Current Practices in Ophthalmology
Series Editor: Parul Ichhpujani

Parul Ichhpujani *Editor*

Glaucoma

Springer

Current Practices in Ophthalmology

Series Editor

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Foreword

Dr. Parul Ichhpujani has—in this text—condensed current teaching about most of the new technologies and concepts in the field of glaucoma. This is a great accomplishment and a useful one.

She set herself a difficult task, as basic concepts about glaucoma, what it is, and how it is best diagnosed and treated are in transition and new technologies arrive daily! Those relatively new to the field may find it hard to believe that as recently as 50 years ago, the diagnosis of glaucoma was "easy"; one simply measured the pressure within the eye! That sadly incorrect method of thinking lingers on, unfortunately. Also, there was a widespread belief that the size of the optic nerve head "cup" was of essential importance in diagnosing and following patients with glaucoma. However, it is now clear that the size of the cup is poorly correlated with diagnostic and functional status and that "cup/disc ratios" should no longer be used; they mislead more than help. It is the pattern of the nerve appearance that is hugely helpful. Some authors now use phrases such as "pressure-independent" glaucoma, while others believe that pressure is in some way always at least partially responsible for the damage that occurs in glaucoma. One of the essential pieces of information—the appearance of the anterior chamber angle—is today incorrectly evaluated in over two-thirds of individuals!

As a result, blindness from primary angle closure glaucoma is the leading cause of permanent blindness—despite being easy to diagnose and treat successfully! Most of those (perhaps more than 90%) with glaucoma do not even get diagnosed, and for the relatively few that do, treatment options are so wildly diverse that the practitioner must wonder what to do.

What is certain is that thinking and acting regarding glaucoma are in a messy transition.

This book is a highly informative read for all interested in the field. The chapters are well-referenced, allowing the reader to go beyond the helpful material in the chapters themselves.

To me the major things to stress are:

- Prior methods of basing diagnosis and care on average values did not and still do not work; data must be personalized. Mean eye pressure, isolated measurement of retinal nerve fiber layer thickness, central corneal thickness, and cup/disc ratios are useless or worse, because they divert the examiner from what is truly essential.
- To be useful, data must be *valid* (i.e., accurate, consonant with reality) and *relevant* (i.e., pertinent for the person being considered). They should also be the result of *socially responsible* data acquisition methods. Valid, irrelevant, unsustainable data should not be obtained. Prior to recommending any test or procedure, the physician needs to ask the following: "Will the data obtained be accurate and relevant for this particular person, and is the cost justified?" Unless the answers to the two questions are a solid "yes," the test or procedure should not be done, unless scientifically sound methods are applied to study the validity, relevance, and sustainability of what is being considered.
- While there is as great deal still to learn, present methods, when applied well, work well for most individuals. There is no substitute for an empathetic, comprehensive, history designed to find symptoms and establish their chronology; an accurate, sensitive means of assessing visual ability; an accurate gonioscopy; a correct evaluation of pupillary responses; an estimate of the intraocular pressure with a simple instrument such as an applanation tonometer or the fingers; and a meticulous evaluation of the optic nerve head through a dilated pupil. There is still truth in the old saying that "the time to try a treatment is before learning that it does not work."
- One of the most exciting next steps is the confirmation by Caprioli and others that following adequate lowering of intraocular pressure fields improves. While this has been suggested in the past, few believed it. The reality of disc improvement has been proven since von Jaeger reported it in 1869; but even now, few recognize that it is common. The clinical implication of this improvement is that it may allow, for the first time, a valid, relevant method of determining how much the intraocular pressure needs to be lowered in order to assure the best chance of no further disease progression.

Those who have the good sense to read this text from start to finish will be better able to determine what they need to do to obtain and interpret and use data that are most likely to be valid, relevant, and socially responsible, so they can be of most help to patients, and, also, to understand better what questions need to be asked and how best to try to answer them.

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About the Editor

Parul Ichhpujani is currently an Associate Professor in the Department of Ophthalmology at Government Medical College and Hospital, Chandigarh, India. She takes care of the glaucoma and neuro-ophthalmology services at her center. She has done her glaucoma training from Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India, and a subsequent clinical research fellowship, under Dr. George L. Spaeth, at Wills Eye Institute, Philadelphia, USA.

She is the member of associate advisory board and education committee of the World Glaucoma Association. She is the associate managing editor of the *Journal of Current Glaucoma Practice*, the official journal of the International Society of Glaucoma Surgery, and is an assistant editor for glaucoma section of the *Indian Journal of Ophthalmology*. She was enlisted in the Powerlist 2015 of *"Best 40 ophthalmologists under 40." She is an Associate Advisory Board member of World Glaucoma Association.*

She is an avid researcher and an academician having co-authored three books, *Pearls in Glaucoma Therapy, Living with Glaucoma, and Smart Resources in Ophthalmology*; and edited five books, *Expert Techniques in Ophthalmology, Glaucoma: Basic and Clinical Perspectives, Manual of Glaucoma, Clinical Cases in Glaucoma: An Evidence Based Approach, and Glaucoma: Intraocular Pressure and Aqueous Dynamics.*

She has contributed several research articles and book chapters in national as well as international books. Dr. Ichhpujani has lectured at regional, national, and international surgical meetings. She serves as a reviewer for many ophthalmology journals.

