Glaucoma Specialist Blog: The "Glog"

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THE FLAMMER SERIES

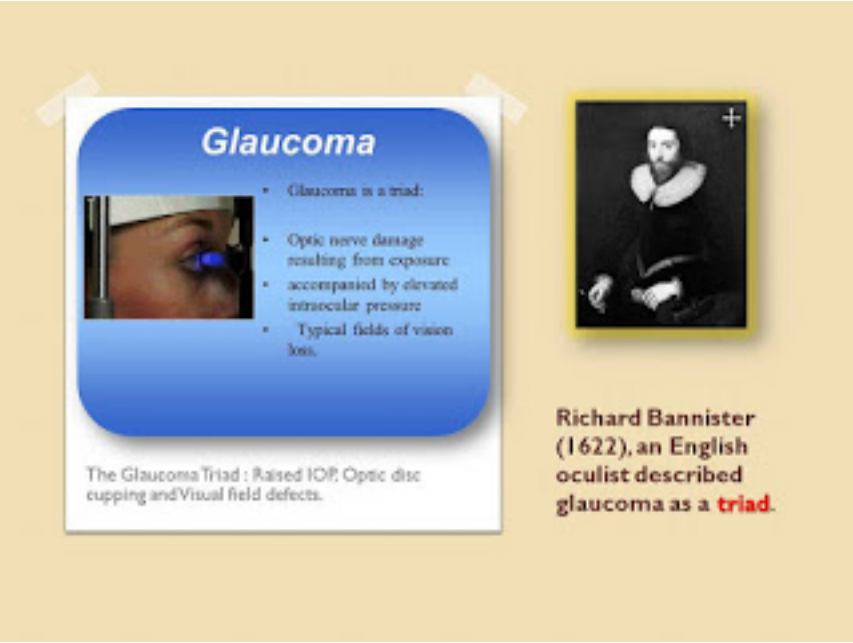
PART IV

IMPAIRED CEREBROSPINAL FLUID CIRCULATION IN THE DEVELOPMENT OF GLAUCOMA

INTRODUCTION

Glaucoma has no characteristic features. It is an amalgamation of signs and symptoms which form the basis for diagnosis of glaucoma in one individual but may be regarded as some other condition or even as normal in others. Richard Bannister (1622 AD) described the "glaucoma triad" of raised intra-ocular pressure (IOP), optic disc cupping and visual field (VF) changes as diagnostic of glaucoma.

https://ourgsc.blogspot.com/2017/05/



However, IOP now has been thrown entirely out of the equation. Ostensibly, high IOP is just a statistical figure. It can occur in an entirely harmless way in certain individuals. It is also surprising that nearly half of all glaucoma patients who have been on apparently well controlled IOP end up with glaucomatous optic atrophy (GOA) in at least one eye during their lifetime. Thus, IOP has become much of an enigma in the development of GOA.

https://www.ncbi.nlm.nih.gov/pubmed/23932216

Structural changes in glaucoma probably occur late. So, GOA may not be seen until significant amount of damage has already been done. What causes GOA? Is it mechanical, vascular, biochemical molecules, translaminar pressure difference or genetic factors which make the optic nerve head vulnerable? Moreover, optic atrophy may also occur in a diverse range of other conditions such as ischemic,

compressive and hereditary optic neuropathies, pointing to a possible common thread running through some of these optic nerve degenerations.

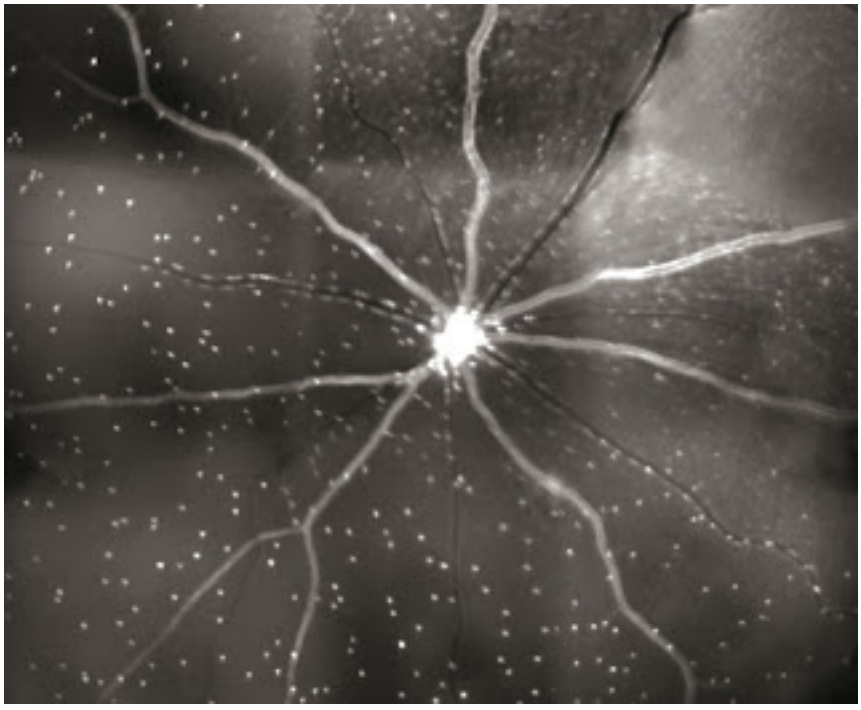
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3083760/

