unlikely. There is no arcuate pattern of ganglion cells in the ganglion cell layer. The ganglion cells are lying randomly and not in any specific arrangement. Only in the nerve fiber layer of the retina do their axons segregate into macular, nasal and temporal fibers. The ar-

uate pattern and horizontal temporal raphe is formed due to isolation of the macular fibers. Therefore, any direct injury due to elevated IOP to the ganglion cells or its apoptosis, can't produce the sharply-defined arcuate field defects. Therefore, the ganglion cell layer can't be the primary site of injury in glaucoma.

Can arcuate field defects be produced if the nerve fiber layer in the retina is the primary site of injury in glaucoma?

Unlikely. Although the arcuate field defects conform to the arrangement of nerve fibers in the retina, it is inconceivable that any direct injury to the NFs due to elevated IOP will destroy the retinal NFs in an orderly sequence from peripheral to central and not destroy the entire retinal NFs at once. In glaucoma, the NFs are being destroyed in an orderly sequence spreading over several years starting with the most peripheral NFs and ending with the most central NFs. Therefore, the nerve fiber layer in the retina or the horizontal superficial nerve fiber layer of the ONH can't be the direct site of injury in glaucoma.

Can arcuate field defects be produced if the 90-degree turn is the primary site of injury in glaucoma?

Most likely. The only area remaining is where the retinal NFs cross the edge of the scleral opening and make their 90-degree turn into the prelaminar region. As the retinal NFs cross the scleral edge, they are supported underneath by their anchorage in the pores of the lamina cribrosa. The pores of the LC secure and fasten the nerve fibers. The LC itself is firmly kept in place in the scleral opening by the border tissue of Elschnig [3]. In normal circumstances, the lamina cribrosa provides a firm underneath support to the NFs during their lifetime.

However, if the border tissue degenerates and the LC starts sinking, then the NFs will be stretched and axotomized at their 90-degree turn against the scleral edge. The most peripheral NFs being closest to the scleral edge will be axotomized first and ending with the most central NFs in an orderly sequence. The sinking of the lamina cribrosa is a prerequisite for the axotomy of nerve fibers.

Chronic glaucoma: A two-stage disease

Elevated IOP, though a definitive cause of chronic glaucoma, can't result in the orderly loss of nerve fibers by its direct action. Therefore, some indirect mechanism must be occurring to produce the orderly loss of nerve fibers in glaucoma. It is hypothesized that chronic glaucoma may be a two-stage disease. The first being a biological stage, followed by a second, mechanical stage.

The first (biological) stage

In the biological stage, there is degeneration of the border tissue of Elschnig (BT) due to chronic ischemia resulting from chronic compression of BT circulation by elevated IOP or by normal range IOP 'acting as elevated IOP' in circulatory compromised subjects.

Why would the border tissue degenerate? The eyeball is supplied by dual circulation, the ciliary and the central retinal artery (CRA). The ciliary circulation is provided by the short posterior ciliary arteries. The border tissue of Elschnig is supplied exclusively by the ciliary circulation and unfortunately does not receive any contribution from the CRA (Figure 5). Chronic glaucoma would probably not occur had the BT received contribution from the CRA as well.

The ciliary perfusion pressure supplying the BT and IOP are opposing forces. Normally, the ciliary circulatory pressure supplying the BT should be higher than IOP for its proper perfusion and healthy maintenance (Figure 6). However, if this healthy relationship is reversed either due to a rise in IOP (i.e. an ocular problem) or if perfusion pressure of the BT becomes lower than the IOP due to conditions such as chronic hypotension (i.e. a systemic problem), then even normal range IOP will take the upper hand and 'act as elevated IOP' [4].

In both scenarios, the IOP becoming higher than the perfusion pressure of the BT will chronically compress the BT circulation resulting in chronic ischemia and its degeneration. Due to degeneration of the BT, the lamina cribrosa becomes loose and detached and starts sinking in the scleral canal. In other words, high-tension glaucoma is an ocular problem whereas normal-tension glaucoma, a systemic problem (Figure 6).

