Conversations in Glaucoma

Joseph J. Pizzimenti, O.D.
pizzimen@nova.edu

Carlo J. Pelino, OD
Cpelino@salus.edu

Course Goals

- To provide clinically relevant information about the glaucomas
  - Topical discussion
  - Case Examples
  - Emphasis on current standards of care
    - Best evidence

The Visual Pathway

- Optic Nerve
- Optic Chiasm
- Optic Tract
- Lateral Geniculate Nucleus
- Optic Radiations
- Visual Cortex

Intraocular Optic Nerve

- AKA “Optic Nerve Head”
- Nerve Fiber Layer
  - Unmyelinated axons
  - Allow max light transmission to photoreceptors
  - Coalesce into bundles as they enter ONH
- Lamina Choroidalis
  - Glial cells with intertwining cell processes
  - Nerve fibers enter ONH and turn to exit the globe at level of choroid

Glaucoma as a Visual Pathway Disorder

Glaucoma as an Optic Neuropathy
Functional Anatomy

- The Optic N. links the eye with the Central Nervous System (CNS).
- Composed of retinal ganglion cell axons that synapse in the lateral geniculate nuclei (LGN).
Aqueous Production in the Ciliary Body

- 75% of aqueous exits through the trabecular meshwork (TM).
- 25% of aqueous exits through uveoscleral channels (Prostaglandins).

Understanding Aqueous Dynamics and the Uveoscleral Pathway

Acute Angle Closure

- Normal aqueous outflow
- Iris pushed forward in Acute Angle Closure (ACG)
- LPI is definitive treatment

New Weight Loss Drug: Qsymia

- Contains topiramate and phentermine
- Myopic shift
- Angle closure

Topiramate

- Narrow anterior chamber angle secondary to ciliochoroidal effusion
Case Studies in the Glaucomas

Case: S.S.
53 y/o BF
CC: Near blur OU
Excellent health, no meds
Exam Findings
- BCVA: 20/20 OD, OS
- PERRL, APD neg
- Blood Pressure: 132/81 mmHg
- TAP: 12mmHg OD/OS @ 3:45pm
- C/D: .65/.65 OD .65/.75 OS
- No disc pallor or edema OD/OS

ON/NFLA Exam OD

ON/NFLA Exam OD

ON/NFLA Exam OS

ON/NFLA Exam OS
**The Glaucomas Defined**

A family of diseases that share an acquired optic neuropathy characterized by:
- Slowly, progressive death of retinal ganglion cells with
- Excavation of the optic disc (cupping) and
- Sequential visual field loss that starts in the mid-periphery

HARRY A. QUIGLEY, MD
Johns Hopkins University’s Wilmer Eye Institute
1997

**Early Diagnosis**

“The best time to diagnose glaucoma is in the pre-perimetric phase. Then, the patient only needs one drop and your targets (IOP) don’t need to be as aggressive”.

Lawrence Stone, MD
Chicago, IL

**The Glaucoma Continuum**

- Multifactorial optic neuropathy in which there is characteristic acquired loss of ganglion cells.
  - Makes room for ON damage (cupping/neuroretinal rim/NFL loss) **without visual field loss**
  - 2003 American Academy of Ophthalmology

**Newer Glaucoma Definition**

Weinreb RN et al. AJO. September 2004.
Combo Definition

• The glaucomas are a multifactorial family of diseases...
• that share an acquired optic neuropathy characterized by...
• acquired loss of retinal ganglion cells that is slowly progressive.

What factor does not appear in the glaucoma definition?

Important Note:

The prevalence of Ocular Hypertension at any age is always greater than the prevalence of glaucoma by a 10 to 1 ratio.

Therefore, a clinician will always have more glaucoma suspects than glaucoma patients.

Is IOP yesterday’s news?

• No!
• IOP is the only clinical risk factor that has been able to be successfully manipulated to date.
• Highest IOP is in the early morning.
• Lowest BP is in the early morning.
• Poor ocular perfusion
• IOP declines during the day.
• Lowest IOP is at night.