What's New in Pathogenesis of Glaucoma

1

Parul Ichhpujani and Suresh Kumar

Glaucoma is an optic neuropathy due to progressive damage to retinal ganglion cells (RGCs), which results in characteristic cupping of the optic nerve head (ONH) and corresponding visual field defects. Despite years of research, the mechanism(s) underlying glaucomatous optic neuropathy (GON) remain unclear. It is believed that the lamina cribrosa is the primary site of injury, and raised intraocular pressure (IOP) is a major risk factor. Three theories have been widely accepted and they include the biomechanical, vascular, and biochemical theories [1].

Biomechanical Theory

Lamina cribrosa: According to this theory, IOP above the tolerable threshold of the ONH resistance results in deformation of the lamina cribrosa and the glial support framework of the anterior part of the optic nerve. Astrocytes and lamina cribrosa cells can sense strain through integrin receptors that tie their cytoskeletons directly to the adjacent fibrillar extracellular matrix. Elevated IOP leads to backward bowing, stretching, and compression of laminar plates within the lamina cribrosa, resulting in elongation of its pores, compression of the nerve fibers resulting in axoplasmic flow stasis in the RGC axons, and eventually RGC death and GON. Remodelling of the lamina cribrosa may predispose to localized compartment syndrome like situation when perfusion pressure lowers. These changes are associated with disk hemorrhages and visual field damage. These are also interpreted as a variant of limited anterior ischemic optic neuropathy like situation with venous congestion in a structurally altered ONH with narrowed pores in the lamina

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cribrosa [2]. With advancement in clinical imaging techniques, lamina cribrosa changes are detectable with optical coherence tomography (OCT) and can be used for diagnosis and management of glaucoma.

Role of intracranial pressure and trans-lamina cribrosa pressure difference: Another concept suggests that compression of the anterior part of optic nerve is also influenced by intracranial pressure (ICP) that may vary according to or independently of IOP fluctuations. Lamina cribrosa forms a pressure barrier between the high-pressure, intraocular space and the low-pressure, retrobulbar cerebrospinal fluid (CSF) space. The difference between the IOP and ICP across the lamina cribrosa is known as the trans-lamina cribrosa pressure difference (TLCPD) [3].

Clinical significance of TLCPD:

- Since the retinal and choroidal venous blood drains through the CSF space, therefore elevated CSF pressure may partly account for increased incidence of choroidal thickening and retinal vein occlusions [4].
- Studies have shown that the lamina cribrosa is significantly thinner in highly myopic eyes vis-a-vis mild or moderately myopic eyes, leading to steep trans-lamina cribrosa pressure gradient, which may explain why high myopes are more susceptible to glaucomatous damage [5].
- In advanced stage of glaucoma, lamina cribrosa becomes markedly thinner; therefore the TLCPD occurs over a shorter distance, resulting in a steeper trans-lamina cribrosa pressure gradient [4].

NTG versus HTG versus OHTN: Recent clinical studies have shown that patients with normal tension glaucoma (NTG) had significantly lower CSF pressure and a higher TLCPD when compared to subjects with no glaucoma. Therefore, it is plausible that a low CSF pressure may be associated with NTG. Low nocturnal systemic blood pressure could physiologically be associated with a low CSF pressure, which results in an abnormally high TLCPD, and this is akin to a similar scenario wherein the IOP is elevated and CSF pressure is normal. This concept explains why patients with NTG have relatively low systemic blood pressure and why eyes with NTG and HTG show similarities in ONH appearance, unlike eyes with a direct vascular optic neuropathy.

Studies have shown that chronic elevation of IOP in animals with experimentally induced ocular hypertension (OHTN) results in RGC death. Recent studies have reported that ICP is higher in patients with OHTN compared with controls [6]. This elevated ICP may be protective for the ONH by decreasing the TLCPD, thus explaining why despite elevated IOP most OHTN patients do not develop POAG. The lamina cribrosa is located more deeply in HTG than in NTG eyes and in NTG eyes than in healthy controls based on enhanced-depth imaging on spectral domain OCT (EDI-SDOCT) measurements. EDI-SDOCT has shown that the lamina cribrosa depth is a helpful parameter to differentiate HTG from normal eyes, but does not reach a good level of diagnostic accuracy for detecting NTG [7].

