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PATHOGENESIS OF CHRONIC GLAUCOMA: A TWO-STAGE DISEASE

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INTRODUCTION

Chronic glaucoma, is an unresolved mystery ever since it was given a separate entity in the 1850s. There are many prevailing glaucoma theories such as the direct mechanical effect of elevated intraocular pressure (IOP) on the nerve fibers (NFs), posterior bowing of the lamina cribrosa (LC) known as cupping, lack of perfusion of the optic nerve head, increased sensitivity of the NFs to IOP, neurodegeneration, apoptosis, autoimmune disorder and others.

However, none of these theories have addressed the crucial pathognomonic feature in glaucoma: the orderly, peripheral-to-central loss of nerve fibers.

The orderly loss of nerve fibers is the reason why perimetry is performed - for the diagnosis and monitoring of glaucoma.

PURPOSE

To determine why the nerve fibers are being destroyed in an orderly sequence, from peripheral to central; the nerve fiber loss is never occurring randomly in glaucoma.

METHODS

Twenty early to end-stage glaucomatous optic discs of the same subjects were compared and analyzed. Significant observation of hallmark features were analyzed in the early to end-stage glaucomatous discs. These hallmark features included temporal pallor, sloping/kinking of blood vessels and notching at the entrance of the arcuate nerve fibers (7 and 11 o'clock positions), the absence of microvasculature and prominence of the scleral edge 360 degrees around the disc margin.

RESULTS

The early glaucomatous optic discs in all of the subjects revealed temporal pallor and lack of microvasculature around the optic disc. As the disease progressed, the pallor of the disc increased and sloping of the blood vessels were noticed at 360 degrees of the disc margin.

Contrary to common belief, there was no enlargement of the physiological cup. The sloping and kinking of blood vessels at the disc margin indicated the lamina cribrosa is sinking in glaucoma. There was increased visibility of the scleral edge in all glaucomatous discs.

Glaucomatous discs with no physiological cups clearly showed sinking of the entire lamina cribrosa. Notching was present at the superior and inferior arcuate nerve fibers at the entrance of the disc. These discs also clearly revealed that the lamina cribrosa was sinking in its entirety.

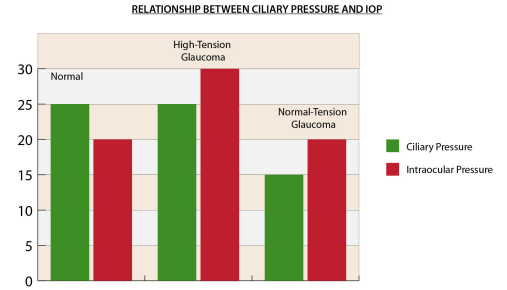
DISCUSSION

In view of the orderly loss of nerve fibers, glaucoma may be a two-stage disease:

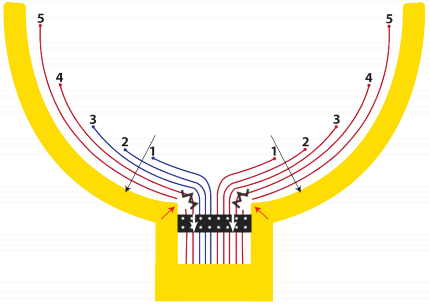
First stage: Degeneration of the border tissue of Elschnig. Ciliary pressure (CP) of the border tissue and IOP are opposing forces. Normally, the CP of the border tissue is higher than IOP for its healthy maintenance. However, if IOP becomes higher than CP, it will compress circulation of the border tissue, resulting in chronic ischemia and border tissue degeneration.

Second stage: The degenerated border tissue results in detachment and sinking of the lamina cribrosa, resulting in stretching and severance of nerve fibers at the scleral edge. The peripheral nerve fibers closest to the scleral edge are severed first, ending with the central nerve fibers in an orderly sequence (see schematic diagram).

DIAGRAMS

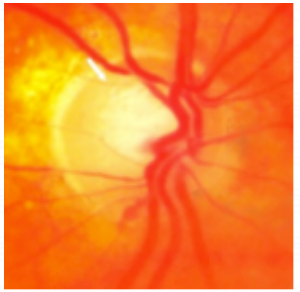


Graphic Diagram. The interaction between ciliary pressure and IOP. Normally, the ciliary pressure supplying the border tissue should be higher than IOP for its good perfusion and healthy maintenance as in column (A). In column (B), the IOP is increased to 30 mmHg due to an ocular problem whereas the 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, even 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 ciliary pressure. HTG appears to be an ocular problem whereas NTG as a systemic problem.

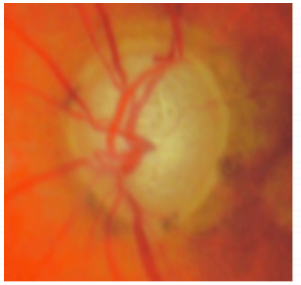


Schematic Diagram. Due to sinking of the LC, the most peripheral and deepest pre-laminar nerve fiber(5) is stretched and severed against the scleral edge first (red arrows). The next-in-line fiber (4) will move towards the scleral edge to occupy the space vacated by the preceding severed fiber and will also get stretched and severed. This process will continue in an orderly sequence until the most-central fiber(1) has moved towards the scleral edge and gets severed.

IMAGES



Glaucoma Disc A. Early stage right eye: prominent scleral edge due to RNFL thinning. Temporal pallor and sloping of blood vessels. No change in size of the original physiological cup



Glaucoma Disc B (same patient). Late-stage left eye: excavated disc due to severance of nerve fibers. Kinking of blood vessels at the scleral edge due to the sinking LC and loss of NFs. Loss of smaller temporal vessels due to their severance. Disc pallor due to severance of vasculature.

CONCLUSION

Sinking of the lamina cribrosa and severance of nerve fibers at the scleral edge can easily explain the orderly, peripheral-to-central loss of nerve fibers occurring in glaucoma. Chronic glaucoma may not be an optic neuropathy, but an optic disc axotomy.