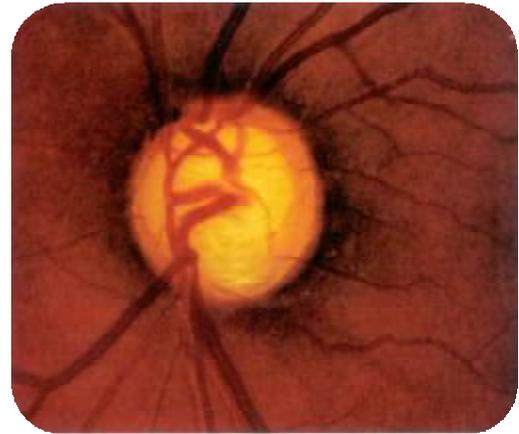


Glaucomatous Optic Neuropathy; Pathophysiology

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Glaucoma is an example of slowly progressive multifactorial optic neuropathy, characterized by excavation of the optic nerve head and loss of ganglion cells and initially their axons, passing through the upper and lower parts of lamina cribrosa where there is lower density of supportive connective tissue⁽¹⁾.



Glaucomatous optic neuropathy probably represents the final common pathway for various mechanisms of injury. Data derived from clinical observations and from animal experiments suggests that the axons of the optic nerve and the retinal ganglion cell somata do not die at the same time but that death can vary between months and many years⁽²⁾. Thus glaucomatous optic neuropathy may not be a chronic degeneration of the whole of the optic nerve and ganglion cell somata but rather a series of acute losses of individual or groups of ganglion cells. It seems therefore reasonable to assume that when a patient is diagnosed initially as having glaucoma, only some ganglion cells are dead, whereas others may range from being “unhealthy” to being “slightly sick” while others are “perfectly normal”⁽³⁾.

Pathophysiology of GON:

It is generally appreciated that IOP alone cannot explain the occurrence of GON in every patient, there is increasing evidence that multiple factors alone or in concert contribute to the progression of GON.

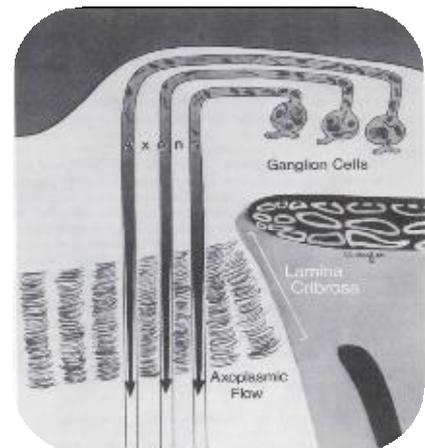
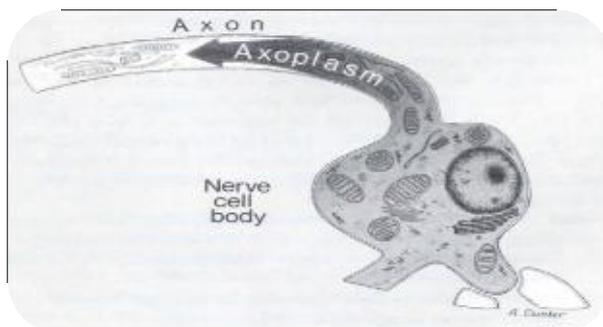
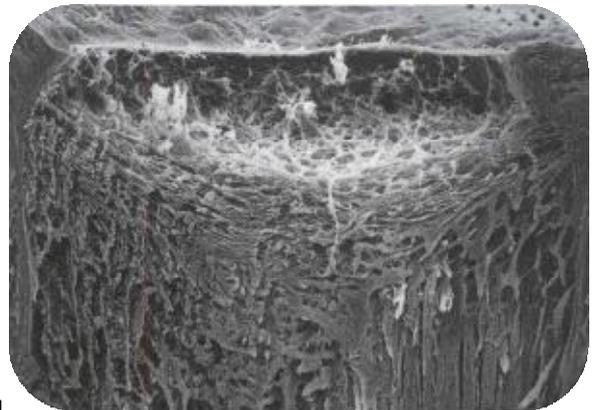
Outlined briefly bellow are several of the current theories regarding the mechanisms of damage in GON.

The mechanical theory:

This theory supports that elevated intraocular pressure “IOP” is the primary mechanism responsible for the damage to the neural cells through biomechanical or structural factors.

