Assessing the Optic Nerve in Glaucoma

Paul P. Lee, MD, JD
University of Michigan

SUNY Downstate
Atlantic City, NJ
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Conflicts of Interests Disclosure

- AAO Foundation – Hoskins Center for Quality and Safety
- American Board of Ophthalmology
- Centers for Disease Control and Prevention
- ARVO Foundation for Eye Research
- University of Michigan
- Duke University / Health System
- Glaucoma Research Fdn
- Private investment
  - Vital Spring Health Technologies
- Consultant and Research funding
  - Genentech
  - Pfizer
  - Novartis
- Intellectual property
  - Statins for glaucoma
  - EMR decision support and data entry
Key Points

- Assessing the nerve is critical to fully using current definitions of disease
- Traditional observation techniques are subject to significant variation, so documentation (especially image) of appearance is important
- Newer approaches will improve our accuracy and power of assessment
Defining the Condition(s)

**Definition of Disease**
- Optic neuropathy
- Acquired
- Characteristic changes
  - Optic nerve OR
  - Nerve fiber layer OR
  - Visual field
- NO IOP requirement

**Severity of Disease**
- Mild
  - Optic nerve or nerve fiber layer changes only
  - No visual field defect
- Moderate
  - Loss outside of central degrees on VF AND
  - In one hemisphere only
- Severe
  - Loss within 10 degrees OR
  - Both hemispheres of VF

**Open Angle**
- Open angle on gonioscopy
Amount of Loss of Optic Nerve to be Detectable by Various Methods

- Serial disc photographs: 10% of area
- Automated visual fields: 35% of NFL
- Kinetic, manual visual fields: 50% of NFL
Figure 1  Boxplots illustrating the distribution of estimated retinal ganglion cell (RGC) counts in glaucomatous eyes with early visual field defects and control healthy eyes.

Retinal Ganglion Cell Count Estimates Associated with Early Development of Visual Field Defects in Glaucoma (using SD-OCT)

Felipe A. Medeiros, Renato Lisboa, Robert N. Weinreb, Jeffrey M. Liebmann, Christopher Girkin, et al

Ophthalmology Volume 120, Issue 4 2013 736 - 744

http://dx.doi.org/10.1016/j.ophtha.2012.09.039
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Figure 2  Distribution of estimated percent losses of retinal ganglion cells (RGCs) in the glaucomatous eyes with early visual field defects. http://dx.doi.org/10.1016/j.ophtha.2012.09.039
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Diagnosis in Glaucoma Care
Wong, et al, Ophthalmology, 111:15-8-14, 2004
(Melbourne, Australia)

- 42 diagnosed and had definite OAG
- 41 with definite glaucoma not diagnosed
  - and 32 probable
  - ~60% seen w/in 2 years of entry exam
- 35 diagnosed without evidence of OAG by study criteria
Documentation of Optic Nerve Around the US – Chart Reviews
## Interobserver Differences $\geq 0.2$ DD

From Feuer, et al, AJO, 2002 (OHTS Reading Center)

<table>
<thead>
<tr>
<th>Study</th>
<th>Group Description</th>
<th>Interobserver Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitchings, et al</td>
<td>3 specialists</td>
<td>8 to 20 %</td>
</tr>
<tr>
<td>Tielsch, et al</td>
<td>2 specialists</td>
<td>17 to 19 %</td>
</tr>
<tr>
<td>Varma, et al</td>
<td>6 specialists</td>
<td>19 %</td>
</tr>
<tr>
<td>Abrams, et al</td>
<td>6 optometrists</td>
<td>29 %</td>
</tr>
<tr>
<td></td>
<td>6 residents</td>
<td>28 %</td>
</tr>
<tr>
<td>Shuttleworth</td>
<td>2 ophthalmologists</td>
<td>3 %</td>
</tr>
<tr>
<td>Feuer, et al</td>
<td>Reading Center</td>
<td>5 to 7 %</td>
</tr>
</tbody>
</table>
Disc Examination

- Use more than one technique
- Follow contour of vessels and not just color
- Compare upper to lower halves
- Identify disc margin as well as possible
ISNT Rule – Glaucoma
Harizman et al, Archives, 2006

• Intact in 79% (52/66) normal eyes
• Intact in 28% (12/43) glaucoma eyes

• Multiple regression (OR)
  – ISNT rule 6.04
  – Disc area 10.75
  – Axial length 2.55
Disc Hemorrhages in OHTS
(Budenz et al, Ophthalmology 2006)

• Stereo photos much more sensitive than exam in detecting

• Increased risk of endpoint

• HOWEVER – 87% reached NO endpoint
Agreement between stereoscopic photographs, clinical assessment, Heidelberg retina tomograph and digital stereoscopic optic disc camera in estimating vertical cup:disc ratio

Top: HRT

Middle: Stereo photos

Bottom: MD’s
European Optic Disc Assessment Trial
(Reus et al, Ophthalmology 2010)

