WHAT WAS GLAUCOMA?

- High IOP
- Optic nerve anomalies
- Neurological diseases which may superficially mimic glaucoma.
- Provocative testing

WHAT IS GLAUCOMA?

- Primary open angle glaucoma (POAG) is a progressive, chronic optic neuropathy in adults where intraocular pressure and other currently known and unknown risk factors contribute to damage and in which, in the absence of other identifiable causes, there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons, often with characteristic damage to the visual field. This is associated with an anterior chamber angle that is open by gonioscopic appearance.

AQUEOUS PRODUCTION AND DRAINAGE

- Trabecular outflow is through the trabecular meshwork. Uveoscleral outflow is through the interstices of the uveoscleral meshwork located on the ciliary face.
- Trabecular outflow is approximately 80% of the outflow and uveoscleral is the remainder.
- The uveoscleral pathway goes to the supraciliary and finally the suprachoroidal space. Uveoscleral flow is pressure independent, representing bulk flow rather than diffusion related phenomena. Flow is unchanged despite elevations in episcleral pressure.
- Contraction of the ciliary body increases trabecular flow which compressing intracellular spaces on the ciliary muscle and decreasing uveoscleral flow.
- The blood aqueous barrier are the non-fenestrated capillaries of the iris, specifically, the zonulae occludens (tight junctions) which join the cell membranes of adjacent vascular endothelial cells of the iris and the non-pigmented ciliary epithelial cells. Fenestrated capillaries do not have the tight junctions and leak. Non-fenestrated capillaries have tight junctions and do not leak (iris). Fenestrated capillaries are in the ciliary processes. However, there are tight junctions at the apico-lateral surface between the cells of the non-pigmented layer.
**AQUEOUS PRODUCTION AND DRAINAGE**

- Aqueous is produced at 2-3 microliter/minute and there is complete turnover every 1-2 hours.
- A resistance and pressure decrease occurs across the inner wall of Schlemm's canal causing the pressure in TM distal to be greater. At elevated IOP, the TM distends and the inner wall moves towards the outer wall of the canal. Giant vacuoles in the wall of Schlemm's canal transports aliquots of aqueous. Giant vacuole formation is pressure dependent. Aqueous in the canal is drained to the episcleral venous plexus. Increased episcleral venous pressure will increase outflow resistance as well as resistance at the trabecular meshwork. Even aqueous itself can increase outflow resistance.

**HISTOPATHOLOGY OF GLAUCOMA**

- **Anterior Segment**
  - Accelerated and exaggerated normal aging changes in anterior chamber angle.
  - Affects both Schlemm's canal and uveoscleral outflow pathways.
  - Increased resistance to outflow at the level of the juxtacanalicular tissues in the trabecular meshwork and inner wall of Schlemm's canal is the site of glaucoma.
- **Posterior Segment**
  - Compression of laminar sheets
  - Distortion of laminar pores
  - Posterior and lateral displacement of laminar sheet
  - Blockage of axonal transport
  - IOP and vascularly induced with death of ganglion cells
  - Deepening and enlargement of optic cup

**NORMAL AGING CHANGES INCLUDE:**

- Loss of trabecular cells. This is greatest in the uveal meshwork and least in the juxtacanalicular zones.
- An increase in the accumulation of pigment within the endothelial cells of the trabecular meshwork.
- Thickening of the trabecular lamellae from an accumulation of material in the basement membrane of the endothelial cells and also the addition of extracellular material within the core of the trabecular beam.
- Fusion of trabecular lamellae from loss of endothelial cells.
- Thickening of the scleral spur from hyalinization of the ciliary muscle.
- Increase in extracellular plaque material (myocillin) in the juxtacanalicular zone.
- Loss of ability to form giant vacuoles along the inner wall of Schlemm’s canal.
- Proliferation of endothelial cells forming the lining of Schlemm’s canal into the lumen of Schlemm’s canal.
- Glaucoma can be viewed as an exaggerated, elevated rate in aging changes.

**SCLERAL RESPONSE TO IOP**

- Important to consider sclera and nerve head as a matched (or mismatched unit)
- Sclera is stiffer in human glaucoma
- Sclera becomes stiffer in experimental glaucoma
- Scleral response is cellular change in fibroblasts
HOW DOES GLAUCOMA DAMAGE OCCUR?

- (Bio)Mechanical compression
- Ischemic vascular
- Excitotoxicity of neural cells
- Genetically pre-programmed cellular suicide (Apoptosis)

Laplace’s Law
\[ \sigma = \frac{pr}{2t} \]
- \( \sigma \) = in-wall hoop stress
- \( p \) = pressure (IOP)
- \( r \) = sphere radius
- \( t \) = wall thickness

HOW DOES GLAUCOMA DAMAGE OCCUR?

