Glaucoma Update

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Disclosures
- None!

Course Objectives
- Considerations in diagnosis
  - Correlations with other diseases
  - Update in diagnostic testing
  - Progression analyses
  - New therapies
  - Medical, surgical, pipeline

Pathogenesis
- Glaucoma is a disease of the optic nerve
  - Optic neuropathy
  - Other neuropathic conditions
    - Alzheimers Disease (AD)
    - Parkinson’s Disease (PD)

Linking Neurodegen. Dz.
- Apoptosis
  - Cause for RNFL loss in GLC
  - Cause for neurodegeneration in AD/ PD
- Chandra, et al. studied death certificates in 1978
  - Significant likelihood for GLC in pt’s w/ AD

Neurologic Cellular Change in Alzheimer's Disease

- Cerebral cortex shrinks
  - Especially hippocampus-memory
- Ventricles enlarge
- Beta amyloid plaques develop
- Protein tau changes

Dementia in Glaucoma pts

- B. Yochim, et al.: presence of cognitive disease in glaucoma patients
  - Influence on compliance
  - Examined 4 surveys of cognitive ability in POAG patients
    - 44% impaired on at least 1 test
    - Ranging from 22% - 32% per test
    - Depressed per measures yet not reported
    - Memory impairment/ executive function loss consistent w/ AD

Not

- Lack of correlation in large or long-term studies:
  - Kesing, et al.: retrospective, n=11,700 POAG pts
    - No increased prevalence of AD
  - Bach-Holm, Kesing et al.: 20-yr longitudinal, n=69, NTG
    - No increased prevalence of AD

Now what???

- Similarities?
  - Amyloid plaques: $A\beta$
    - Found in RNFL of induced GLC-rats
  - Amyloid precursor protein (APP)
    - Found in ONH of induced OHTN-rats
  - Caspases
    - Role in inducing apoptosis
    - Found in GLC and AD
  - Tau proteins
    - Affected in retina and CSF
  - Neurofilaments (NF)-triplet proteins
    - Common to cells damaged in POAG and AD

So....

- Glaucoma signaling early AD
- Similarities in therapies
  - Esp. neuroprotection
Does AD cause POAG or V/V?
- We can’t prove it, AD features:
  - RNFL thinning
  - Retinal amyloid β and phosphotylated tau
  - Caspase activation
  - RGC apoptosis
  - Tau protein in vitreous and CSF
- Alzheimer’s optic neuropathy

Glaucoma and Dementia/ AD
- Possible links/ similarities
- Show some correlations
  - Esp concern in normal tension
  - Dementia role in compliance
    - Sx over topical
- CSF pressure decreased in POAG/ AD

What’s up with CSF

CSF and GLC
- Decreased cerebrospinal fluid pressure (CSFP) associated with glaucoma progression
- Pressure gradient across lamina cribosa
- Decreased CSFP with age/ increased POAG

Role of LC
- LC separates intraocular and subarachnoid environments
- Creates translaminar pressure
- Gradient allows flexion of LC= impact on RGC axons

CSFP and LC
- ONH in papilledema
  - Anterior flexion of LC/ loss of cup
  - No glaucomatous change on resolution
- Opposite in high IOP
  - Posterior bowing of LC
  - Torsion on RGC axons/ ischemic?
- Could CSFP be the factor in NTG/ LTG?
- Narrower ON-subarachnoid space
CSFP and Glaucoma Therapy

Glaucoma when we sleep
- Progression overnight
  - Argue: IOP control with Alpha vs CAI and diurnal variation
- What if it’s oxygen, not IOP

Sleep Apnea
- Studies show correlation in Obstructive Sleep Apnea Syndrome (OSAS)
- Higher prevalence of GLC in sleep apnea
- Higher prevalence of sleep apnea in GLC
- Increase prevalence and more severe RNFL/ HVF defects

Oxygen and ONH
- NAION: “I woke up and couldn’t see”
- Perfusion pressure
  - Barbados Eye: twice the risk of GLC with low MAP
    - Diastolic-IOP >50
- OSAS: blood flow but low O2

Dysfunction of O2 Demand
- NTG: defect in autoregulation
  - Impacted by OSAS
  - Altered hormonal release
  - Abnormal coagulability
    - Platelet activation
  - Supine Position
    - IOP incr., decr. Blood flow
    - Dietary iron?
- Consider OSAS risk factor for NTG

Meeting the O2 demand
- Continuous positive airway pressure (CPAP)
  - Increased blood oxygen
  - Increased IOP
  - Decreased BP

