Glaucoma: Non-IOP Mechanisms

IOP Dependent and Independent Mechanisms in Glaucoma

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Objectives

1. Understand the basis of high IOP mechanisms in glaucomatous optic neuropathy
2. Understand the relationship between blood pressure and IOP as defined by ocular perfusion pressure
3. Understand the relationship between cerebrospinal fluid pressure and optic neuropathy
4. Understand non-pharmacological measures in contemporary glaucoma management

Overview

- Non-IOP Risk Factors
  - Genetics, Diabetes, Lifestyle Factors
- Ocular Perfusion Pressure
  - disclaimer: partially IOP related
  - systemic blood pressure
- Obstructive Sleep Apnea
- Cerebrospinal Fluid Pressure
  - The next "BIG" thing
- Nutrition, exercise and lifestyle in glaucoma: a literature review

CASE MZ

72 years old
High Cholesterol
IOP range 17-20mmHg OD, OS
+ Family History
CCT= 550 microns OD, OS

What other History might be important?

- Family History
- Ocular History
  - Topical steroid use
- Medical History
  - Diabetes
  - Systemic Hypertension

Disclosures

- Michael Chaglasian has the following disclosures:
  - Advisory Boards:
    - Allergan, Inc., Alcon Labs, Carl Zeis Meditec
- The content of this presentation is in no manner influenced by any of the aforementioned parties or companies

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Glaucoma: Non-IOP Mechanisms

Disc Photos

Visual Fields

IOP Is the Most Prominent and Consistent Glaucoma Risk Factor

- Ocular Hypertension Treatment Study (OHTS)
  - CCT of less than 555 μ has higher risk
  - IOP: every 1mmHg higher (>22) increased risk by 10%
- Early Manifest Glaucoma Trial (EMGT)
  - Every 1mmHg of IOP reduction lowers risk of progression by 10%
- Advanced Glaucoma Intervention Study (AGIS)
  - IOP always under 18mmHg or a mean of 12mmHg has a lower risk of progression
- Collaborative Normal-Tension Glaucoma Study
  - 30% reduction of IOP reduces risk of progression
Glaucoma: Non-IOP Mechanisms

**Mechanism Of IOP and Axonal Damage**

- Partial ischemia of disc
- Axonal damage
- Ganglion cells

**Mechanism Of IOP Damage**

- IOP
- Peripherally originating fibers
- Proximally originating fibers
- Larger laminar plexus at the defect area
- Lamina cribrosa

**Progression of Excavation**

- Normal optic nerve
- Optic nerve
- Optic cup
- Optic disk
- Early glaucoma
- Optic disk
- Optic cup
- Early damage
- Advanced glaucoma
- Optic disk
- Optic cup
- Severe damage

**Paradox**

- 90% of patients with elevated IOP DO NOT develop glaucoma
- 30-50% of patients with glaucoma DO NOT have IOP over 21 mmHg

**Factors Affecting IOP**

- Exercise can provide a transient 20% decrease.
- Alcohol and marijuana lower IOP – though very transiently and unpredictably.
- Steroids (topical/oral) increase IOP.
- Caffeine has NO effect.
- External pressure on eye (lids, fingers)
- Elevated body temperature, raises IOP.
- Numerous hormonal influences.
IOP is Positional

Lying down raises IOP (2-4 mmHg), by increasing episcleral venous pressure and causing a decrease in aqueous outflow.

Factors Affecting IOP

- Lying down raises IOP (2-4 mmHg), by increasing episcleral venous pressure and causing a decrease in aqueous outflow.
  - Supine position, Postural / Positional effect

IOP is Positional

Intraocular Pressure Changes and Ocular Biometry During Sirsasana (Headstand Posture) in Yoga Practitioners

*Ophthalmology* 2006; 113:1327-1332.

**Conclusion:** There was a uniform 2-fold increase in the IOP during Sirsasana, which was maintained during the posture in all age groups irrespective of the ocular biometry and ultrasound pachymetry. We did not demonstrate a higher prevalence of ocular hypertensives in this cohort of yoga practitioners nor did the risk factors contributing to glaucoma show any correlation with magnitude of IOP raise during the posture.