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**HOW DOES GLAUCOMA DAMAGE OCCUR?**

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**WHAT IS REALLY HAPPENING IN GLAUCOMA?**

- Glaucomatous damage involves impaired microcirculation, altered immunity to stress, excitotoxicity, oxidative stress, chronic ischemia, structural changes to drainage channels, subsequent neurotrophin deprivation, and apoptosis.

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**THE GLAUCOMA CONTINUUM**

- RNFL change (detectable)
- SWAP VF change
- SAP VF change
- VF change (mod)
- VF change (severe)
- Blindness

**Risk factors**
- IOP
- C:D ratio
- CCT
- Age
- Other

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**THE GLAUCOMA CONTINUUM**

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**Risk factors**
- OHTS
- CIGTS
- AGIS
- Simms, St. Louis

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**Risk factors**
- EMGT
- OHTS
- CIGTS
- AGIS
- Simms, St. Louis
**EPIDEMIOLOGY OF GLAUCOMA**

- In 2013, the number of people (aged 40-80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040.
- More than 2.7 million Americans aged 40 and older are affected. Half are unaware/undiagnosed.
- The prevalence of glaucoma in the United States is 22 percent higher than it was 10 years ago.
- #2 cause of blindness. #1 cause in non-whites.
- Approximately 4% of glaucoma patients become blind.
- However, not everyone with glaucoma has a 4% risk of becoming blind – some may be much higher or lower.
- Prevalence of ocular hypertension is always greater than glaucoma.
- Prevalence of glaucoma increases with age.

**POPULATION-BASED THESSALONIKI EYE STUDY**

- Population of 2,554 participants aged 60 years or over found a 50% rate of undiagnosed glaucoma.
- Prevalence of 66.7% over-diagnosed glaucoma was also found. Only one-third of the patients who had been previously diagnosed with glaucoma had the diagnosis confirmed in the study. The vast majority were undergoing treatment, and a smaller proportion had had laser or surgery.
- Implications: One-third of subjects with undiagnosed glaucoma had progressed to advanced stages. On the other hand, fear of blindness, side effects of unnecessary treatment, increased costs for individuals and society, and the waste of clinical resources are consequences of over-diagnosis.

**GLAUCOMA’S ECONOMIC BURDEN**

- Direct cost estimates for the approximately 2 million US citizens with glaucoma are $2.9 billion. However, these figures likely underestimate the true societal costs if all were to be treated since about half of patients with glaucoma are unaware.

**GLAUCOMA’S ECONOMIC BURDEN**

- The financial burden of glaucoma increases as disease severity increases.
- 4-fold increase in direct costs as severity increased from ocular hypertension through advanced glaucoma to end-stage glaucoma/blindness.
- Average direct costs per patient per year were $623, $1915, and $2511, respectively. The majority of costs were medication-related at all severity stages.


GLAUCOMA RISK FACTORS

- IOP
- Age
- Race
- Family History
- Corneal thickness
- Diabetes
- Hypertension
- Hypotension
- OPP
- Sleep apnea
- CSF pressure
- Corneal hysteresis

ELEVATED IOP:

- This is the most significant risk factor overall
- IOP which is statistically abnormal is not necessarily physiologically abnormal for an individual eye. Conversely, IOP that is statistically normal is not necessarily physiologically normal for an individual eye. Thus, there is no clinically useful level of IOP to differentiate all normals from all people with glaucoma

DIURNAL VARIATION OF IOP

- Glaucoma patients tend to have greater IOP variations
- It has been shown that the diurnal IOP curve is not consistent over time and is not symmetrical between eyes of the same person
- IOP variation is generally not considered to be an independent risk factor for glaucoma

Diurnal Variation in IOP

- Historically, we were all taught that IOP is lower at night and highest in the early morning hours…

- Virtually all IOP measurements take place during waking hours… but what REALLY happens to IOP when patients are sleeping?


- 103 patients evaluated in a sleep laboratory
  - 33 young, healthy volunteers (18-25)
  - 35 older, healthy volunteers (40-74)
  - 35 older glaucoma patients (40-79)
- IOP measured every 2 hours using a pneumatonometer in both the seated and supine positions during the diurnal/wake period (7 am to 11 pm), and in the supine position during the nocturnal/sleep period.

- **Conclusions:**
  - IOP is higher at night (11:30 pm – 5:30 am) and while supine; this is true for both normals and glaucoma patients.
  - Likely due to elevation of episcleral venous pressure
  - Average supine IOP during office hours ≥ peak nocturnal IOP in glaucoma patients.