**Diagnosis Discussion**
- Questions regarding details of pathogenesis, risk factors, etc.?

**Diagnostic Update**
- Review newer details/ analyses on:
  - Optical coherence tomography
    - GCC, progression/trend analysis
  - Visual field
    - GPA on HVF, Octopus

**Ganglion Cell Complex**
- Eval ganglion cells, dendrites and axons about the macula
- Preferentially affected in GLC?
- Measured on OptoVue, Cirrus, Spectralis

**GCC diagnostics**
- Early studies point to superiority-TD vs FD
- Equivalent GLC detection to RNFL
- Complimentary relationship
- Can’t look at just 1 result

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Progression Analyses

- Cirrus: guided progression analyses
  - Event based vs trend based
    - Sensitivity vs specificity
  - Linear regression trend
    - Point by point
    - 2 baseline, up to 6

GPA efficacy/accuracy

- JH Na: evaluated OCT GPA to progression per expert analysis on ONH and HVF as well as HVF GPA (discussed later)
  - Poor correlation to expert analysis
    - Is this the point?

Case example

RTVue

- RNFL trend analysis
- 6 region of ONH graphed out
Spectralis
- Glaucoma Module Premium Edition (GPME)
  - Anatomic positioning system
  - Rim Analysis
  - BMO-MRW
  - Progression analysis
  - Event: circumpapillary RNFL
  - Trend: sector RNFL measures

BMO-MRW

Spectralis progression analysis

Humphrey Visual field
- Visual Field Index
  - % of normal
  - Glaucoma progression Analysis (GPA)
  - 10-2 in early stage
  - Correlates to GCC

VFI
- What is it?
  - Visual Field Index

GPA
- Utilizes change in VFI
  - Less affected by cataract/media changes
  - Center weighted, correlating with RGC density
- Total of 5 exams must be available
- Plots 2 baseline exams at top, current VF at the bottom
- Progression graphs plot VFI as a function of age
Progression analysis

- A single solid dot indicates this point is not changing significantly (+)
- An open triangle indicates that has changed by a significant amount on one test ($\Delta$)
- A half filled triangle = that point has changed significantly on 2 visits (△)
- A filled triangle = that point has changed significantly on 3 visits (▽)

Octopus perimeter

- Eye Suite perimetry
- Cluster analysis
- Polar graph
- Trend analysis

Centervue-Compass

• 24-2 VF with imaging of fundus
• Fundus related perimetry

10-2

• When is it used in glaucoma
• Historically end stage
• New thoughts:
  – 24-2, 30-2 have 4 points within GCC area
  – 10-2 and ganglion cell complex
    » Correlates effectively

10-2 in early glaucoma

• GCC tells us macula is important
• >30% of RGCs in macula
• Central 8 degrees
• Central RGC, esp. PMB susceptible
• Yield central arcuate (esp superior), or widespread VF defect

DC Hood, et al. Early glaucoma involves both deep focal and shallow widespread retinal nerve fiber damage of the macular region.

DC Hood, et al. The Nature of macular damage in glaucoma as revealed by averaging optical coherence tomography data.

RGCs in macula

Macular Vulnerability Zone
Revisiting Hysteresis

- OHTS study highlighted importance of CCT
  - <555 microns had 3x conversion risk vs. > 588 microns
  - Is it IOP or structural effect
  - What about refractive Sx/ corneal disease?
- Hysteresis: measure of viscoelastic dampening of cornea
  - Stronger correlation with GLC and progression?

Survey Said?????

- How many have a pachymeter?
- How many have an ORA?
Ocular Response Analyzer

- Akin to NCT testing
- Measures initial applanation and rebound
  - Difference is hysteresis
  - Hysteresis vs pachymetry
- Cornea corrected IOP
  - Stable post refractive Sx

Hysteresis and Glaucoma

- Lower hysteresis
  - Greater risk of glaucoma
  - Greater risk of progression
- Stability
  - Hysteresis and corneal resistance factor change with LASIK
  - ccIOP remains stable
    - Post refractive Sx
    - ORA vs Goldmann

ORA example 1

- 62yo Healthy AAM
- IOPs GAT: 31,30 OD 21,21 OS
  - iCare: 30 OD 20 OS
- Pachs 510, 510
- Hysteresis 5.5 OD 8.9 OS
- IOPcc: 32.5 OD 19.7 OS

ORA example 1

- -41 µm
- -26 µm
ORA example 1 review
• IOP: OD >> OS
• Slight C/D asymmetry
• Some VF defects—exciting?
• Some RNFL thinning
  • Definite asymmetry
  – Dramatic asymmetry and low hysteresis

