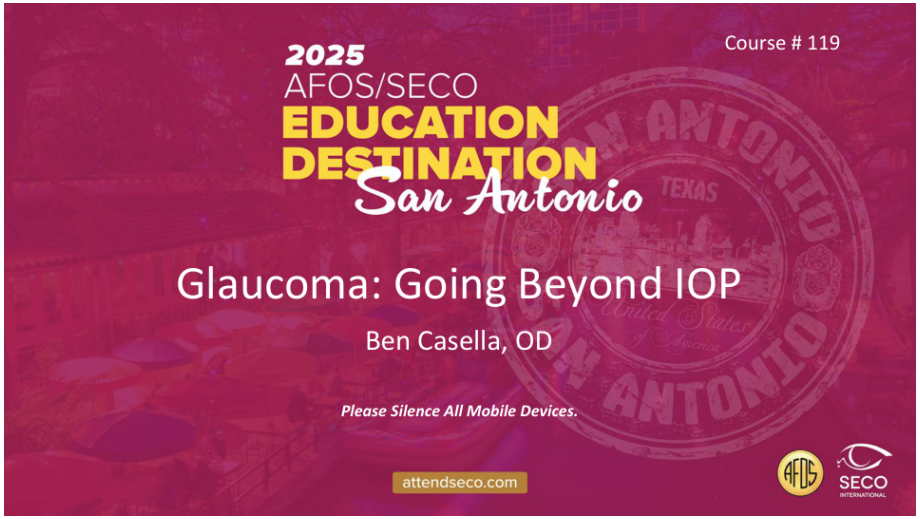
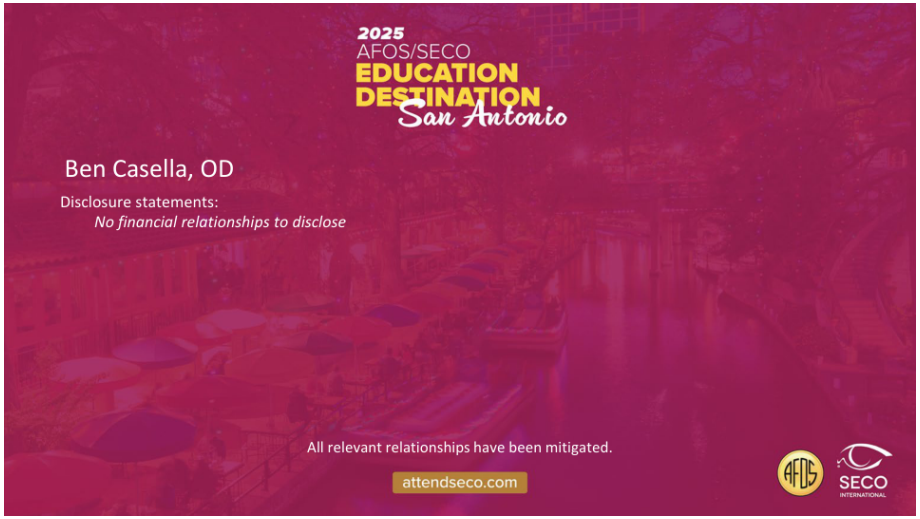
Slide 1



Slide 2



Slide 3

Glaucoma: Going Beyond IOP

Benjamin Casella, O.D., FAAO

Slide 4

Disclosures

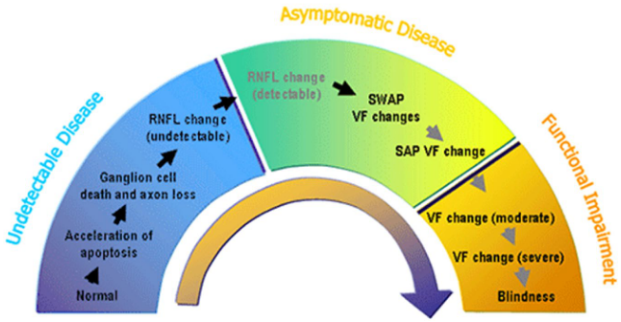
- None

Slide 5

Glaucoma Defined

- Acquired
- *Family* of neuropathies
- Excavation of the ONH
- Retinal ganglion cell death
- Visual field loss

Slide 6



Weinreb RN et al. Amer. Journal Ophth. Sept. 2004.

Slide 7

Glaucoma Defined

- What's missing from the definition of glaucoma?
- IOP!

Slide 8

Glaucoma: so much more than IOP

- Increased IOP is the number one risk factor for the development and progression of glaucoma
- It's also one of the only *modifiable* risk factors!