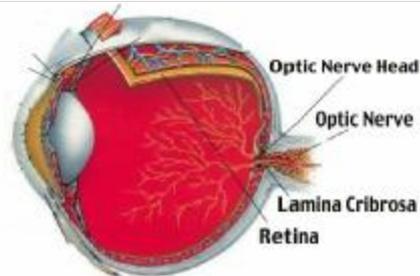
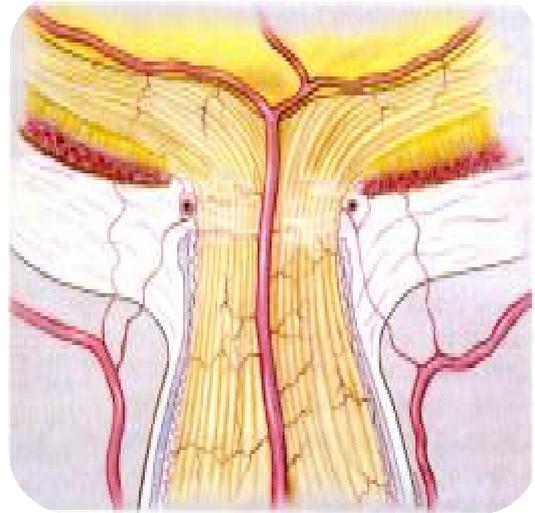
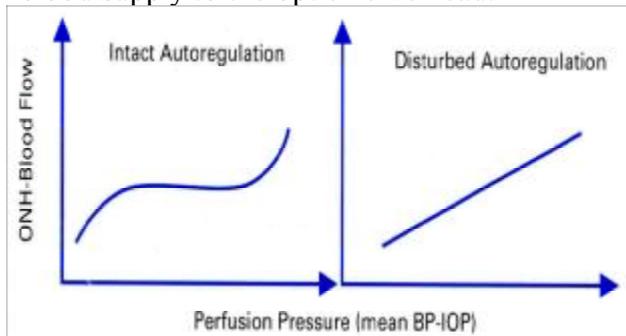
Increased IOP above the tolerable threshold of the optic nerve resistance leads to deleterious effects on the lamina cribrosa and the glial support structures of the anterior part of the optic nerve.

The mechanical effect of elevated IOP results in backward bowing, stretching and compression of laminar plates within the lamina cribrosa, this leads to misalignment of the fenestrations within the lamina cribrosa, kinking and compression of the nerve fibers resulting in inhibition of axoplasmic flow in the axons of the ganglion cells their death and GON.



The vascular theory:

This theory proposes that the basic pathogenic mechanism responsible for the death of ganglion cells in glaucoma is an insufficient blood supply to the optic nerve head.



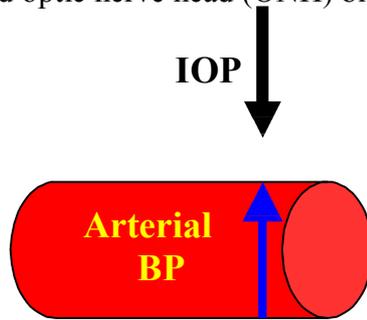
Epidemiological and laboratory evidence demonstrates that elevated IOP is not the sole cause of optic nerve injury in glaucoma. Among individuals treated for glaucoma, approximately 20%-30% lose vision despite maximal IOP lowering medically or surgically⁽⁴⁾. Therefore it is proposed that vascular perfusion of the neural tissue within the optic nerve is deficient in glaucoma. Healthy vascular perfusion in the ON head depending on many factors mainly: The systemic blood pressure, the IOP and the autoregulatory mechanism, (the auto regulation of the blood flow is defined as the ability of the tissue to maintain its blood flow relatively constant, despite moderate variations of perfusion pressure). The retina and ONH are autoregulated⁽⁵⁾.

Disturbance of any of these factors results in optic nerve head ischemia.

In laboratory studies, the axoplasmic flow of ganglion cell axons is obstructed by interrupting the short posterior ciliary circulation and these results in ganglion cell death.

Combination of mechanical and vascular theories:

A relationship of elevated IOP and optic nerve head (ONH) blood flow is known:



Intraneural capillary perfusion pressure in the ONH is equal to the systemic blood pressure (the intravascular pressure) minus the intraocular pressure (the extravascular pressure)

Thus decreased blood pressure (hypotension) or increased IOP leading to drop in the perfusion pressure of the ONH vasculature.

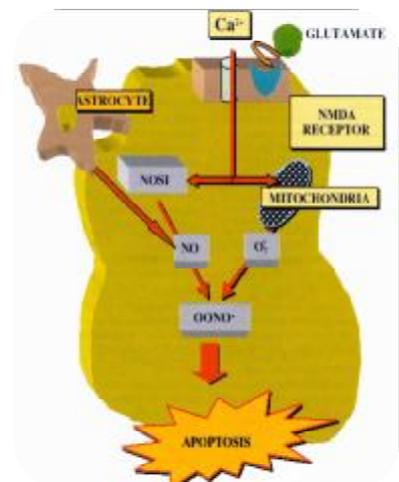
Decreased ONH circulation and a tendency to elevated IOP are two known occurrences in elderly individuals who have a great susceptibility to develop GON. There is evidence that significant nocturnal systemic arterial hypotension can occur in some individuals theoretically, compromising the blood supply to the optic nerves, and these persons may develop normal tension glaucoma with GON.