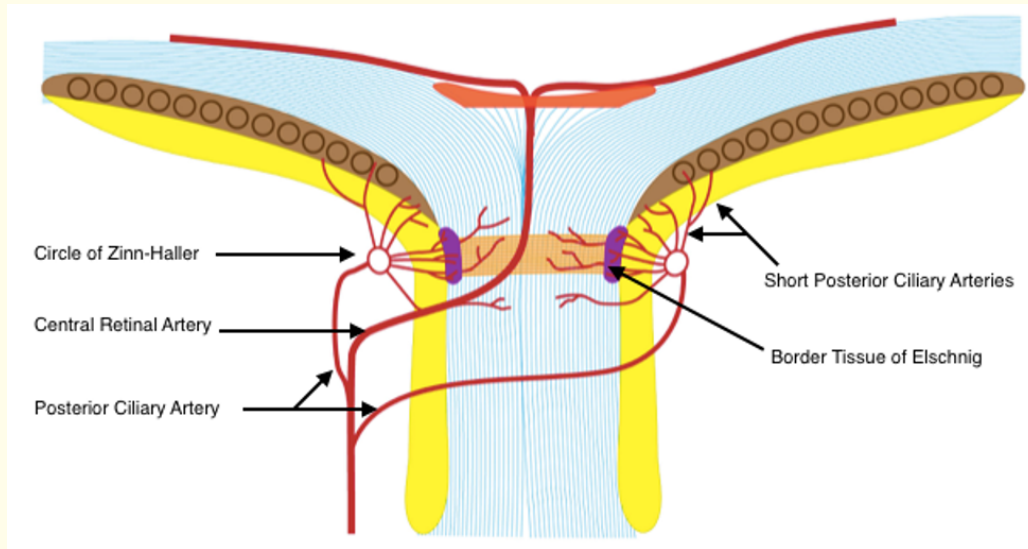


Figure 5: Schematic diagram: Blood Supply of the Border Tissue. Short posterior ciliary arteries form the circle of Zinn-Haller which supply the LC and border tissue of Elschnig. The central retinal artery is destined for the retina and does not contribute to the border tissue.