Slide 9

Other risk factors

- Increasing age
- Female gender
- Sub-Saharan African descent (more so for POAG)
- Asian descent (more so for CACG)
- Northern European descent (more so for pseudoexfoliation)
- Genomic/genetic predispositions

Slide 10

Other risk factors

- Thin central corneas!!!
- Glial cell dysfunction

Slide 11

Other risk factors

- Caffeine correlated with increased incidence of glaucoma
- Alcohol intake correlated with increased IOP in a linear fashion

Slide 12

Epidemiology

- 80 million affected worldwide
- Expected to rise to 110 million by 2040
- Major cause of blindness despite treatment
- Current worldwide incidence of 3.54% of individuals between ages 40-80

Slide 13

Reasons for blindness

- No diagnosis
- Delayed diagnosis
- Ineffective treatment
- Non-compliance

Slide 14

- Advanced disease at initial presentation correlates strongly with progression despite low IOP with treatment regimen
- Worldwide, as many as 15-20% unilaterally blind 20 years after diagnosis was made
- CNGT Study found 20% progressed despite a 30% IOP reduction
- Whole-brain MRI studies of NTG patients show 16-20% have micro-infarcts in their cerebra

Slide 15

IOP Control

- To date, there is no glaucoma treatment proven that it should come before lowering IOP
- Current IOP medications / classes
  - Newer combinations
  - Newer classes
  - Some medications have quietly gone generic

Slide 16

IOP Control

- MIGS
  - Microscopic devices to increase aqueous outflow

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IOP Control

- Laser treatment
  - LiGHT Study
    - SLT effective and affordable in the U.S.

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Non-IOP Pressures

- Episcleral venous pressure
  - Pressure in veins/venules of the episclera
  - Also measured in mmHg
  - Typically bottoms out around 8-10mmHg on average
  - Acts as pressure barrier to IOP
  - Affects aqueous drainage rates in a linear fashion
    - Rate-limiting step for IOP reduction

Slide 19

EVP

- Typically 8-10mmHg
- Can be elevated for a number of reasons
  - Cardiovascular disease
  - Vasculitis
  - Tumor
  - Thyroid ophthalmopathy
  - CHF
  - Thrombosis
- Can mimic conjunctivitis (corkscrew appearance to venules)

Slide 20

EVP

- Rise in EVP of 0.8mmHg +/-0.2mmHg correlates to a 1mmHg rise in IOP
- EVP can be transiently affected by changes in head position

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Lowering EVP

- Rho-kinase inhibitors may lower EVP in addition to lowering IOP
- Intracameral bimatoprost causes enhanced venous outflow by selectively dilating episcleral venous system without affecting arteries or A-V anastomoses
  - *Topical* prostaglandin analogs dilate venous and arterial system

Slide 22

Lowering EVP

- Cromakalim prodrug (CKLP1)
  - Opens ATP-sensitive potassium channels
  - Net result is lower EVP
    - Thus, lower attainable IOP
  - Lowering EVP lowers IOP by the same ratio
  - Likely greater efficacy combined with another glaucoma medication
  - Current published studies are non-human primate
    - Up to 20% response with q.d. dosing in normotensive glaucoma models
    - No apparent effect on systemic blood pressure

Slide 23

Non-IOP Pressures

- CSFP
- Cerebospinal fluid pressure
- Pressure in one's central nervous system
- If high can cause papilledema

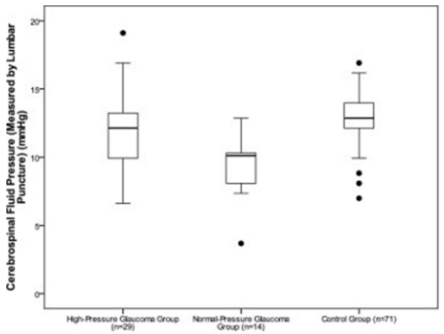
Slide 24

CSF

- Cerebrospinal fluid
  - Lamina cribosa acts as a pressure barrier between IOP and CSFP
  - Low CSFP may (functionally) act as high IOP

"Cerebrospinal fluid pressure in glaucoma" (Ren et al) is a prospective study on this relationship

Slide 25



Ren et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthal. Feb. 2010.

Slide 26

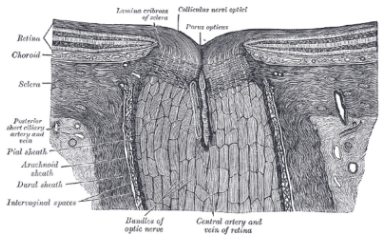
CSF

- Berdahl et al found glaucoma patients tended to have lower CSFP by reviewing over 30,000 charts of patients who have lumber punctures
- CSFP declines with age
  - About 25% from age 50 to age 90
- CSFP tends to *increase* with increasing BMI

Slide 27

CSF

- Area of interest is the lamina cribrosa
  - Anatomical location of pressure gradient between CSFP and IOP
  - Where ONH fenestrates as it exits the globe



Slide 28

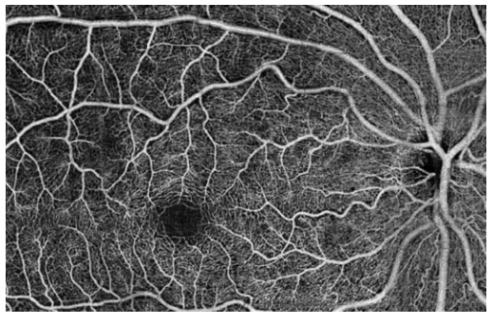
Non-IOP Pressures

- OPP
  - Ocular perfusion pressure
  - Difference between arterial blood pressure and IOP
  - Low OPP may increase risk for OAG

Slide 29

What about OCT-A?