Questions and Comments?

Pathophysiology

Mechanical Compression Theory

• Abnormally high IOP causes direct damage to the optic nerve head, fibers.
• Elevated IOP causes a backward bowing of the lamina cribrosa, kinking the axons as they exit through the lamina pores.
• This may lead to focal ischemia, deprive the axons of neurotrophins, or interfere with axoplasmic flow, triggering cell death.
Pathophysiology

- Apoptosis Excitotoxicity Theory
  - Genetically-programmed cell death
  - Elevated IOP and/or Reactive Oxygen Species (ROS) may precipitate the production of excessive glutamate
  - Glutamate kills retinal ganglion cells via neurotransmitter excitatory toxicity.

Pathophysiology

- Vascular/Ischemic Theory
  - Cell death is triggered by ischemia, whether induced by elevated IOP or as a primary insult.
  - Onset of vascular dysfunction causing insufficient blood supply to nourish the nerve fiber layer and/or optic nerve.
Vascular/Ischemic

- Ocular Perfusion Pressure (OPP)
  - Poor (low) ocular perfusion leads to tissue ischemia, resulting in glaucomatous optic neuropathy.
- Vasoprotection
  - Prevention of damage resulting from vascular dysfunction.

Sehi M, Flanagan JG, Zeng L

Ocular Perfusion Pressure (OPP)

- OPP has 2 components:
  - Mean brachial artery blood pressure:
    - \( BPm = \frac{2}{3} DBP + \frac{1}{3} SBP \)
  - Intraocular pressure (IOP)
- Ocular perfusion pressure (OPP):
  - OPP = \( \frac{2}{3} BPm - IOP \)
- Modified formula
  - OPP = DBP - IOP

OPP = DBP - IOP

Decreased OPP can result from:
- Increased IOP
- Decreased DBP

Take-home on OPP

- Therefore, BP and HR should be checked on all GLC suspects and patients at each visit.

Example:

DBP = 60 and IOP = 15

OPP = 45

OPP < 50 is a risk factor for glaucoma/progression

Sehi M, Flanagan JG, Zeng L
Intracranial Pressure and IOP

The optic nerve travels through two pressurized regions: the intraocular/orbital space and the intracranial space. Recent studies have shown that ICP is lower in patients with OAG and NTG. Conversely, ICP appears to be higher in patients with ocular HTN. The relationship between IOP and ICP may play an important role in the development of glaucoma.

Large Normal Optic Disc

In normal eyes, the size of the optic cup increases with the size of the optic disc. The neuroretinal rim is widest in the inferior disc region, followed by the Superior and the Nasal disc sector. It is smallest in the Temporal disc region (ISNT rule).

Disc/NFLA/GCC Changes

- Narrowing of neuroretinal rim, particularly in infero-temporal or the supero-temporal sectors.
- RNFL Dropout
  - Decreased visibility of the nerve fiber layer, often seen as a change in the normal rank of visibility: infero-temporal > supero-temporal > supero-nasal > infero-nasal.
  - Localized defects in the nerve fiber layer.
- Ganglion Cell Loss at the Fovea (OCT)
- Early damage may be overlooked in small discs.

Optic Nerve Size

Size of cup varies with size of disc
Large discs have large cups in healthy eyes

Identify small and large optic discs
Small discs: avg vertical diameter <1.5 mm
Large discs: avg vertical diameter >2.2 mm
Signs of Optic Nerve Damage
- Cup/Disc ratio asymmetry between the eyes of 0.2 or greater in either H or V
- Concentric enlargement of cupping
- “Notching” of the neuroretinal rim
- Optic disc hemorrhage (Drance Hemorrhage)
- A sign of progression
- Acquired Optic Pits
- Peripapillary Atrophy (Alpha and Beta Zones)

Beta zone peripapillary atrophy is more closely associated with visual field loss and neuroretinal rim loss in patients with glaucoma.