What about VF changes? Why are there just a handful of techniques available to record the VF? Then too, a Humphrey VF chart may not resemble a printout from an Octopus perimeter for the same patient. Dr Hasnain mentions that glaucomatous field loss correlates fully with the arrangement of nerve fibers while in the retina, but DOES NOT correlate at all with the arrangement of nerve fibers after they have made their 90^0 turn into the prelaminar region. The characteristic glaucomatous field loss such as arcuate scotoma and Ronnie's nasal step cannot be produced if the primary site of injury is in the prelaminar area or lamina cribrosa and beyond, according to Dr Hasnain.

https://ourgsc.blogspot.com/search?q=hasnain

DARC (Detection of Apoptosing Retinal Cells) technology, a technique which can identify retinal ganglion cell (RGC) damage at a very early stage, has shown random damage to RGCs which cannot explain the classical VF defects on a Humphrey Visual Field Analyzer.

https://ourgsc.blogspot.com/search?q=DARC



How can apoptosis like this produce visual field changes seen on perimeters?

This brings me to the current topic. Prof Flammer has published a great deal on the vascular aspects of glaucoma. However, an article co-authored by him sheds some light on the role of cerebro-spinal-fluid (CSF) pressure (intracranial pressure or ICP) in the pathogenesis of glaucoma.

Clinical and Experimental Ophthalmology 2008; 36: 308–311
doi: 10.1111/j.1442-9071.2008.01735.x

Clinical Controversy

Is open-angle glaucoma caused by impaired cerebrospinal fluid circulation: around the optic nerve?

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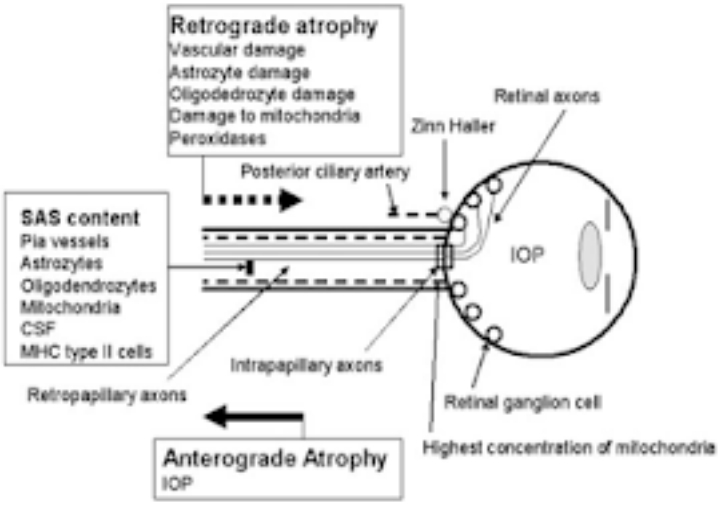
The optic nerve is regarded as an extension of the brain. Like other parts of the CNS, the optic nerve (ON) is covered by the dura, arachnoid and pia mater. The optic nerve is exposed to IOP within the eye and to ICP due the presence of CSF in the sub-arachnoid space (SAS). The lamina cribrosa demarcates these two pressurized zones (eye vs. SAS) and the pressure difference between them is called “translaminar pressure difference” (TPD) (IOP-ICP=TDP). There is increasing evidence that TDP could play an important role in the pathophysiology of glaucoma.

Figure 1. Schematic diagram of mechanisms leading to the anterograde and retrograde atrophy of the optic nerve. CSF, cerebrospinal fluid, MHC, major histocompatibility complex, IOP, intraocular pressure, SAS, subarachnoid space.