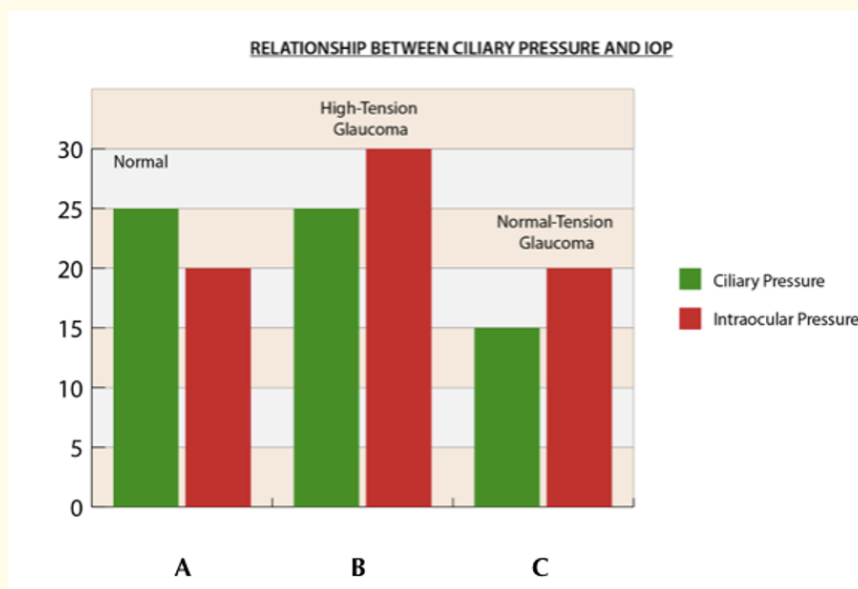


Figure 6: Graphic diagram: The Interaction Between Ciliary Circulatory Pressure and IOP. Normally, the ciliary systemic pressure supplying the border tissue should be higher than IOP for its proper perfusion and healthy maintenance as in column (A). In column (B), the IOP is increased to 30 mmHg due 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 circulatory pressure to 15 resulting from systemic problems such as chronic hypotension, the normal IOP at 20 mmHg is now 'acting as elevated IOP', resulting in normal-tension glaucoma. Note: In (B) and (C), the situation is reversed - IOP becomes higher than the ciliary pressure. HTG appears to be an ocular problem whereas NTG, a systemic problem.

Degeneration of the border tissue during the first stage may take several years before the second stage begins. The first stage is latent, which may also be called pre-perimetric glaucoma. This latent period will vary among subjects depending on their level of IOP, circulatory issues, and inherent integrity of their border tissue. For example, the thinner BT as in high myopic subjects will lead to its early degeneration. Further, subjects with sleep apnea will have early border tissue degeneration due to their poor oxygen saturation.

Therefore, chronic glaucoma becomes a multi-factorial disease but IOP is still the only primary risk factor. It would take longer for degeneration of the BT to occur in subjects with fewer risk factors compared to those with more risk factors. Subjects with fewer risk factors will be able to tolerate elevated IOP for a longer period of time compared to those with more risk factors. Therefore, their latent pre-perimetric period will be longer. This may explain ocular hypertension lasting for several years in some subjects. Following the degeneration of the border tissue, the sinking of the lamina cribrosa is the start of the second stage [5-10].

The second (mechanical) stage

The second or mechanical stage is initiated by sinking of the lamina cribrosa resulting from the degeneration of the border tissue. The second stage may also be called perimetric glaucoma.

The lamina cribrosa, a multi-layered rigid connective tissue plate, densely packed with NFs is kept firmly in place in the scleral opening by the BT. This border tissue is a collagenous tissue acting as an ‘O’ ring seal for the lamina cribrosa. In addition to the BT, the 360 degrees of retinal NFs also keep the LC in place similar to as roots anchor a tree.

Due to degeneration of the border tissue, the lamina cribrosa becomes loose and detached and starts sinking in the scleral canal. Due to sinking of the LC, the most peripheral (deepest) NFs (being closest to the scleral edge) will be stretched and axotomized against the scleral edge first (Figure 7). Following axotomy of the peripheral fibers, the next-in-line fibers will move peripherally to the scleral edge to occupy the space vacated by the preceding axotomized fibers.

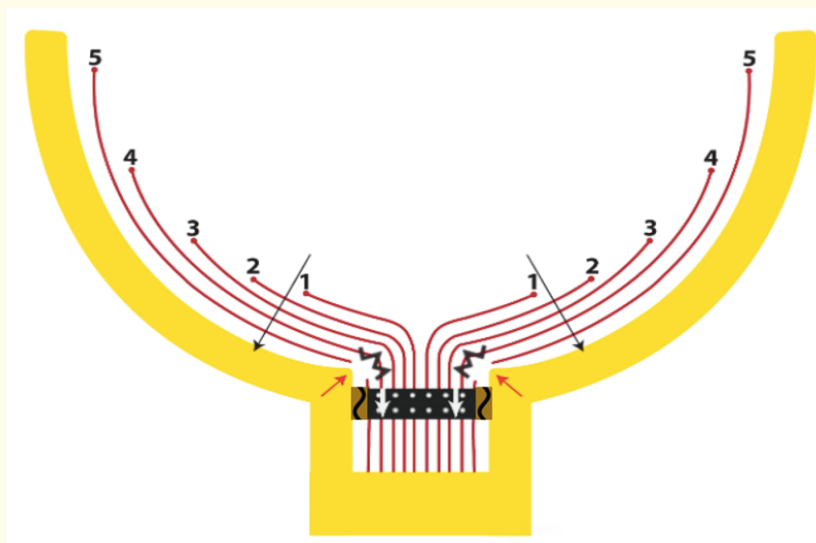


Figure 7: Schematic diagram: The Orderly Axotomy of Nerve Fibers in Chronic Glaucoma. Due to sinking of the LC the most peripheral and deepest nerve fiber (5) is stretched and severed against the scleral edge first. The next-in-line fiber (4) will move towards the scleral edge to occupy the space vacated by the preceding fiber and will also get stretched and severed. This process will continue in an orderly sequence until the most central fiber (1) is axotomized.