Vascular Theory

Elevated IOP also causes intraneural ischemia resulting from decreased ONH perfusion. Vascular perfusion of the ONH depends on three factors: systemic blood pressure, IOP, and the autoregulatory mechanism. Intraneural capillary perfusion pressure in the ONH is equal to the systemic blood pressure minus the IOP. Thus either decreased blood pressure or increased IOP leads to drop in the perfusion pressure of the ONH vasculature [8].

Additionally, IOP fluctuation results in vascular dysregulation which is worse than reduced circulation due to a stable elevated IOP or arteriosclerosis. Compromised ocular blood flow leads to reperfusion injury which, because of its repetitive nature, is detrimental. In NTG, endothelin-1 (ET-1) may have both a local and systemic component of vascular dysregulation, while in HTG, effect of ET-1 may be primarily localized to ocular tissue. Thus, ET-1 antagonism may be developed as a possible new approach for the treatment of both NTG and high-tension glaucoma (HTG) [9].

Neurochemical Theory

Since mechanical and vascular theories failed to explain glaucomatous optic neuropathy in all cases of glaucoma, the possible role of neurochemical mechanisms leading to glaucomatous neurodegeneration have been explored. These biochemical mechanisms include the role of reactive oxygen species (ROS), nitric oxide (NO), excitatory amino acids, caspases, protein kinases, tumor necrosis factor-alpha, metalloproteins, and neurotrophins [10].

An unstable ocular perfusion, an unstable oxygen supply, and a dysfunctional autoregulation result in oxidative stress and release of ROS within the axons of the ONH [11]. The increased outflow resistance can be explained by apoptosis and inflammation at the level of the TM, secondary to ROS stimulation.

Role of mitochondria: RGC mitochondrial dysfunction increases with glaucoma progression, and this leads to an imbalance in ROS production and detoxification. Müller cells have to work harder to maintain the level of chemicals released from activated microglia and astrocytes to nontoxic levels for the already compromised RGCs.

As the disease progresses, Müller cells are increasingly overburdened and are unable to cope with the neurochemical overload in the extracellular space, which leads to overstimulation of receptors associated with RGCs. Individual RGCs with defined receptor profiles are stimulated at different times by these neurochemicals which causes calcium influx that results in mitochondrial collapse and cell death [12].

Role of immune system: The eye is an immune-privileged site and ocular structures are protected from immune reactions and innate pathogens. However, injury or disease result in breakdown of the blood-retina barrier or changes in cytokine milieu and thus may compromise this immune privilege.

NO- and ROS-induced damage causes antigen-specific immune activation in retina [13]. These insults act through common final pathways that activate cellular proteases and eventually cause neuronal programmed cell death. So, these retinal proteins may be related to the development of GON.

However, there is also an opposing view that immune responses in glaucoma may be both neuroprotective or neural destructive [14]. For example, T-cell-mediated immune responses may initially be beneficial to limit neurodegeneration, but secondary recruitment of circulating T cells through an antigen-mediated process results in chronic autoimmune neurodegeneration. This in turn is associated with a failure to control stress-induced and aberrant immune response cascade.

Is It Apt to Label Glaucoma, "Ocular Alzheimer's"?

Research has shown that glaucoma patients are four times more likely to have dementia. RGC death in glaucoma is hypothesized to involve chronic amyloid β neurotoxicity, which causes apoptosis by binding to neurotrophin receptor $p75^{NTR}$ or through the accumulation of protein aggregates mimicking Alzheimer's disease at the molecular level, which is also being explored.

Glymphatic Theory

Another recent hypothesis is the existence of an ocular "glymphatic system," analogous to the "glymphatic system" in the brain [15, 16]. The retina is an extension of the CNS and shares embryological, anatomical, and physiological similarities to the brain; therefore, it seems plausible that the branches of the central retinal vessels in the retina are also surrounded by paravascular spaces with the same properties as the paravascular spaces in the brain.

Hu and coworkers have used multimarker immunohistochemistry to show evidence of a glymphatic system in mice, primates, and human retinas [17]. They found an $AQP4^{+}$ glial network ensheathing the entire retinal vascular system. Löffler and colleagues have also provided support for lymphatic structures in mice retinas similar to the glymphatic system in the brain [18].

In glaucomatous eyes, altered lamina cribrosa framework may mechanically interfere with the glymphatic flow through it by decreasing the elimination of neurotoxic substances, such as amyloid β, and resulting in subsequent GON.

This paravascular flow restriction may be in proportion to the amount of the TLCPD. Wostyn and coworkers have hypothesized that restriction of normal glymphatic flow at the level of the lamina cribrosa may lead to progression of glaucoma in patients with nocturnal hypotension and systemic hypertension [15].

Though a lot of research has been carried out to ascertain the precise pathogenesis of glaucoma, but the results have not yet been clinically utilized in management of glaucoma to halt or reverse the disease progression. However the future seems to be bright for deciphering the elusive pathways that define the disease. Figure 1.1 broadly elucidates the various theories for pathogenesis of glaucoma.