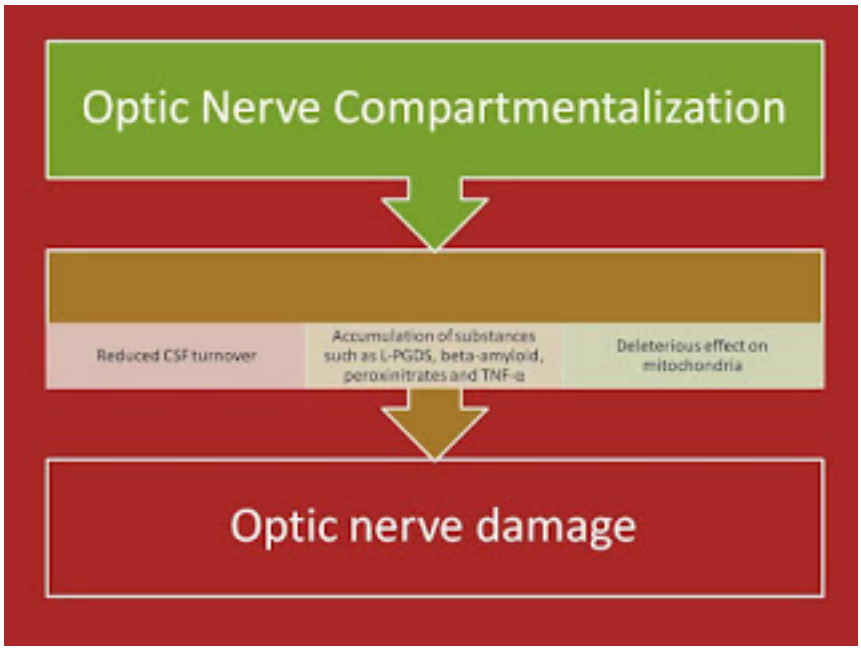


Disc cupping is assumed to represent a typical morphological pattern of anterograde atrophy of axons on their way from the intraocular to the retrolaminar portion of the ON. However, there is a possibility that in some cases the primary damage occurs in the ON and then a retrograde process leads to the

destruction of RGCs. This direct damage to the ON is attributed to the environment of the nerve especially to the surrounding CSF.

The ON is distinct from other cranial nerves in that it is surrounded by CSF throughout its entire length. The subarachnoid space (SAS) enveloping the ON may become or act as a separate CSF compartment in patients with normal-tension-glaucoma (NTG). CSF-cisternography, using an iodinated contrast agent (Lopamidol), has demonstrated blockage (stasis) and impaired influx of CSF from the chiasmal cistern into the SAS of the ON in normal-tension-glaucoma.

The ON compartment syndrome (and impaired CSF turnover) develops through postulated mechanisms such as inflammatory changes and mechanical stress on the arachnoid and it's trabeculae as well as glial cells in the ON. This leads to increased expression of MHC II cells, tumor necrosis factor-alpha (TNF-α) and endothelin.



The apices of the meningoepithelial cells (MECs) lining the arachnoid layer face the SAS. These cells are highly reactive to various stimuli such as increased ICP and inflammation due to meningitis and arachnoiditis, as well as mechanical stress.

MECs also produce a rather unique factor called L-PGDS (Lipocalin-type Prostaglandin D Synthase). Upregulation of L-PGDS is demonstrated in αβ-crystalline positive oligodendrocytes and astrocytes in chronic multiple sclerosis. Elevated L-PGDS contributes to apoptosis of PC12 neuronal cells. Conversely, L-PGDS appears to protect the perineuronal oligodendrocytes from apoptosis.

Studies have shown that when high concentration of L-PGDS is added to neuronal cultures the proliferation of astrocytes can be markedly inhibited in vitro.

L-PGDS could also act through the synthesis of prostaglandins which regulate vascular tone. ON compartmentalization leads to reduced CSF turnover; accumulation of substances such as L-PGDS, beta-amyloid, peroxinitrates and TNF-α; as well as possibly an effect on mitochondrial function. These are detrimental to the health of the ON.

The concept of an ON-compartment syndrome offers an entirely new approach to the understanding of the pathophysiology of visual loss in patients with NTG. A disturbance of CSF components following compartmentation would cause damage to axons, astrocytes and mitochondria. It would also severely affect the blood vessel tone of the pial plexus supplying the ON in the SAS, leading to cupping of the optic disc and retrograde atrophy with loss of VF and ultimately involve the central visual acuity.

Physiologically, the difference between IOP (avg. 14.3 mmHg) and ICP (avg. 12.9 mmHg) in the supine position is small. A higher TPD may lead to abnormal function and damage of the ON due to changes in axonal transportation, deformation of the lamina cribrosa, altered blood flow or a combination thereof, leading to GON.

A meta-analysis of TPD published in “Nature” found that ICP was significantly lower in patients with primary open angle glaucoma, particularly NTG, than in healthy subjects. TPD was almost two times higher in patients with NTG and nearly five times higher in patients with high-tension-glaucoma (HTG), compared to healthy controls.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4815687/

As the optic nerve head is exposed to both IOP and ICP, the TPD becomes an important parameter and its reduction might assist in halting the progression of glaucoma.

It is easy to define glaucoma as a “multifactorial” neurodegenerative disorder. These factors unfortunately, are multiplying by each passing day. Instead of presenting a clearer picture they are muddying the waters. The only hope is that out of chaos order will come and one day a better understanding of these factors will help us in determining the pathogenesis of glaucoma and thereby lead us to more positive treatment outcomes.

ABOUT THE AUTHOR

Dr Syed Shoeb Ahmad is just a "regular guy" with an interest in glaucoma.

Posted by Syed Shoeb Ahmad