In ocular hypertensives, the Inferior/Temporal of the optic nerve is most likely to sustain damage when that eye converts to frank glaucoma.
Asymmetry greater than 0.2 in C/D is found in only 1% of normal pop.; thus highly indicative of glaucoma.

Glaucoma Quiz

- Optic disc hemorrhages are most often associated with:
  a. Notching of neural rim
  b. Bean-potting
  c. Disc pallor
  d. Small c/d ratio

Disc hemmases are more ominous in Normal Tension GLC

Drance Hemorrhages tend to occur at disc margin or on neuroretinal rim, as opposed to hemess from PVD or HTN.
Glaucomatous Cupping

Inferior disc heme—>Inf NFL d/o will produce a superior VF defect

Pallor of the neuroretinal rim is 90% specific for non-glaucomatous optic atrophy.

Questions and Comments?

There is great clinical value in combining perimetry with OCT.¹


Fourier (Spectral) Domain-OCT Glaucoma

Laser Image

Thickness Map

Cross-section

Deviation Map

Scanning Lasers Pre-OCT
2-D and 3-D volumetric data cubes

TSNIT w/comparison

Analysis Elements

Optic Nerve Head calculations are presented in a combined report with RNFL thickness data. Key parameters are displayed in table format.

### Analysis Elements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OD</th>
<th>NV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average RNFL Thickness</td>
<td>10 µm</td>
<td>15 µm</td>
</tr>
<tr>
<td>RNFL thickness (mm)</td>
<td>0.5 mm</td>
<td>0.7 mm</td>
</tr>
<tr>
<td>Disc area (mm²)</td>
<td>1.2 mm²</td>
<td>1.6 mm²</td>
</tr>
<tr>
<td>Cup area (mm²)</td>
<td>0.3 mm²</td>
<td>0.5 mm²</td>
</tr>
<tr>
<td>Vertical CD ratio</td>
<td>0.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Cup Volume (mm³)</td>
<td>0.33 mm³</td>
<td>0.27 mm³</td>
</tr>
</tbody>
</table>

Ganglion cell analysis

The Structure/Function Debate

- Disc cupping and nerve fiber layer losses of up to **40%** have been shown to occur prior to actual visual field deficits.
- In OHTS, conversion to GLC was first manifested by neuroretinal rim changes.

Do we still need VF in GLC diagnosis/management?

- Yes. VF analysis is here to stay and improving.
  - Functional testing helps confirm diagnosis and guide treatment.
  - VF cannot be the sole test used to determine when a patient has undeniable glaucomatous damage, and it should not be used in isolation as the benchmark for treatment.
Automated threshold testing (eg, Humphrey 24-2) is still the “gold standard” to rule out any glaucomatous visual field defects.

Which one is best for my practice?

Emerging VF technologies and algorithms may enable detection of NFL loss at an earlier stage
- SITA-SWAP (Blue/Yellow) Testing
- FDT (Frequency Doubling Threshold VF)
- FDF (Flicker Defined Formed) “Edge” Perimetry

Consider these modalities when SAP results are normal, but you still suspect glaucomatous damage.*
FDT Then….

And Now….

2003

Chinrest adds stability and accuracy --->

2013

FDT

Frequency Doubling Technology

Humphrey Matrix Perimeter

FDT test results correlate with SAP and can detect defects earlier.

Higher Sensitivity of FDT Compared to SAP

Frequency Doubling Theory

- Retinal nerve fibers classified into:
  - ____-cellular
  - (or M-cells)
  - ____-cellular
  - (or P-cells)
- Selective perimetry (FDT/HEP) targets M-cells.

Frequency Doubling Theory

- "non-linear" M-cells are usually the first to die in glaucoma.
- FDT specifically tests for visual field loss due to M-cell neuron death.

Right Eye Single Field Analysis

FDT

Standard

-
FDF Perimetry

- The Heidelberg Edge Perimeter (HEP) uses a flicker-defined form (FDF) stimulus that selectively stimulates M-cells.