### Central Corneal Thickness

- **CCT impacts applanation measurement**
  - Can lead to misdiagnoses or treatment changes
- Thin corneas are a risk factor for glaucoma development, progression, structural and functional changes, conversion from OHTN
- Pachymetry measurement and conversion models may themselves be error sources
  - No validated algorithm to correct IOP based upon CCT
- No proven association with CCT and any other structural abnormality


### Blood Pressure

- **Hypertension**
- **Hypotension**

### Ocular Perfusion Pressure: Terminology

- **SPP** – Systolic Perfusion Pressure
  - $SPP = SBP - IOP$
- **DPP** – Diastolic Perfusion Pressure
  - $DPP = DBP - IOP$
- **MPP** – Mean Perfusion Pressure
  - $MPP = \frac{2}{3}DBP + \frac{1}{3}SBP$

Mean Arterial Pressure = $\frac{2}{3}DBP + \frac{1}{3}SBP$
**OCULAR PERFUSION PRESSURE**

**Blood Pressure**

**OCULAR PERFUSION PRESSURE (OPP)**

- **Baltimore Eye Survey**
  - Lower OPP strongly associated with prevalence of POAG
- **The Egna-Neumarkt Study**
  - Lower DPP associated with a higher risk of having glaucomatous optic nerve damage
- **Proyecto Ver Study**
  - Persons with Diastolic Perfusion Pressure < 50 mmHg had a four-fold higher risk of having POAG compared to those with Diastolic Perfusion Pressure of 80 mmHg
- **Los Angeles Latino Eye Study**
  - Persons with Low Diastolic and Systolic perfusion pressures had a higher risk of having POAG
- **Barbados Incidence Study**
  - 4-year and 9-year risk of developing glaucomatous optic nerve damage increased at lower SPP, DPP, MPP

**Ocular Perfusion Pressure and Glaucoma Progression**

**Higher IOP Negatively Impacts Perfusion Pressure**

**Lower Diastolic, Systolic, or Mean Pressure Reduces Perfusion Pressure**

**Perfusion Pressure Is a Result of A Delicate Balance Between IOP and Blood Pressure**

**OCULAR PERFUSION PRESSURE (OPP)**

- **Glaucoma medications can affect OPP**
  - Prostaglandin analogs and carbonic anhydrase inhibitors increase DPP at all time points
  - Beta blockers decrease DPP from 4 am – 4 pm but not at other times
  - **Alpha agonists reduce DPP at multiple time points**

**FAMILY HISTORY**

- Direct relative- parent, sibling, child
- History of blindness very important
The Blame Game

- Diabetes
- Migraine
- Sleep Apnea

After all, can’t just about everything be blamed on these three?

DM Associated with Increased Risk of Glaucoma

- Blue Mountains Eye Study
- Beaver Dam Eye Study
- Framingham Eye Study
- Los Angeles Latino Eye Study
- Numerous Others

But some haven’t shown the relationship
**POSSIBLE REASONS DIABETES IS A RISK FACTOR FOR GLAUCOMA**

- Widespread vascular dysfunction
- Localized vascular dysfunction at the optic nerve
- Oxidative damage
- Diabetes medications
- Diabetics get more eye exams

**THE BLAME GAME**

- Diabetes
- Migraine
  - Collaborative Normal Tension Glaucoma Study identified migraine as a risk factor for NTG
- Sleep Apnea

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**THE BLAME GAME**

- Diabetes
- Migraine
- Sleep Apnea

After all, can’t just about everything be blamed on these three?

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Impaired blood flow in OSA
**Systemic Complications of OSA**

- HTN
- Type 2 DM
- Congestive Heart Failure
- Coronary Artery Disease
- Atrial Fibrillation
- OSA is an independent RF for stroke.

**SLEEP APNEA AND GLAUCOMA**

- Sleep apnea is a recognized risk factor for cardiovascular and neuro-vascular disease
- Creates profound changes in oxygenation, circulatory hemodynamics and inflammatory factors
- Sets up bouts of repeated episodic hypoxia
- Perhaps a risk factor for glaucoma – Why?
  - Hypo-oxygenation of blood and sympathetic vasoconstriction may lead to optic nerve hypoxia
  - Should we include this as a risk factor consideration?

**GLAUCOMA PREVALENCE IN OBSTRUCTIVE SLEEP APNEA**

Glaucoma prevalence: 5.7-27%

**OBSTRUCTIVE SLEEP APNEA PREVALENCE IN GLAUCOMA**

OSA prevalence: 20-55%

**NEGATIVE STUDIES**

*The Assessment of Sleep Apronea as a Risk Factor in Glaucoma*
CEREBROSPINAL FLUID PRESSURE

- Optic nerve and sheath are a compartment
- CSF pressure can impact blood flow
- Low CSF seen in pts with glaucoma at lower levels of IOP
- Systemic nocturnal hypotension leads to lower CSF?
- Elevated IOP with normal CSF causing same problems?