“New” Risk Factors

- 24 Hour IOP
- Fluctuation of IOP
- Ocular Perfusion Pressure

Nocturnal IOP and Glaucoma

- Most individuals spend 1/3rd of day asleep in recumbent position
- Habitual IOPs of most untreated glaucomas higher during nocturnal/sleep period than office hours
  - IOP measured sitting during day and supine position at night
- Important to understand and recognize this
  - May explain why glaucomatous damage occurring in certain individuals
Our Understanding of Diurnal and Nocturnal IOP Has Been Expanded By Recent Studies

How to Measure Nocturnal IOP

- Pneumatonometer:

Sleep in Head Up Position

New Risk Factors to Consider in Glaucoma:

- Ocular Perfusion Pressure
  - definitions
  - clinical studies
  - impact of topical medications
Ocular Perfusion Pressure

- The differential between arterial BP and IOP
  - Ocular perfusion is regulated to maintain constant blood flow to the optic nerve despite fluctuating blood pressure and IOP
  - The major cause of reduced blood flow is thought to be secondary to vascular dysregulation in susceptible patients, resulting from abnormal auto-regulation
    » Adjustment of blood flow into anterior optic nerve in response to changes in BP and IOP

Ocular Perfusion Pressure (OPP): Terminology

- OPP – Ocular Perfusion Pressure
- SPP – Systolic Perfusion Pressure
- DPP – Diastolic Perfusion Pressure
- MPP – Mean Perfusion Pressure

OPP and Glaucoma: Hemodynamics

- SPP = SBP – IOP
- DPP = DBP – IOP
  - easiest to use, good evidence
- MPP = 2/3 mean arterial pressure – IOP
  - Arterial Pressure = DBP + 1/3 (SBP – DBP)
  - May best reflect perfusion physiology

OPP and Glaucoma: Impact of IOP and BP


Higher IOP Negatively Impacts Perfusion Pressure

Evidence Supporting Role of OPP in Glaucoma

- Clinical studies
- Epidemiologic studies
  - Cross sectional and cohort
  - Clinical trial cohort

The Baltimore Eye Survey

- Cross sectional study of African Americans and Caucasians in Baltimore, MD.
- Lower OPP strongly associated with prevalence of primary open angle glaucoma (POAG).
- Six-fold excess of POAG in subjects with lowest category of OPP.

DOPP: Proyecto Ver

- Cross-sectional study of Hispanics in Nogales and Tucson, AZ.
- Found lower DPP associated with increased risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.
**Los Angeles Latino Eye Study: Ocular Perfusion Pressure**
- Cross-sectional study of 6,357 Latinos, >40 years in Los Angeles, CA.
- Persons with low diastolic and systolic perfusion pressures had a higher risk of POAG.
- DOPP <50 mmHg, the prevalence of glaucoma rapidly increases linearly.

**OPP and Glaucoma: Newest Evidence**
- Barbados Eye Study (BES):
  - 9-Year Risk Factor Study
- The Early Manifest Glaucoma Trial (EMGT):
  - Predictors for Long-term Progression

**Barbados Eye Study: 9-Year Follow-Up**

**Studies Summary**
- These large studies provide strong evidence among different populations for the relationship between vascular deficits and the prevalence, incidence and progression of glaucoma.
- Some Limitations,
  - no direct measure of ocular blood flow
  - Varied definitions of hypertension

**Clinical Control of OPP**
- Lower IOP improves OPP
- Remains number 1 goal !!
- Measure blood pressure on your patients
- Higher systemic BP improves OPP, but you do not necessarily want to raise BP:
  - Stroke #3 cause of death in US behind CVD & CA!
  - Avoid drugs that lower systemic BP beyond patient’s desired systemic control.
  - Avoid nocturnal hypotension.
  - Communicate with PCP

**Nocturnal Hypotension and OPP**
- Low blood pressure (BP) at night, coupled with high IOP in supine position, compromise OPP.
  - ? Up to 50% of patients with HTN
  - Using systemic BP meds in the AM to minimize nocturnal hypotension makes sense.
- Using IOP lowering drugs that lower IOP while sleeping makes sense.
  - Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense.
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24 Hour Blood Pressure

- 24 Hour Monitor

24 Hour Blood Pressure

- Supine
- Sitting

Brimonidine Neuroprotective?

Overview:
- to compare brimonidine to timolol maleate in preserving visual function in low-pressure glaucoma
- randomized, double-masked, multicenter clinical trial

Outcome
- Low-pressure glaucoma patients treated with brimonidine who do not develop allergy are "less likely to have field progression than patients treated with timolol."