The continuous axotomy of nerve fibers would result in further sinking of the lamina cribrosa due to loss of anchorage provided by the NFs. This cascade of sinking and axotomy will become self-propagated until all the NFs are severed and depleted. This may explain why glaucoma can't be halted despite maximal lowering of IOP. Glaucoma may not be an optic neuropathy, but an optic disc axotomy.

The production of the arcuate field defects

As the lamina cribrosa sinks, the entire temporal NFs (macular, superior and inferior arcuate) are being axotomized simultaneously. However, the arcuate fibers, being fewer in number, compared to the macular fibers are depleted earlier giving rise to the sharply-defined arcuate field defects [11,12]. The macular fibers last until the end-stage due to their abundance (Figure 8). The arcuate fibers are not being selectively destroyed due to their undue sensitivity to IOP but depleted earlier in glaucoma due to their being fewer in number compared to macular fibers. This may explain the production of arcuate field defects in the early stages of glaucoma.

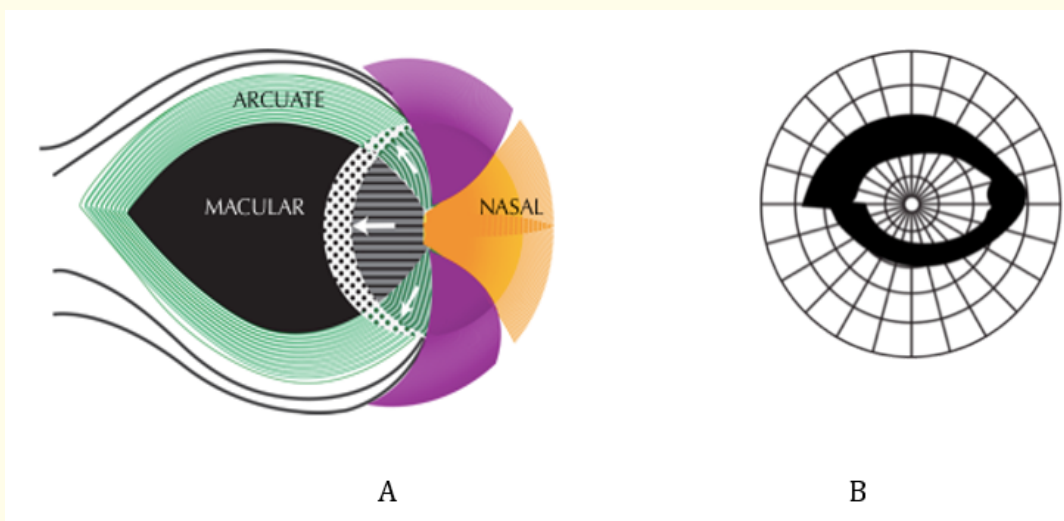


Figure 8: Schematic diagram: The Production of Arcuate Scotomas. Due to sinking of the lamina cribrosa, all the temporal NFs'- macular, superior and inferior arcuate - are being severed simultaneously (A). However, the arcuate NFs being fewer in number compared to the macular NFs are depleted earlier, resulting in sharply-defined arcuate field defects (B).