It is therefore difficult to separate the mechanical and vascular mechanisms as isolated causes of GON in a given patient.

The neurochemical theory:

This theory proposed that the neuronal injury in GON is of a chemical nature. In some patients with typical GON, elevated IOP or demonstrable circulatory insufficiency are not present. Some investigations showed that a number of substances have a damaging effect on neural cells such as:

The excitotoxins: these are excitatory neurotransmitters, they are found in a certain concentrations in normal tissue. If it is present in a high concentration it becomes toxic to neurons e.g. The glutamate it is recently found in high amounts in the vitreous body of glaucomatous eyes⁽⁶⁾.



Intracellular calcium: uncontrolled intracellular calcium accumulation may occur and this can cause neuronal damage and subsequent cell death.

Vascular endothelial cells (VEC) products: VEC produce a number of compounds that exert a variety of vascular and chemical effects, some of them are:

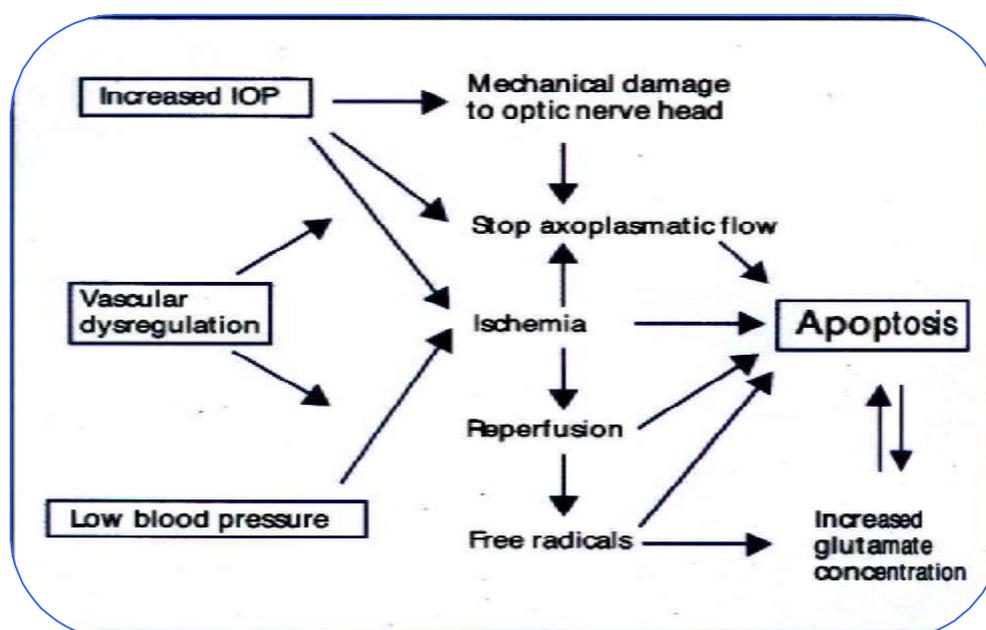
1- Nitric Oxide: which besides acting as neurotransmitters it has vasodilating effect; it has also a toxic effect on neurons. In primary open angle glaucoma, the nitric oxide synthase (NOS) are present in increased amount in the optic nerve. It has been postulated that excessive NO produced by astrocytes plays a major neurodestructive role in the chronic destruction of axons in the optic nerve head that is characteristic of glaucoma⁽⁷⁾.

2- Endothelins: it has a vasoconstrictive effect on optic nerve head. Its role in the pathogenesis of GON is under investigation.

Oxygen free radicals: may also have a role in ganglion cell damage.

Combination of mechanical, vascular and neurochemical mechanisms:

This theory proposes that elevated IOP leads to decreased blood flow in the ONH and this ischemia leads to excessive production of the neurotoxic chemicals⁽⁸⁾ (mentioned above) and the end result will be GON.



Genetically determined risk factors:

The followings may be considered as predisposing factors for the development of GON:

- Vascular disregulation (Raynauds disease, systemic hypotension, etc).
- Decreased tolerability threshold and resistance of optic nerve head.
- A weak lamina cribrosa.
- Neuronal signaling abnormalities which lead to apoptosis (a form of genetically programmed cell death).

Importance of understanding the pathogenesis of GON:

Understanding the pathophysiology of GON helps in offering glaucoma patients a good strategy that targets the multiple aspects of this disease: reducing the IOP, maximizing the vascular supply and promoting neuroprotection.

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