- AJO Mar 2011

Case WS

- 75 yo male
- + HTN w/ multiple BP meds x 20+ yrs
  - 105/68 in office
  - 5’5”, 142 lbs
- CCT= 532µ

- Initial IOP 23 mmHg
  - Now repeatedly 11-13 mmHg over 5+ years

- Current Medication:
  - PGA

- Good compliance and follow up
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Case

- Q= What is the Explanation?
- Compliance?
- Other Potential Risk Factors:
  - 24 Hour IOP
    - IOP of 12 mmHg @ 2PM = ?? @ 2AM ~ 18 mmHg
  - DOPP
    - DBP of 68 mmHg @ 2PM = ?? @ 2AM ~ 58 mmHg
  - ? DOPP @ 2AM = 58 - 18 = 40 mmHg

Latanoprost Reduces Noct/Diurnal IOP. Timolol has No effect during Nocturnal period.

Case WS

- Is there anything else that can be done?
- **Possibly:**
  - Offer Nocturnal IOP control
  - Offer Improved DOPP

  **Add a CAI BID**

  **Letter to PCP, explain OPP and Low BP related Risk**

  **? Adjust BP Meds**

Summary: OPP and Glaucoma Progression

- Low ocular perfusion pressure (OPP) is an important risk factor for glaucoma
- OPP is amenable to modification by lowering IOP and improving perfusion pressure
- New strategies are needed to take advantage of this modifiable risk factor


Obstructive Sleep Apnea and Glaucoma

OSA – Daytime Symptoms

- Sleepiness
- Chronic fatigue
- Decreased cognition
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OSA and The Eye

- Associations:
  - Glaucoma
  - NAION
  - Papilledema
  - Floppy eyelid syndrome

Sleep Apnea: Association

- 0% (0 of 2) - younger than 45 years,
- 50% (3 of 6) - 45–64 years,
- 63% (5 of 8) - older than 64 years
- Inquire about in high risk patients.

Sleep Apnea: Not a Risk Factor

Conclusions: This nested case-control study does not support a large impact of sleep apnoea on the eventual development of glaucoma relative to other putative risk factors.

Sleep Apnea: No Relation to Glaucoma

- RESULTS: Among the 2,590,961 individuals in the study, 1,566 (6.0%) had 1 or more sleep apnoea diagnoses. The hazard of open-angle glaucoma was no different among persons with sleep apnoea either treated (adjusted hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.82 to 1.18) or untreated with continuous positive airway pressure (HR, 1.01; 95% CI, 0.99 to 1.03) and individuals without sleep apnoea. Similar findings were observed when assessing the hazard of normal-tension glaucoma developing (P > .05 for both comparisons). A significant

Issues with Data/Conclusions

- Failure rate of beta blockers
  - much higher than our collective clinical experience: EMGT, OHTS
  - Extrapolating the Kaplan-Meier survival graph to 5 years would predict a 100% progression rate for the patients taking timolol
- Side effect rate of brimonidine
  - ~30% drop out due to side effects (0.2%)
- Degree of IOP lowering in treatment groups
  - Approximately the same between the 2 drugs

Still Another “Pressure”
A pressure imbalance between the two circulating fluids of the nervous system may be the cause of glaucomatous damage to the optic nerve.

- The ICP is lower than normal in POAG and NTG and elevated in OHT.
- Findings suggest that an elevated ICP in OHT may counterbalance the high IOP, thus potentially preventing or slowing glaucomatous damage to the optic nerve.
- Conversely, a reduced ICP in patients with NTG may increase their risk of developing glaucoma.
Cerebrospinal Fluid Pressure and Glaucoma

- Questions to address
  - Do all POAG patients have low CSF?
  - Conversely do all patients with low CSF develop POAG?
  - Does CSF pressure measured by lumbar puncture represent CSF pressure in the optic nerve subarachnoid space?
    - Is the optic nerve subarachnoid space CSF Pressure really low in POAG?
  - How would we diagnose and treat POAG patients in context of a low CSF?
    - Is there any non-invasive method to explore the orbital CSF pressure?

Other lifestyle considerations in glaucoma

- Yoga – inverted postures detrimental based upon currently available evidence
  - 7 PubMed papers RE Sirasana
- Aerobic exercise – seems to lower IOP
  - High variability among studies

Controversial topics in lifestyle-associated glaucoma management

- Stress reduction
- Meditation
- Cold avoidance
- Dietary supplementation
- Avoid dramatically low body weight/fat
- Avoid major fasting periods

Mechanism of Glaucoma has gotten complicated:

![Diagram](image)

Summary

- What to do Now:
  - Measure IOP much more frequently.
  - Consider situations of low IOP:
    - Thin Central Corneal Thickness.
  - Record Medical History and Systemic Medications
  - Measure Blood Pressure, Calculate Ocular Perfusion Pressure.