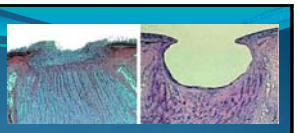

Glaucoma

Back to basics

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Competing interests

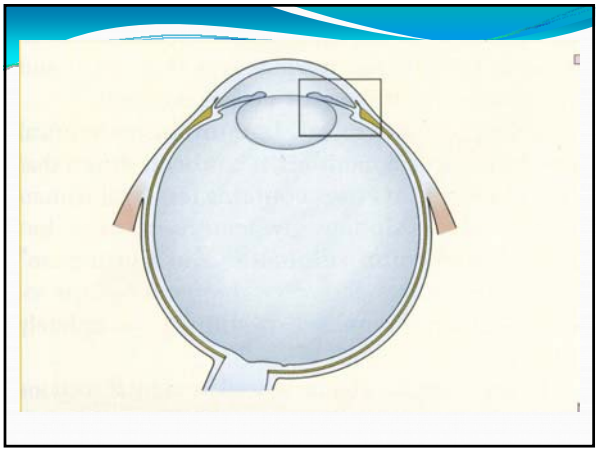
- None

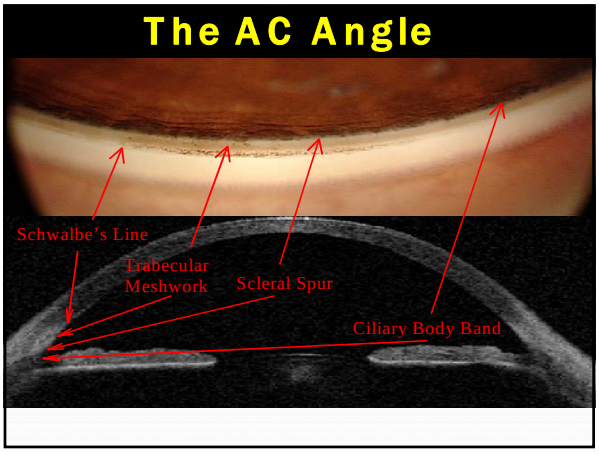
What is glaucoma?

- Definition:
  - "Ocular tissue damage at least partially related to intraocular pressure"
  - Where glaucoma is concerned agreement is limited among clinicians and scientists.

Anatomy of anterior chamber

- Anteriorly by corneal endothelium
- Peripherally by trabecular meshwork, portion of ciliary body and iris root
- Posteriorly – anterior iris surface and pupillary area of anterior lens surface
- Deeper centrally than peripherally





Why do we need aqueous humor?

- Shape, optical properties, to globe
- Nourishment to cornea and lens
- Refraction 1.33332

Nutrition and aqueous humor

- The avascular structures of the anterior segment of the eye, the lens and the cornea
  - depends upon a constant turnover of the surrounding aqueous to deliver nutrients
  - wash out metabolic waste products.

IOP dynamics

- In healthy eyes
  - Production matched closely to outflow
  - Major variations in outflow because of trabecular meshwork
  - Uveoscleral outflow is relatively constant at various pressure levels

Resistance to outflow

- Little resistance offered by sheets of trabecular meshwork
  - Unless debris and pigment accumulated
- Schlemm's canal little to no resistance
- External collector channels aqueous veins – negligible resistance
- **Location of highest resistance is**
  - Juxtacanalicular tissue
  - Endothelium of inner wall of Schlemm's canal

Ciliary body

- 1 of 3 portions of uveal tract
- Ciliary body
  - Muscle
  - Vessels
  - Epithelia lining ciliary processes
  - Autonomic nerve terminals

Ciliary body muscle

- Longitudinal fibers
  - Attach ciliary body to limbus
- Circular fibers
  - Anterior and inner portions of ciliary body
- Radial fibers
  - Connect longitudinal and circular fibers

Ciliary process

- Ciliary process is the functional unit responsible for production of aqueous humor secretion.
- Ciliary process are made of
  - 1) Capillaries
  - 2) Stroma
  - 3) Epithelia
- Ciliary process capillaries occupy the center of each processes.
- Two layers of ciliary epithelium surround stroma
  - Pigmented epithelium
  - Nonpigmented epithelium

