GLAUCOMA BEYOND INTRAOCULAR PRESSURE

Essay

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LIST OF ABBREVIATIONS

BDNF	*Brain derived neurotrophic factor*
CCT	*Central corneal thickness*
DCT	*Dynamic contour tonometry*
DMP	*Diastolic blood pressure*
GAT	*Golden applanation tonometry*
GON	*Glaucomatous optic neuropathy*
HRT	*Heidelbery Retinal tomography*
IOP	*Intra-ocular pressure*
LC	*Lamina cribrosa*
MOPP	*Mean ocular perfusion pressure*
NO	*Nitric Oxide*
NOS	*Nitric Oxide synthase*
NTG	*Normal tension glaucoma*
OBF	*Ocular blood flow*
OHT	*Ocular hypertension*
ONH	*Optic nerve head*
OPA	*Ocular pulse amplitude*
ORA	*Ocular response analyser*
OSAS	*Obstructive sleep apnea syndrome*
PAOG	*Primary open agnle glaucoma*
RI	*Reperfusion injury*
RGC	*Retinal ganglion cell*
RNFL	*Retinal nerve fiber layer*
SBP	*Systolic blood pressure*

INTRODUCTION

Glaucoma is one of the leading causes of blindness worldwide.[1] Primary open angle glaucoma is a multifactorial optic neuropathy characterized by progressive retinal ganglion cell death and associated visual field loss.[2]

Yet after years of extensive research the exact cause of glaucomatous optic neuropathy remains unclear.[3] Although elevated intraocular pressure (IOP) currently remains the focus of therapy, some glaucoma patients continue to experience disease progression despite lowering of IOP. One third of all Caucasian with primary open angle glaucoma patients have an IOP within the average range of 10-21 mmHg. Such patients with normal tension glaucoma (NTG) show typical pathological cupping of the optic nerve as well as characteristic visual field defects.[4]

Elevated intraocular pressure (IOP), ischemia, elevated glutamate levels, excessive production of nitric oxide and free radical generation, oxidative stress and deprivation of neurotrophic factors can trigger the apoptotic mechanisms in retinal ganglion cells (RGCs), and a combination of these factors would lead to RGC apoptosis in glaucoma[5].

Neuroprotection in glaucoma refers to the ability to preserve anatomic and functional integrity of the RGCs, thus preserving the visual field.[6]

AIM OF THE WORK

Management of glaucoma has been directed to decreasing IOP but still glaucomatous optic neuropathy and visual field loss occur inspite of controlling it, the goal of this work is to discuss risk factors that may be avoided or treated to control disease progression.

PATHOGENESIS OF GLAUCOMATOUS OPTIC NEUROPATHY

Glaucomatous optic neuropathy (GON) consists of the following basic components: loss of neural tissue, activation of glial cells, tissue remodeling and change of blood flow.[7]

1- LOSS OF NEURAL TISSUE

Glaucoma is no longer viewed simply as elevated intraocular pressure (IOP) that damages the optic nerve. In addition to high IOP, functional evidence is rapidly accumulating that suggests damage to the optic nerve may be initiated or sustained by several factors including ischemia, excitotoxicity, neurotrophin insufficiency, inflammatory cytokine damage, aberrant immunity, or other factors not yet defined. These different harmful influences then likely act through common final pathways that eventually activate the cellular proteases that accompany neuronal programmed cell death.[8] (Fig 1)

Glaucomatous optic neuropathy implies not only loss of retinal ganglion cells and their axons, but also a loss of neural cells in the lateral geniculate nucleus and to some extent even of the visual cortex. It is not known whether the retinal ganglion cell

(RGC) loss is due to a primary insult on the cell body or on the axons. The fact that the glaucomatous damage is often bundle-shaped indicates that the primary lesion might be in the optic nerve head.[9]

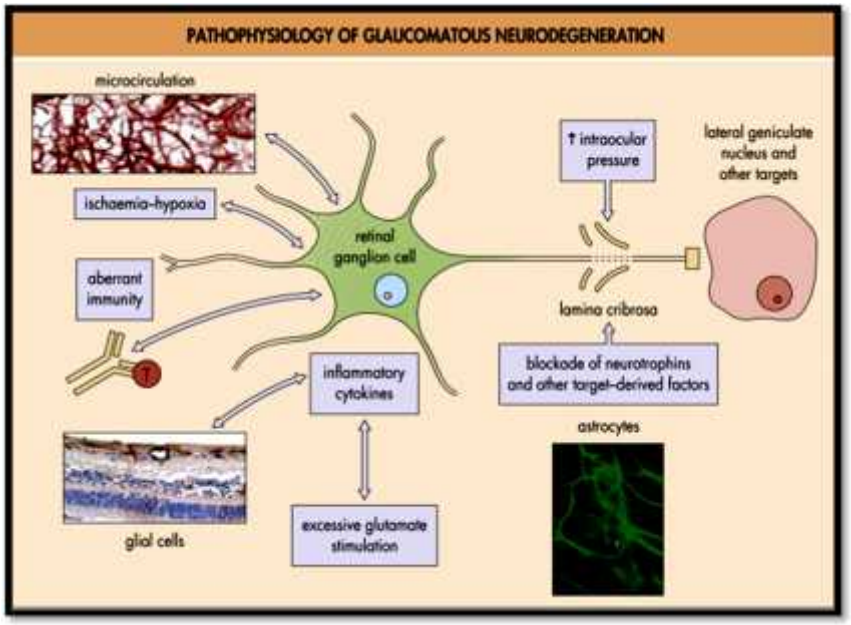

Fig. (1) Mechanisms contributing to pathophysiology of glaucomatous neurodegeneration.[10]

The Mechanical Theory

It suggests that optic nerve fibers are compressed by high IOP, when traversing a rigid structure called lamina cribosa, leading to problems in axonal transport (Fig. 2).[11]

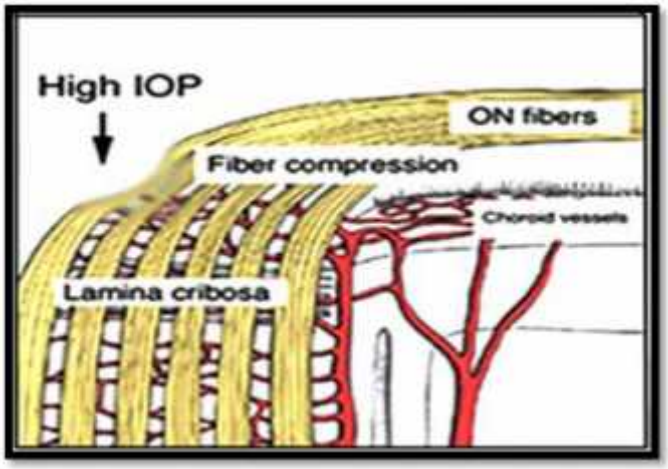

Fig. (2): RGC axons grouped as nerve fibers exit the eye through the optic nerve head , the place where RGC axons are hypothetically initially damaged by high IOP when traversing the lamina cribosa.[11]

In the 1990s, it was found that trophic factors, including brain-derived neurotrophic factor (BDNF), is retrogradely transported from the RGC axonal terminals to the cell bodies of the neurons and that trophic factors are essential to RGC survival. Thus, RGC axon compression was shown to reduce axonal transport of trophic factors causing RGC death by trophic insufficiency, as was first demonstrated in experimental glaucoma in rats and nonhuman primates in 2000.[12]

The Ischemic Theory

It points to alterations in ONH blood supply as the main factor in the progressive death of RGCs. A considerable support has been gained in the past few decades for this theory in which