Conclusion

The arcuate field defects in the paracentral area (10 - 20 degrees) in the early stages of glaucoma are the pathognomonic feature of glaucoma. The retinal NFs originate from the ganglion cell layer of the retina. Since the ganglion cells are lying randomly in the ganglion cell layer, direct injury to RGCs or their apoptosis couldn't produce arcuate field defects. However, the axons of the RGCs assume a specific pattern in the nerve fiber layer of the retina. The NFs are segregated into nasal, temporal, macular and arcuate fibers in the nerve fiber layer of the retina and this continues in the superficial nerve fiber layer of the ONH until the NFs make their 90-degree turn towards the lamina cribrosa.

The arcuate scotoma and Ronnie's nasal step correspond fully with the arrangement of NFs in the nerve fiber layer of the retina and in the superficial nerve layer of the ONH until they make their 90-degree turn towards the lamina cribrosa. However, the arcuate pattern is lost in the LC due to NFs becoming vertically oriented after their 90-degree turn. Since there is no arcuate pattern of nerve fibers in the lamina cribrosa, any injury to the NFs within the LC couldn't produce arcuate field defects. Thus, the arcuate field defects do not validate the lamina cribrosa as the primary site of injury in glaucoma. The only area remaining is where the nerve fibers make their 90-degree

turn in the ONH. Any injury at this site will still be able to produce arcuate field defects. It appears logical the 90-degree turn may be the primary site of injury to the nerve fibers.

Due to sinking of the lamina cribrosa, the nerve fibers become stretched and axotomized starting with the most peripheral NFs and ending with the most central in an orderly sequence. The entire temporal fibers (macular, superior, inferior arcuate) are being axotomized simultaneously. However, the arcuate NFs being fewer in number compared to the macular fibers are depleted earlier resulting in the sharply-defined arcuate field defects. This also explains the occurrence of arcuate field defects in the early stages of glaucoma. In summary, chronic glaucoma may not be an optic neuropathy, but an optic axotomy.

Bibliography

1. Shields MB. "Textbook of Glaucoma, 3rd Edition". Baltimore MD. Williams & Wilkens (1992).
2. Duke-Elder S and Barrie J. "Diseases of the Lens and Vitreous, Glaucoma and Hypotony". System of Ophthalmology Volume X1. London: Henry Kimpton (1969).
3. Wolff E. "Anatomy of the Eye and Orbit Revised by Last RJ". 6th Edition. London: H.K. Lewis and Co (1968).
4. Hasnain SS and Hasnain A. "Pathogenesis of Chronic Glaucoma: A Two-Stage Disease". *EC Ophthalmology* 10.5 (2019): 357-363.
5. Hasnain SS. "Scleral Edge, Not Optic Disc or Retina is the Primary Site of Injury in Chronic Glaucoma". *Medical Hypothesis* 67.6 (2006): 1320-1325.
6. Hasnain SS. "The Mystery of Glaucoma: Solving With a Different Approach". Textbook (2018).
7. Hayreh SS. "Structure and Blood Supply of the Optic Nerve". In: Heilmann K, Richardson KT, Editors. Glaucoma Conceptions of a disease. Stuttgart: Theime (1978).
8. Hasnain SS. "Pathogenesis of Orderly Loss of Nerve Fibers in Glaucoma". *Optometry: Open Access* 1.2 (2016): 110.
9. Yang H., et al. "Posterior (Outward) Migration of the Lamina Cribrosa and Early Cupping in Monkey Experimental Glaucoma". *Investigative Ophthalmology and Visual Science* 52 (2011): 7109-7121.
10. Yang H. "Optic Nerve Head (ONH) Lamina Cribrosa Insertion Migration and Pialization in Early Non-Human Primate Experimental Glaucoma". Poster Presentation ARVO Meeting (2010).
11. Zeried FM and Osuagwu UL. "Changes in the Retinal Nerve Fiber Layer and Optic Disc Algorithms by Optical Coherence Tomography in Glaucomatous Arab Subjects". *Clinical Ophthalmology* (2013): 1941-1949.
12. Hasnain SS. "Arcuate Field Defects in Glaucoma". *Ophthalmology Update* (2013).

Volume 11 Issue 2 February 2020

©All rights reserved by Syed S Hasnain and Aziz Hasnain.