Can Glaucoma be a Neurodegenerative Disease?

Syed S. Hasnain, MD  M. Ahmad Iqbal M.D.
Salma Iqbal O.D.  Abbas S. Hasnain J.D.

It is widely stated that glaucoma may be a neurodegenerative disease such as Alzheimer’s, Parkinson’s, and ALS. The reason glaucoma is considered a neurodegenerative disease is due to unexplained death of neurons in the lateral geniculate nucleus (LGN) and of the neurons in the visual cortex occurring concurrently with the death of the retinal ganglion cells (RGCs). Based upon the forthcoming arguments, this article will attempt to demonstrate that glaucoma cannot be a neurodegenerative disease.

It is an established fact, in glaucoma, that the peripheral vision and arcuate fibers are selectively destroyed first, whereas the central vision fibers remain until the end-stage of the disease. In other words, the nerve fibers or their RGCs are being destroyed in a specific sequence and in an orderly fashion in glaucoma. Finding this systematic mechanism may be the key to discovering the true pathogenesis of glaucoma.

On the other hand, in neurodegenerative diseases like Parkinson’s, Alzheimer’s or ALS, the degeneration of the neurons occurs randomly and haphazardly. If glaucoma is a neurodegenerative disease, we face another dilemma: why, in glaucoma, does neurodegeneration always start precisely first with those RGCs which serve the peripheral vision and not occur randomly? The random destruction of the neurons is characteristic of a neurodegenerative disease, as a result the course of such a disease varies in each individual. Therefore, this distinction alone should keep glaucoma apart from the group of neurodegenerative diseases.

Before I discuss further I would like to mention briefly about history of term ‘cupping’ of the optic disc which seems to be the core problem in glaucoma. The term cupping was given by Heinrich Muller in 1856 and endorsed by the majority of the ophthalmologists of the time. It was believed that the optic disc was being cupped or excavated by the direct mechanical pressure of high IOP. However, there was one dissenter. In 1864, Dr. Dixon disagreed that cupping was caused by direct effect of raised IOP. He argued that if the mechanical force of high IOP was strong enough to cause cupping of the disc, then the same force should have also displaced the lens and iris forward as well. But his opinion was turned down by another prominent ophthalmologist, Sir William Bowman, and since then the term cupping has become synonymous with glaucoma. One hundred years later (1960s), we introduced the term ‘cup-to-disc ratio’ which gave further credence to cupping theory (Figure 1).

This article will attempt to illustrate that the term cupping was mistakenly given 150 years ago, which has misguided us. If cupping is indeed occurring, then I salute those who gave us this term by using their rudimentary ophthalmoscope (without electricity/battery) in the early stages of ophthalmology.

Returning to the subject of neurodegeneration: why are the RGCs and neurons of the LGN being destroyed simultaneously in glaucoma? In order to answer this question, we may have to replace the present cupping disc paradigm of glaucoma with a ‘sinking disc’ paradigm. The phenomenon of cupping implies that the problem starts from the center of the optic disc and extends peripherally. As we know, the central vision fibers originate closer to the disc and lie superficial (closer to vitreous) and exit from the central part of the disc. In contrast, the peripheral vision fibers originate from the distant retina or farther from the optic disc.
and lie deeper (closer to sclera) and exit closer to the edge of the scleral opening. If cupping was occurring, then the central vision fibers should be destroyed first, and peripheral vision fibers last, but the opposite is occurring in glaucoma.

Now the further question arises as to why the peripheral fibers are being destroyed first in glaucoma. To answer this, I hypothesize that the optic disc may be sinking\(^3,4\), not cupping in glaucoma. Due to sinking of the disc, the prelaminar nerve fibers, prior to their entry in the lamina, are being stretched as one end is attached to the RGC and the other end anchored in the sinking optic disc and thus ultimately severed against the scleral edge. Since the peripheral nerve fibers lie deeper and exit closer to the scleral edge, the peripheral fibers would be the first to be affected and severed whereas the central fibers later if sinking of the disc is occurring. This is exactly what is revealed by glaucomatous visual fields (Figure 2). Furthermore, severing of the axons would result in retrograde degeneration of the RGC and Wallerian degeneration of the distal axon leading to the death of the neurons of the LGN. Wallerian degeneration may explain the death of the neurons in the LGN and also in the visual cortex. Sinking of the disc would become self-propagated due to progressive severance of 360 degrees of nerve fibers which also provide anchorage to the disc as roots do to a tree. The process of sinking disc would continue until all the nerve fibers are cut against the scleral edge.

Since then I have proposed that nerve fibers are being severed, not atrophied in glaucoma: Do we have any evidence for it? Before we discuss this issue I would like to define the atrophy of an organ. Atrophy is defined as an abnormal decrease in size or mass of a developed organ or a tissue due to disease. Atrophic organs though shrunk in mass are normally visible and don’t disappear unless the involved tissue is very small and has atrophied to microscopic level. On the other hand, severance is simply the cutting of an organ/tissue resulting in its total disappearance. An example would

---

**Figure 1.** Optic Nerve Cupping in Glaucoma. It is ultimately the loss of the nerve fibers which causes loss of peripheral vision first and, later, central vision.

**Figure 2.** Humphrey’s Field Analyzer Visual Field Report. These plots represent visual field graphically. The center of the field is at the intersection of the axes. Shading represents areas of vision loss that is proportional to the darkness of the shading. Some variations in the visual fields can occur that are NOT associated with glaucoma.
be whether the leg is atrophied due to stroke or severed (amputated) due to gangrene. It will be important to keep this distinction in mind for ensuing discussion whether the nerve fibers are being atrophied or severed in glaucoma.