Edge Perimeter Printout

SITA-SWAP

Blue-Yellow Perimetry

Humphrey Field Analyzer

SITA-SWAP

- Blue-Yellow
- Detects early damage several years before present on SAP
- Now faster with SITA-SWAP

Glaucoma Quiz

Because of the unique anatomy of the retinal nerve fiber layer, glaucomatous damage causes characteristic:

a. Diffuse visual field defects
b. Localized defects
c. Hemianopic defects
VF Loss

Back to our patient…

What is your assessment at this point?

What is your plan?

Case Report: S.S.

Assessment
- Glaucoma Suspect OS>OD
- Inf/Temp notch OS w/NFL D/O
- NFL D/O OD

Plan
- RTC for in the AM for:
  - TAP
  - CCT
  - Gonio
  - VF
  - Scanning laser NFLA imaging

Gonioscopy:

Documentation should include the following:

- Identify all structures seen
- Grade amount of pigment in trab meshwork
- Note any abnormalities

Gonioscopy:
Corneal Thickness

CCT in OHTS

The Ocular Hypertension Treatment Study (OHTS) showed CCT to be a powerful predictor of development of glaucoma. Eyes with CCT of 555 microns or less had a threefold greater risk of developing glaucoma than those w/CCT > 588 microns. Mean CCT in OHTS was 578. Analysis of the subgroup of African Americans showed that the mean CCT was 555.

Plan

Next visit:
- TAP: 14mmHg OD/OS @ 7:00am
  12/14 @ 8:00am, 12/13 @9:00am, 13/13 @10:30
- Subsequent visits revealed highest IOP at 14 mmHg
- CCT: 522 OD/508 OS
- Gonio: all angles open to SS/CB w/no abnormalities
- VF
- Scanning laser NFLA imaging

OD
24-2 SF

OS
24-2 SF
What is your final diagnosis?

Does this patient have GLC?
If so, what kind?

What is your plan?

Treat one eye?
Treat both eyes?
Monitor w/o Tx?

Actual Management
- Prostaglandin analogue
- 1 gt hs OD and OS
- RTC 1 mon
- TAP 10 mmHg OD and OS 9 mmHg
- 1 year later, no progression

Normal Tension Glaucoma
- Glaucomatous optic nerve head abnormalities and sequential visual field loss without a documented Hx. of IOP above the "normal" range (no recorded pressure over 24 mmHg in either eye).
- CNTGT
Ocular Hypertension and Normal tension are not clinical entities. They are meaningless statistical constructs.

Von Graefe concluded that all glaucoma optic nerves were associated with high pressure based on finger tension.

Samples from older European derived populations.

IOP without POAG had a mean of 15. Less than 2% of the general population was expected to have IOP greater than 21 or 22. Uncommon had become abnormal.

Population surveys found a number of patients normal IOP, NTG entered as a clinical entity.

Questions and Comments?

The future of glaucoma management lies in treating what causes glaucoma instead of what glaucoma causes.

Conclusions

- Glaucoma is both a medical and a surgical disease.
- The “art” of effective GLC management is to individualize treatment, being sensitive to patient’s psycho-social makeup and QOL issues.
- The “science” of effective GLC management is based on the best current evidence and technology in combination with “old school” clinical skills.

Percentage of eyes with POAG and screening IOP lower than 22 mm Hg

<table>
<thead>
<tr>
<th>Study</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltimore Eye Study</td>
<td>59%</td>
</tr>
<tr>
<td>Beaver Dam Eye Study</td>
<td>32%</td>
</tr>
<tr>
<td>Melbourne VI Project</td>
<td>39%</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>39%</td>
</tr>
</tbody>
</table>

If the prevalence (risk) of glaucoma increases in patients with higher IOP, how can half the patients with POAG have a screening IOP lower than 22 mm Hg?

Because the vast majority of the population has IOP<22

Thank you!
Carlo and Joe