Aqueous fluid

- Carefully controlled filtrate of blood produced by ciliary body
- Source of antioxidants for the corneal endothelium and the lens
- Carries oxygen similar to the interstitial fluid
- Helps maintain shape of globe
- Also serves as a shock absorber

TABLE 1-3 ➤ COMPARISON OF SOME COMPONENTS OF BLOOD WITH AQUEOUS FLUID

Component	Blood Concentration[1]	Aqueous Concentration[2]
Albumin	4.4 gm/100 ml	.006 gm/100 ml
Ascorbate (vitamin C)	1.3 mg/100 ml	19 mg/100 ml
Bicarbonate	27 mmol/litter	20 mmol/liter
Calcium	4.8 mg/100 ml	.01 mg/100 ml
Cholesterol	195 mg/100 ml	–[3]
Globulin	2.9 gm/100 ml	.005 gm/100 ml
Glucose	98 mg/100 ml	47 mg/100 ml
Hemoglobin	15 g/100 ml	None
Hydrogen ions (as pH)	7.4	7.5
Phosphate	3.8 mg/100 ml	2.1 mg/100 ml
Potassium	105 mmol/liter in red blood cells	.005 mmol/liter
Sodium	150 mmol/liter	150 mmol/liter
Triacylglycerols	88 mg/100 ml	–[3]

Aqueous humor formation

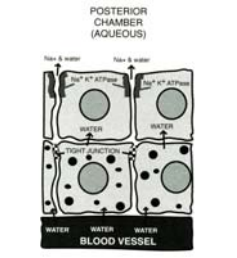
- Aqueous humor secreted by ciliary epithelium of ciliary process and enters posterior chamber.
  - Diffusion-lipid soluble substances
  - Ultrafiltration-Water and water-soluble substances
  - Secretion- larger size substances or greater charge (80-90% aqueous humor formation)
- The aqueous humor then flows around the crystalline lens and trough the pupil to anterior chamber.

Rate of aqueous humor production

- Ocular flurophotometry studies show circadian rhythm
- 2.97 ± 0.77 microlitre per minute
  - 8AM to noon
- 2.68 ± 0.64 microlitre per minute
  - afternoon
- 1.28 ± 0.43 microlitre per minute
  - Midnight to 6 AM

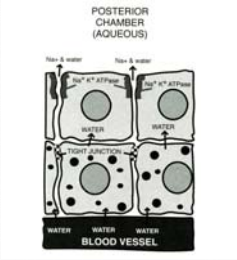
Aqueous formation

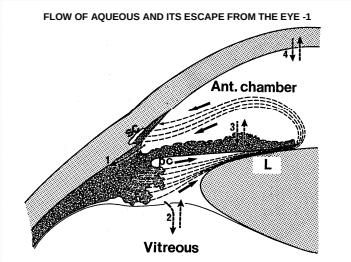
- Active process- works against concentration gradient
- Two enzymes Na, K-ATPase, and carbonic anhydrase
- Inhibition of Na, K-ATPase or carbonic anhydrase decreases aqueous production- glaucoma management!



Aqueous humor and Na,K-ATPase

- NA, K-ATPase is predominantly bound to plasma membrane of non-pigmented epithelium
- Sodium ions pushed into anterior chamber to which the water follows.
- glaucoma management!





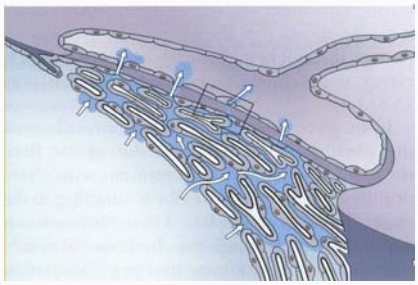
Aqueous Humor Outflow

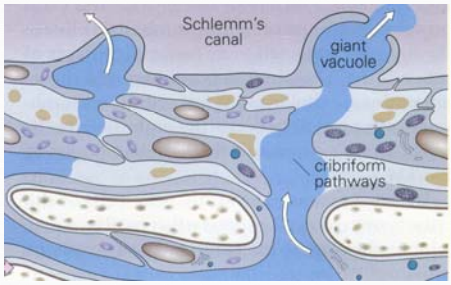
- Aqueous humor leaves the eye passive bulk flow via two pathways.
  - Through the trabecular meshwork
  - Trabecular or Conventional route