Returning to the evidence for severing of the nerve fiber: Although we may never see the actual process of severing of the nerve fibers, we may conclude this by deductive reasoning of the events taking place in glaucomatous disc. The continuous severing of the nerve fibers is supported by the phenomenon of progressive thinning of the RNFL as observed on optical coherence tomography (OCT) (Figure 3). The end-stage histology of glaucomatous disc resembles an empty bean-pot. In studying the histology of the bean-pot, its opening appears to be that of scleral opening, its dilated belly is formed by dura mater and its base composed of necrotic tissue. Interestingly, the bean-pot appears quite huge compared to the size of original disc. Is this large bean-pot really a deeply cupped disc (lamina)? Is the lamina so distensible that its excavation has assumed the shape of a large bean-pot? If so, then the lamina should be forming the walls of the bean-pot, if not, then where did the lamina and atrophied nerve fibers disappear? Why don’t we see atrophied nerve fibers in bean-pot as we see them in the histology of optic atrophy such as due to multiple sclerosis? I believe the bean-pot is not a deeply cupped disc. The empty bean-pot appears to be the leftover area which once housed the disc. Most likely, the lamina is lying at the bottom after all the nerve fibers have been cut and disappeared. Thus, the end-stage glaucomatous disc resembling a bean-pot can only be explained by severance, not due to atrophy of the nerve fibers.

In studying the optic atrophy caused by multiple sclerosis or other conditions, the atrophic discs in these conditions are flat (non-excavated). There is neither sloping/kinking of the blood vessels at the disc margin nor excavation of the disc indicating that flat atrophic discs are not associated with sinking. Since these discs are not sinking, there is no severing of the nerve fibers and thus no excavation is occurring in these conditions. The histology of the flat disc atrophy reveals shrunken and collapsed nerve fibers, but no empty bean-pot as in glaucoma. Therefore, histologically, flat disc atrophy and glaucomatous disc are distinctly different. In conclusion, the nerve fibers are being atrophied in flat disc atrophy whereas the nerve fibers are severed in glaucomatous disc.

Regarding arcuate field defects: How is it possible that raised IOP or neurodegeneration or any other pathology would cause the degeneration only of the superior and inferior arcuate fibers or their RGCs solely, leaving others unscathed in the early stages of glaucoma? The severing, not atrophy, of the nerve fibers may explain the sharply defined arcuate field defects occurring in the early stages of glaucoma. Due to inherent temporal tilt of the optic disc, the entire group of temporal fibers (macular, superior and inferior arcuate) are being stretched and severed. However, the superior and inferior arcuate fibers being fewer in number compared to the macular fibers will be depleted earlier, resulting in arcuate field defects/ring scotoma. The wedge shaped defects in retina which sometimes we see in glaucoma patients are empty spaces created by the severance and thus disappearance of nerve fibers. Regarding arcuate field defects: How is it possible that raised IOP or neurodegeneration or any other pathology would cause the degeneration only of the superior and inferior arcuate fibers or their RGCs solely, leaving others unscathed in the early stages of glaucoma? The severing, not atrophy, of the nerve fibers may explain the sharply defined arcuate field defects occurring in the early stages of glaucoma. Due to inherent temporal tilt of the optic disc, the entire group of temporal fibers (macular, superior and inferior arcuate) are being stretched and severed. However, the superior and inferior arcuate fibers being fewer in number compared to the macular fibers will be depleted earlier, resulting in arcuate field defects/ring scotoma. The wedge shaped defects in retina which sometimes we see in glaucoma patients are empty spaces created by the severance and thus disappearance of nerve fibers.

In conclusion, the nerve fibers are being atrophied in flat disc atrophy whereas the nerve fibers are severed in glaucomatous disc.
of the arcuate nerve fibers, not due to their atrophy. We do not observe such empty gaps in flat disc atrophy conditions such as due to multiple sclerosis and other conditions.

The vertical enlargement of the physiological cup may be due to severance and depletion of the superior and inferior arcuate fibers which occurs in early stages of glaucoma. The enlarged vertical cup/disc ratio may not be a risk factor but may be representing cases in which glaucoma has already been initiated. Otherwise, how do we explain that vertical, and not the horizontal cup/disc ratio, is a risk factor for glaucoma? Severing of the macular fibers occurring concurrently with the superior and inferior arcuate fibers from the very early stages of glaucoma may explain the thinning of the macular ganglion cell complex as observed on OCT. There are two events which appear to be taking place in glaucoma. First, the sinking of the disc. Second, the severing of the nerve fibers as a result of sinking disc. The severance of the nerve fibers and excavation of the disc in vivo has shown the posterior migration of the lamina cribrosa from the very early stages of glaucoma as far back as pia mater or in other words total sliding outward of the lamina from the scleral opening. This is very significant discovery as it suggests that lamina cribrosa is detachable from the scleral wall, then how can a loose and rigid lamina cribrosa also become cupped at the same time? EDI findings support the phenomenon of sinking, not cupping of the disc. If true, then chronic glaucoma may be a mechanical problem, a herniation of the disc, not a neurodegenerative disease.

References

4. Hasnain SS. Scleral edge, not optic disc or retina is the primary site of injury in chronic glaucoma. Medical Hypothesis 2006; 67(6) :1320-1325.