ORA example 2
• 61 yo AAM
• SysHx: (+)DM since 2009 last 3: 7.1, 8.4, 11.5%
• OcHx: Trauma OS-Rock
• IOP Ranges Untreated: 15-22 OD, 16-30
  OS 8 readings total
• CCT: OD: 599 OS 585
• ORA: IOPcc CH
  OD: 12.5 8.8
  OS: 19.9 5.4

Gonio: possible AR OS? Per student/resident

ORA example 2 review
• Asymmetric IOP, but not that high
• C/D—not alarming?
• VF normal
• OCT possibly borderline vs artifact
• *Asymmetric and low hysteresis makes the diagnosis
ORA example 2—closer look

ORA—not just for research

- Gives information that can help make the Dx
- Give input into risk of progression
- You could possibly get one at the same approximate price as a new NCT
  - Per reps at AAO
  - CPT code is coming this year

ORA examples

- All hysteresis/ Ocular Response Analyzer examples are courtesy of Andrew Rixon, O.D., F.A.A.O. of the Memphis VAMC

What’s new in IOP?

Monitoring IOP

- Diurnal variation
- Sleep studies
- Home iCare
- CL infused sensor

Diurnal variation

- Drance suggested concern in 1963
- POAG and NTG fluctuate more
  - Greater fluctuation = progression
- AGIS: 1mm Hg fluctuation = 30% increased risk of VF progression


iCare tonometry
- Rebound tonometry
  - Measures the impact time of a probe colliding with the cornea
  - Higher IOP=harder surface=shorter contact time
- Home iCare
  - Well tolerated, effective w/ caregiver
  - Utilized in Asia, FDA clearance in US

24 hour monitoring
- Telemetry
  - Practical?
- CL infused with sensor
  - In development
  - ? Correlates with IOP
  - Effects of CL wear/ dryness, etc.

New Therapies
- Topical
  - Adenosine agonists
  - RhoKinase Inhibitors
  - Latanprostene Bonud
  - Surgical
    - Microstents
    - ECP with phaco
    - Cyclodestructive procedures

Adenosine agonists
- Adenosine
  - G-protein activation
  - Shrinkage of cell volume, remodeling of MMP= increased TM outflow
  - Inhibition of A3 receptor may reduce aqueous production

Adenosine agonists
- Currently investigated by:
  - Santen
  - Can-Fite (oral)
  - Inotek
  - Acucela/Otsuka

https://www.youtube.com/watch?v=9Ov4VZXAZN4
Adenosine agonist efficacy

Rho-associated coiled coil-forming protein kinase (ROCK)
- Rho: GTP-ases role in actin assembly
- Affects actin in TM, Schlemm’s, & ciliary muscle
- Inhibitors relax TM and Schlemm’s
- Increased TM outflow
- Selectivity of ROCK inhibitors challenging

ROCK inhibitors
- Currently in trials with:
  - Aerie
  - Inspire
  - Kowa
  - Senju/ Novartis

Rock efficacy
- IOP reduction up to 28%
- BID dosing
- Some show inferiority to prostaglandin
  - Mechanism likely additive
- SE: injection

Latanoprostene Bunod
- Nitric oxide donating prostaglandin
  - 2 prong Tx
    - PGA and NO
    - NO: relaxation of CM and TM=
      enhanced TM outflow
  - Found superiority to latanoprost and timolol
    - No PGAs have this claim

LB efficacy
- IOP reduction 7.5-9.1 mm Hg
- SE: comparable to PGA/latanoprost
Others
• Serotonin
• Actin
• Punctal plug delivery
• New beta blockers

Discussion

Surgical management
• Microshunts/stents
• Endocyclophotocoagulation with Phaco, IOL

Micro-invasive glaucoma shunts (MIGS)
• Tube vs trab study
• Aim to bypass TM or enhance Schlemm’s
  • iStent
  • Hydrus
  • InnFocus

iStent
• Ab interno, in conjunction with phaco IOL
• TM bypass shunt
  • Smallest human implant

iStent
• Single or double implant
• Primary: 5mm Hg IOP decrease
• Excellent safety profile
Memphis Results

Hydrus
- Scaffolding of Schlemm’s
- 8 mm opening
- 3 clock hours
- Mean IOP reduction 34%
- Post op hyperemia most common SE

Current trials

Other stents
- CyPass
- Aquesys

InnFocus
- Ab- externo
- More like conventional tube
- No large plate assoc.
endocyclophotocoagulation

- Longstanding therapy
- Reduced aqueous production
- Now in conjunction with Phaco IOL

Results

Thank you

Any Questions?

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