TM → Inner wall of Schlemm's canal into its lumen

↓

Collector channels, aqueous veins and episcleral venous circulation





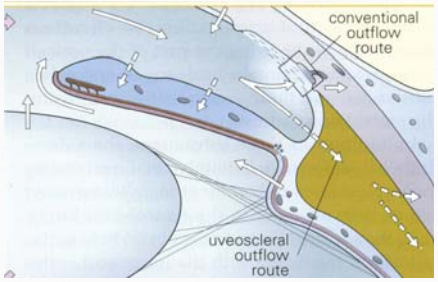
Aqueous Humor Outflow-2

- Uveoscleral or posterior or unconventional route

Across iris root, uveal meshwork and the anterior face of ciliary muscle

↓ → Through the connective tissue between the muscle bundles, through suprachoriodal space.

↓ → Out through sclera



Aqueous Humor Outflow-3

- Trabecular outflow 70-95%
- Uveoscleral outflow 5-30%

- Both total and trabecular outflow decline with age

Factors affecting IOP: Long-term

- Genetics
- Age
  - Increase of IOP with age
- Gender
  - M=F 20-40 yrs of age
  - Females greater increase in IOP post 40 yrs of age
- Refractive error?

Factors affecting IOP: Long-term

- Season – Higher IOP in winter compared to summer
- Blood pressure – increase in IOP
- Body weight

Factors affecting IOP: Short-term

- Diurnal variations
- Postural variations: Supine cause increase
- Exercise: Decrease in IOP
- Blinking and forceful closure causes increase
- Wearing tight neck tie
  - Valsalva maneuvers
- Mueller maneuver –
  - attempted inhalation against a closed glottis, which actually causes a decrease in IOP

Factors affecting IOP: Short-term-2

- Food and drugs
  - Alcohol
  - Caffeine
  - Tobacco
  - Heroin and Marijuana

24- hour variations

Pattern of IOP

- Supine position IOP higher than seated IOP
  - Episcleral venous pressure is increased thus there is an increase in IOP
- 24 hour supine IOP measurement
  - Night time IOP still higher than day time IOP
  - Thus episcleral venous pressure cannot explain all the increase in IOP
- Ambient light has – no effect

24-hour Pattern of IOP

Glaucoma vs. Healthy

- Both diurnal and noctornal IOP curves are higher in glaucoma patients
- Absolute change from diurnal to noctornal is less
- Difference between the groups with respect to IOP at night is reduced.

24-hour Pattern of IOP
Glaucoma vs. Healthy

- IOPs peak at 7.30 AM (glaucoma) IOPs peak at 5.30 AM (Ocular healthy)
- 5.30 AM to 7.30 AM
  - Ocular healthy decrease in IOP
  - Glaucoma increase in IOP

Summary

- IOP is a variable that is dynamic and in flux
- Various factors affect IOP measurements
  - Short term
  - Long term
- Secretion- accounts for major production in aqueous humor (AH)
- Sodium potassium ATPase and Carbonic anhydrase are important enzymes in production of AH
  - Can be altered - management of glaucoma

Summary cont…

- Patterns of IOP varies in ocular healthy when compared to glaucoma patients
- This may in part explain its pathophysiology

Optic nerve head

- Arbitrarily divided into 4 parts
  - Surface nerve fiber layer
  - Prelaminar region
  - Lamina Cribrosa region
  - Retrolaminar

Surface Nerve Fiber Layer

- Inner most portion
- Predominantly nerve fiber
- **Axonal bundle acquire more interaxonal glial tissue** as this structure is followed posteriorly

Prelaminar Region

- Also called anterior portion of lamina cribrosa
- Predominant structure: nerve axons and astrocytes with significant increase in astroglial tissue

Lamina Cribrosa Region

- Fenestrated sheets of scleral connective tissue
- Astrocytes separate the sheets and line the holes
- Bundle of axons leave through these holes

Retrolaminar Region

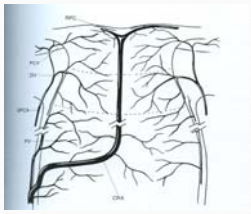
- Decrease in astrocytes
- Myelin is acquired
- Axonal bundles surrounded by connective tissue
- Posterior limit is not clear but about 3 to 4 mm

Vasculature

- Arterial supply
  - Posterior ciliary artery main supply to optic nerve
  - Except for NFL that is supplied by retinal circulation.