- OCT angiography



Slide 30

OCT-A

- Noninvasive
- The “contrast” is vascular movement during the cardiac cycle
- Can be used to map retinal blood flow in a specific area of interest

Slide 31

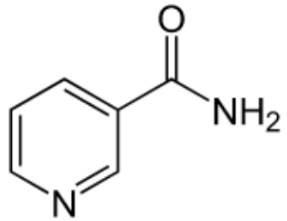
OCT-A

- Glaucomatous nerves shown to have attenuated vasculature and around 25% decreased blood flow index compared to healthy optic nerves
- Need to communicate with PCPs so that optimal blood pressure control can be achieved
- Decreased perfusion shown to correlate with visual field pattern standard deviation
  - Thus, OCT-A may be incorporated into diagnosis and staging of glaucoma

Slide 32

Vitamin B3

- Nicotinamide
- Oral supplementation may *improve* mitochondrial function of retinal ganglion cells



Slide 33

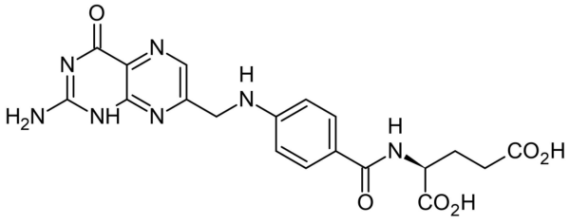
Vitamin B3

- Nicotinamide and nicotinamide riboside
  - Emerging as viable adjunct therapies to perhaps *improve* visual function
  - Nicotinamide adenine dinucleotide precursors
  - NAD essential for proper cell functioning
    - involved in metabolic activities
    - protection against reactive oxygen species
    - aids in the performance of various enzymes
    - maintenance of mitochondrial function.

Slide 34

Vitamin B9

- Folic acid
- Oral supplementation may improve homocysteine metabolism
  - Homocysteine shown to be higher in normotensive glaucoma
  - Higher levels linked to several neurological conditions



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Vitamin B9

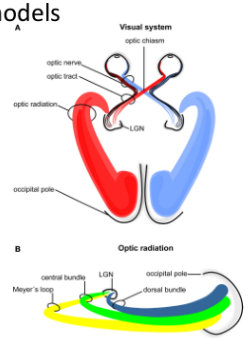
- Higher levels in one's blood associated with reduced risk of glaucoma

- Also associated with decreased risk of:
  - Cardiovascular events
  - Cancer
  - AMD
  - CRVO

Slide 36

That's right. Glaucoma is a neurological disease

- Damage in lateral geniculate nucleus seen after induction of OHTN in non-human primate models



Slide 37

You are what you eat

- Nitrate intake increases nitric oxide levels
- Leads to lower IOP and may enhance ocular blood flow
  - Carrots
  - Beets
  - Celery
  - Spinach
  - Kale
  - Cabbage
  - Grapes
  - Watermelon
  - Hotdogs

Slide 38

The not-so-distant future

- Inexpensive supplements such as nicotinamide may prove to be very useful in the arena of glaucoma
- Gene therapy aimed at reversing mutations would be more of a one-stop shop approach but faces regulatory impediments
- Stem cell therapy continues to make advances in hopes of achieving retinal ganglion cell regrowth

Slide 39

Perhaps…….

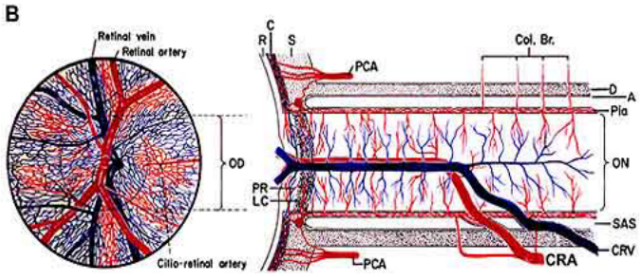
- Minocycline treatment in mouse glaucoma models slows neurodegeneration when given in early disease state
  - Effect on inflammation by limiting several pro-inflammatory cytokines
- Valproic acid also reduces inflammation after retinal ganglion cell injury

Slide 40

We almost left out *Gingko biloba*!

- Tree native to eastern Asia
- Rich in antioxidants
- Has anti-inflammatory effects
- Oral supplementation has been shown to improve ocular blood flow and cerebral blood flow

Slide 41



It’s complicated