CEREBROSPINAL FLUID PRESSURE (CSF)

- Studies have shown that the anatomy of the optic nerve head including the intraocular pressure, the anatomy and biomechanics of the lamina cribrosa and peripapillary sclera, retrobulbar orbital cerebrospinal fluid pressure and the retrobulbar optic nerve tissue pressure may be of importance for the pathogenesis of open angle glaucoma
- Low cerebrospinal fluid pressure may play a role in the pathogenesis of normal (intraocular-) pressure glaucoma

CSF AND GLAUCOMA

- Recent clinical studies reported that patients with normal pressure glaucoma had lower cerebrospinal fluid pressure and a higher trans lamina cribrosa pressure difference when compared to normal subjects.

ASSESSING THE RISK FACTORS

- IOP- yes, diurnal variation- no
- Family history
  - Likely yes, if close and real
- Thin cornea- yes
- Low OPP
  - Likely, in some patients
- Diabetes
  - Likely yes
- Migraine
  - Possibly
- Sleep Apnea
  - Yes if you want it, no if you don’t
- Low CSF pressure
  - Possibly, but what does it matter?

POAG: FINAL RULES

- Take the appropriate amount of time and collect the appropriate amount of information prior to making a diagnosis. Do not rush to make a diagnosis.
- Don’t rely on a single field or tonometry
- Insist that the nerve match the field
- Don’t forget gonioscopy
- Consider risk factors
- Consider risk of visual disability
- Don’t neglect other causes
  - Undiscovered secondary glaucoma
  - Meds - both past and present
  - It may not be glaucoma
Optic Disc Evaluation for Glaucoma

Glaucoma Suspect Based upon Disc Appearance

- Larger discs will have larger cups, but rims are intact
  - Glaucoma is over-diagnosed in larger discs and under-diagnosed in smaller discs

Evaluating the Disc in Glaucoma

- Characteristic glaucomatous neuropathy
  - Focal rim damage, not generalized concentric enlargement
You talk about glaucoma in cup-to-disc ratios

Critical Disc Evaluation
- Size
- Rim color
- Focal rim defects (notching)
- Hemorrhages
- RNFL defects
- Parapapillary atrophy
Notching/focal rim loss

"Abnormal" bean potting

Bayonetting

normal

abnormal

Image 1

Image 2

Image 3

Image 4

Image 5

Image 6
Disc Hemorrhages

- Inferior, inferior temporal, superior, and superior temporal regions of the disc are most susceptible and account for virtually all true glaucomatous disc hemorrhages
- Typically occurs where notches and RNFL defects occur

Hemorrhages at other areas of the disc (nasal and temporal) tend to not be associated with glaucoma.
Structural/Functional Relationship in Glaucoma as the Disease Progresses

- Visual field changes occur later in the disease.
- The optic disc often changes before visual fields.
- The RNFL often is the first change in glaucoma.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Loss</th>
<th>VF</th>
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<tbody>
<tr>
<td>Early</td>
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<td>Moderate</td>
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<tr>
<td>Severe</td>
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</table>
Less-Critical Disc Evaluation

- Bean-potting
- Vessel baring (baring of a circumlinear vessel)
- Nasalization
- Laminar dot sign
NOT ALL ‘OMAS’ ARE GLAUCOMA; OTHER THINGS CAUSE ‘CUPPING’

- Pituitary adenoma
- Craniopharyngioma
- Meningioma
- Ischemioma
  - Anterior ischemic optic neuropathy (AION)/Retinal infarcts
- Retinaloma
- Congenitaloma
- Coincidentaloma
- Misdiagnosoma

“THE CUPPED DISC: WHO NEEDS NEUROIMAGING?”

- Patients with glaucoma were:
  - Older
  - Better visual acuity
  - Greater vertical loss of neuroretinal rim
  - More frequent disc hemorrhages
  - Less neuroretinal rim pallor
  - Field defects along the horizontal


“THE CUPPED DISC: WHO NEEDS NEUROIMAGING?”

- Patients with mass lesions:
  - Visual acuity less than 20/40
  - Vertically aligned visual fields defects
  - Optic disc pallor in excess of cupping
  - Age younger than 50 years


MORE INDICATIVE OF A COMPRESSIVE MASS LESION THAN GLAUCOMA

- Younger age
- Lower levels of visual acuity
- Vertically aligned visual field defects
- Neuroretinal rim pallor

Ode To a Cupped Disc

Oh, to have a cupped disc pink.
That my friend hath a glaucomatous stink.
But to have a cupped disc pale,
Call this glaucoma and you shall fail.
Disc and field damage that is one-sided
Simply cannot be abided.
It might be trauma, infarct or meningioma.
But if the rim is cut always remember,
Nothing notches a nerve like glaucoma.