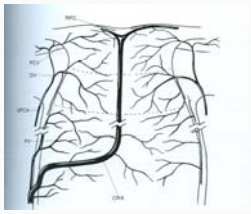
Blood vessel supply surface NFL

- Main supply Arteriolar branches of CRA



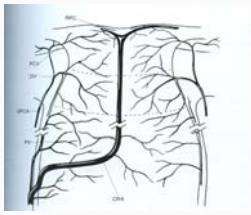
Blood vessel supply to prelaminar and laminar regions

- Primary supply SPCA
- Also supply peripapillary choroid



Blood vessel supply to Retrolaminar region

- Medial and lateral perioptic nerve SPCA



Capillaries

- Derived from both retinal and ciliary circulation
- Resemble retinal capillaries
- Do not leak fluorescein may represent nerve-blood barrier
- Decrease in number posterior to lamina

Venous drainage

- Entirely through central retinal vein

Astroglial support

- Provides continuous layer between nerve fiber and blood vessels of optic nerve head
- Thick and thin astrocytes have been described
  - Thin: Accompany the axons in NFL
  - Thick: Direct axons from prelaminar to laminar region

Connective tissue support

- Lamina cribrosa
  - Glaucoma pathogenesis takes place at level of lamina cribrosa

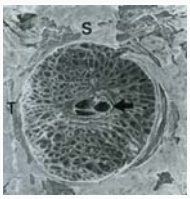
Lamina Cribrosa

- Porous region of sclera
- Specialized extracellular matrix
  - consist fenestrated sheets of connective tissue and occasional elastic fibers
- Hyaluronate is found in surrounding the myelin sheaths
- Hyaluronate decreases with age and further decreases with increase IOP

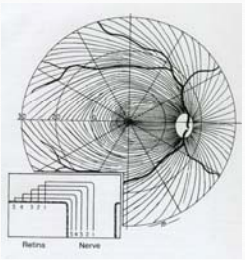
Analysis of pores of lamina cribrosa

- Healthy: round in eyes with physiologic cupping
- Glaucoma: Compressed pores

Regional differences of pores



Retinal nerve fiber layer



- Arcuate fibers occupy superior and inferior temporal regions.
- Axons from peripheral retina take more peripheral position.
- Papillomacular fibers spread approx 1/3rd of the distal optic nerve primarily inferior temporal.
- It also intermingles with extramacular fibers (may explain retention of central vision).

Axonal facts

- 700,000 to 1.2 million
- Large variation
- Count of axons increase with increase in area.
- Axon fiber diameter 0.65 to 1.10 µm
- Axons of all sizes are mixed throughout although mean diameter appear to be more common nasal segment.

Influence of age on ONH

- Size 95% before age of 1
- Connective tissue of lamina cribrosa incompletely developed
  - Greater susceptibility to damage
  - Potential for reversible cupping.
- Progressive loss of axons 4,000 to 12,000 a year (lower end most likely)

Influence of age on ONH-2

- Selective loss of fibers with age
  - Quigley and group.
- Not confirmed by others investigators

Summary ONH

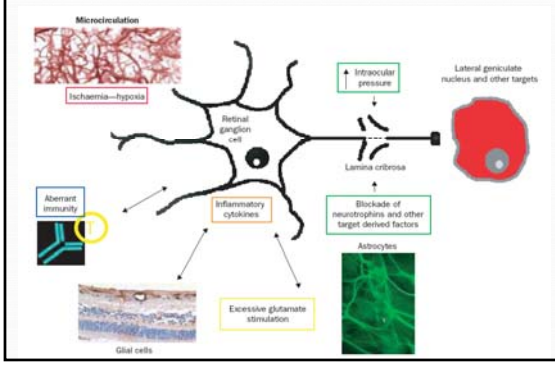
- Arbitrarily divided in to 4 parts
- Main blood supply posterior ciliary artery
- Venous drainage central retinal vein
- Pores of lamina cribrosa different at different regions
  - May explain vertical elongation
  - May explain selective resilience of macular fibers

Pathophysiology of glaucoma

Basics

- Glaucoma is a neurodegenerative disease characterized by the slow, progressive degeneration of retinal ganglion cells
- Glaucoma neuroretinal rim decreases with concomitant increase in cupping at optic disc
- Other neuropathies result in pallor of ONH rarely enlargement of cupping
- Glaucoma damage is not limited to retinal ganglion cell axons, soma and dendrites
  - Neurons in LGN and visual cortex are also lost.

Factors contributing pathophysiology in glaucoma



Theories, theories everywhere which theory to pick

What is the cause of glaucoma?

- 1858 Müller ➡ Elevated IOP cause direct compression and death
- 1858 von Jaeger ➡ Vascular abnormalities cause optic atrophy
- 1968 axoplasmic flow problems
  - Lambert, Vogel, Zimmerman

Anatomic and histopathologic studies

- Direct method
- Limitations-specimens have advanced glaucoma

Excitotoxicity - Glutamate

- When glutamate injected-
  - Subcutaneously
  - Intravitreally → **Death of RGC**
  - In-vitro – Petri dish
- Glutamate –mediated death seen when overstimulation of
  - NMDA receptors (N-methyl-D-aspartate
  - Kainate glutamate receptors → **Increase in intracellular calcium**

Glutamate mediates photo receptor- bipolar cell and bipolar cell and RGC synaptic transmission

Glutamate toxicity

- Chronic low-dose glutamate is toxic
- Glutamate concentrations has been shown to increase in vitreous
  - Both monkeys and patients
- This theory is controversial.

Target-derived growth factors

- RGC survival depend upon certain neuronal growth factors, neurotrophins (e.g. brain-derived neurotrophic factor).
- Axonal compression at lamina cribrosa block retrograde axopalsmic flow.
- These include superior colliculus and pretectal nuclei
- Death may also result from deprivation of such factors

Nitric oxide

- Beneficial at certain concentration as a vasodilator.
- Neurotoxic in higher concentration
- Inhibits mitochondrial function and disrupts DNA

Important point to remember

- Each theory or hypothesis has a strong support but they are not exclusive of each other.

In-vitro models

- Experimental models of ocular hypertension.
- Optic nerve crush
- Ocular ischemia

- All these models cause RGC death.
- Interpret results with caution

Mechanical theory

- Physical alterations, misalignment of fenestrae, back bowing of lamina cribrosa may lead to obstruction.
- Compression of ganglion cell axon impairs the trophic factor axonal flow transport causing death of cell.
- Support to this theory damage with elevated IOP occurs despite intact blood vessels.

Vascular theory

- Ischemia at least plays a role in the obstruction of axoplasmic flow in response to elevated IOP.
- Retina depends on good blood flow for its metabolic needs
- Dysfunction in auto regulation.
- Difficult to establish as experiments are difficult to conduct.

Perfusion pressure

- Difference between arterial and venous pressure
- Mean ocular perfusion pressure = mean BP – IOP
- Blood vessel resistance also determines blood flow
- Autoregulatory mechanism is present in retinal vessels to maintain blood flow regardless of perfusion pressure
- However this mechanism fails in glaucoma

Two types of autoregulatory mechanisms exist

- Metabolic
- Myogeneic

- Metabolic- Endothelial cells secrete these
  - Vasodilators – nitric oxide
  - Vasoconstrictors – e.g. endothelin 1

- Myogenic- operates when blood flow above normal
  - Mechanism unclear

Evidence in favor of vascular theory

- Delayed filling of superficial vessels of optic nerve in glaucoma
- Association of NTG with migraines
- Excessive peripheral constriction of vessels to cold- **Raynaud's phenomenon**
- Nocturnal blood flow different in glaucoma patients
- Greater plasma concentration of endothelin-1

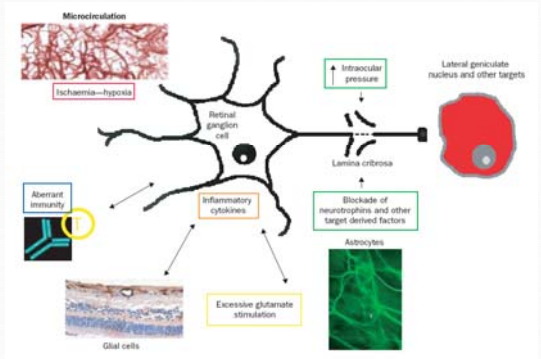
Mechanovascular theory

- Both mechanisms that is vascular and mechanical damage play a role in glaucomatous pathology.

Apoptosis

- Regardless of mechanism of damage to retinal ganglion cells- death of RGC in glaucoma is ultimately via apoptosis
- Genetically coded program- when activated leads to cell death.

Factors contributing pathophysiology in glaucoma



Apoptosis

- Programmed cell death
- Occurs in:
  - Photoreceptors secondary to excessive light exposure
  - Conjunctival cells secondary to ocular preservatives
  - Corneal epithelial/ keratocytic cells after wounding

Apoptosis (cont 2)

- Eliminates excess cells during organizational development; controls tissue size
- May accompany the development of cancer, immune reactions, or the presence of toxins

Apoptosis Process

- Cell decreases size; contents become concentrated

↓

- nucleus fragments

↓

- cell separates into small bodies

↓

- these are phagocytosed w/o an inflammatory response

Summary on theories

- Various components may contribute to pathogenesis in glaucoma
  - Elevated IOP, Glutamate, vasoregulators, immunological effects ,obstruction of axoplasmic flow may be involved in pathogenesis of glaucoma.
- It is not clear whether mechanical or vascular factors are primary.
- All these factors may be responsible to some degree.

All roads lead to apoptosis

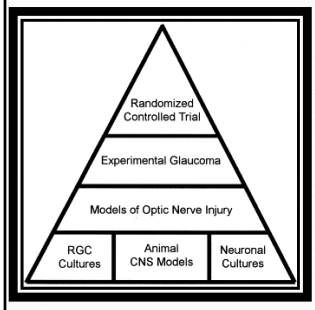
Neuroprotection concepts

- Any method that prevents or slows the death of neurons is considered neuroprotective
  - In that definition all treatments are neuroprotective
- However when one talks about neuroprotection
  - Prevent destructive cellular events
  - Enhance survival of cells after damage

Drugs in neuroprotection

- None of the drugs that are approved for use in glaucoma patients
  - Indication of neuroprotection
  - Marketing claim of neuroprotection

So is there any evidence ?



A pyramid diagram illustrating the levels data supporting use of a therapy, ranging from weakly relevant at the bottom to highly relevant at the top.

Levin LA: Retinal Ganglion Cells and Neuroprotection for Glaucoma
Surv of Ophthalmol 2003

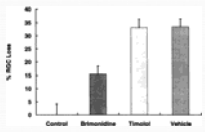
Any drug –to be deemed neuroprotective

- Four criteria
  - 1) the agent must have a target in the retina;
    - Yes they are present
  - 2) it must be neuroprotective in animal models;
  - 3) it must reach neuroprotective concentrations in the posterior segment after clinical dosing;
  - 4) it must be shown to be neuroprotective in controlled clinical trials.

Brimonidine- alpha-2-agonist

Are you a neuroprotective agent?

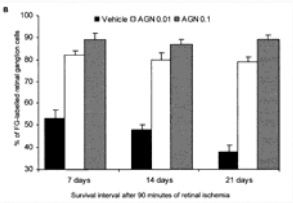
Neuroprotection in animal model



- Rat model
- IOP high for 10 days
- Then medications given subconjunctival (3 weeks)
- IOP not lowered
- 50% less damage with Brimonidine treated animals

WoldeMussie IOVS 2001

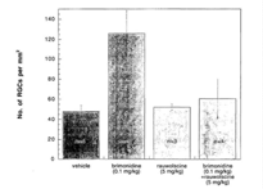
Neuroprotection in animal model -2



- Ischemia model
- Ligation of ophthalmic vessels
- Pretreatment with
  - Alpha 2-selective agonist

Lafuente et al. *Invest Ophthalmol Vis Sci. 2001;42:2074–2084*

Neuroprotection in animal model-3



- Optic nerve crush model
- Two weeks post treatment
- Rauwolscine is alpha-2-antagonist

Yoles et al. *IOVS*, January 1999, Vol. 40, No. 1

Possible mechanism of neuroprotection of brimonidine

- inhibit pro-apoptotic mitochondrial signaling
- inhibition of pro-apoptotic signaling molecules, including
  - BAD (BCL-2 associated death promoter)
  - caspase-9,
  - and activation of anti-apoptotic molecules such as NF-kappaB

Summary neuroprotection

- Evidence building in favor of neuroprotection.
- Animal studies not exactly same as human glaucoma so it is difficult to extrapolate
- Considerations of various factors in management should be given when choosing medications
- Clinical trials are needed to substantiate further claims of neuroprotection

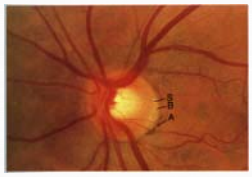
Clinical appearance of Optic Nerve Head

Physiologic Neural Rim

- Traditionally lot of emphasis is given on the cup.
- The neural rim is the tissue responsible for cupping and loss of visual field.
- C/D ratio is an indirect measure because large diameter nerve head may be associated with thinner rim but stable number of neurons

Physiologic Neural Rim -2

- In a healthy optic disc neural rim is broadest
  - Inferiorly
  - Superiorly
  - Nasal
  - Temporally
- Larger disc area correlates positively neural rim



Retinal Nerve Fiber Layer

- Striations seen ophthalmoscopically
- Visible only after certain critical thickness is reached.
- Best seen at poles
  - Inferior
  - Superior
  - Temporal
  - Nasal

Retinal Nerve Fiber Layer -2

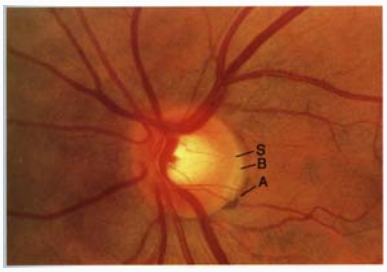
- NFL decrease with age
- Visibility of NFL correlates with width of neural rim and caliber of retinal artery

Peripapillary pigment variations

- Scleral lip: A thin, even white, 360 degree. Represents anterior extension of sclera between choroid and optic disc.
- Chorioscleral crescent or zone beta: broader, more irregular area of depigmentation. Represents retraction of RPE and thinning or absence of choroid.

Peripapillary pigment variations

- Zone alpha: Peripapillary crescent of increased pigmentation.
- Represents malposition of embryonic fold with double layer or irregularity of RPE.
- Found adjacent to zone beta or next to disc if zone beta is absent.



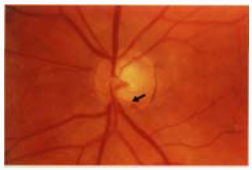
Peripapillary pigment variations

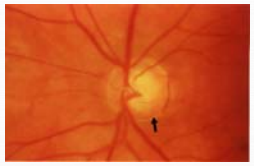
- A greater Zone beta area-to-disc area ratio found to be associated with greater risk of glaucomatous damage.

Disc hemorrhages and pathogenesis

- Supports vascular hypothesis
- Some sort of dysregulation
- Does not always mean worst glaucoma

3 years later





Conclusions

- Understanding anatomy and physiology of aqueous humor dynamics and optic nerve helps understand pathogenesis in glaucoma
- Pathogenesis in glaucoma is complex
- Lowering pressure – is treatment of choice
- Neuroprotection concept needs further research
- Optic nerve is the site of damage

- More to come in POAG lecture…