- 243 ophthalmologists in 11 countries
- MD range of accuracy from 61% to 94%
- More recent graduates w/ better sensitivity; no difference in spec
- Better as severity of glaucoma increased (especially MD)
CT Interpretation in Acute Stroke

- Overall sensitivity of detecting hemorrhage 82%
- Correct decision regarding thrombolysis 77%

- Achieving 100% sensitivity
  - Emergency physicians 17%
  - Neurologists 40%
  - Radiologists 52%
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The receiver operating characteristic curves for rim volume, rim area, and glaucoma probability score parameters obtained by confocal scanning laser ophthalmoscopy.
Comparison of SD-OCT for RNFL thickness vs. HRT-III (CLSO) rim area

http://dx.doi.org/10.1016/j.ophtha.2012.06.009
Spectral Domain OCT Analysis
Lisboa R, et al (Weinreb), AJO 2013

- 262 eyes of 187 patients and 190 eyes of 100 control patients
  - Including mild cases OAG
- Average RNFL thicknesses
  - High res protocol 3.45 mm
  - Centered on disc
  - Quality of > 15 dB (0 to 40)
- Likelihood ratio from AUC analyses and Bayes’

- 86 um as threshold
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Figure 3  The receiver operating characteristic curves for discriminating glaucomatous eyes with early visual field defects from healthy eyes for the estimated retinal ganglion cell (RGC) counts and the average retinal nerve fiber layer (RNFL) thickness.

Using SD-OCT (Cirrus).

http://dx.doi.org/10.1016/j.ophtha.2012.09.039
Examples of patients with glaucoma illustrating the significant discordance between results of confocal scanning laser tomography (CSLT) and MRA with HRT and spectral-domain optical coherence tomography (SD-OCT).

A - Normal MRA, abnormal SD-OCT
B – Abnormal MRA, normal SD-OCT
C – Normal MRA, normal BM-HRW (red line), abnormal BM-MRW (green line)
Receiver operating characteristic (ROC) curves illustrating the diagnostic performance of SD-OCT retinal nerve fiber layer thickness (RNFLT), Bruch's membrane opening-horizontal rim width (BMO-HRW), and Bruch’s membrane opening-minimum rim width (BMO-MRW)

MRA1 = borderline classified as normal
MRA2 = borderline classified as abnormal

http://dx.doi.org/10.1016/j.ophtha.2012.09.055
Enhanced Detection of Open-angle Glaucoma with an Anatomically Accurate Optical Coherence Tomography–Derived Neuroretinal Rim Parameter

Balwantray C. Chauhan, Neil O'Leary, Faisal A. AlMobarak, Alexandre S.C. Reis, Hongli Yang, Glen P. et al

Ophthalmology Volume 120, Issue 3 2013 535 - 543

Figure 6  Pre- and posttest probability of the various global parameters based on cutoff values yielding 95% specificity. Data comparing circumpapillary retinal nerve fiber layer thickness (RNFLT), Bruch's membrane opening-horizontal rim width (BMO-HRW)
Enhanced Depth SD-OCT Imaging Detects Lamina Cribrosa Thickness Differences in Normal Tension Glaucoma and Primary Open-Angle Glaucoma

Hae-Young Lopilly Park, So Hee Jeon, Chan Kee Park

Ophthalmology Volume 119, Issue 1 2012 10 - 20

http://dx.doi.org/10.1016/j.ophtha.2011.07.033
Automated Detection of DR
Abramoff MD, Neimeijer M, Russell SR. Expert Rev Med Dev 2010

Performance
• “... performance of the algorithms measured in ROC only slightly lags behind the sensitivity and specificity of the experts.”
• “... the system can always match the sensitivity of the human expert – but at a lower specificity.”
• “the cost per patient for automated detection to be ... [US $ 0.25 ]

Future Efforts
• “... further measurable improvements in detection performance have become difficult to achieve.”
• “... validation on well-defined populations of patients with diabetes ... are more urgent than further algorithm development.”
Retinal Arterial Analysis

Risk of progression to OAG from OHT


• Risk of development of incident OAG over 10 years
• Central retinal artery calibers
  – OR of 1.77 for each SD lower caliber
  – OR of 1.87 after adjusting for IOP
  – OR of 1.76 after adjusting for ocular perfusion pressure
  – Persists even within IOP < 20 and c/d < 0.6 subgroup

Pressure attenuation index = length / diameter; net effect is smaller diameter with higher PAI value of main IT and ST arterioles
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• Newer approaches will improve our accuracy and power of assessment ... and may change how we define the disease
Personalized Monitoring Schedules for Patients with Open-Angle Glaucoma

A Tool for Physicians Developed Using Filtered Forecasting Techniques

Joshua D. Stein, MD, MS
University of Michigan W. K. Kellogg Eye Center
World Glaucoma Congress, Vancouver, July 17, 2013

Wouldn’t it be great to have a glaucoma monitoring system that could….

- **Quickly assimilate information** on IOP, Visual Field performance, and structural Optic Nerve changes to determine if disease is stable or worsening

- **Be personalized**, dynamically incorporating new information obtained at each new visit with existing historical information to help determine whether treatment regimen should be changed
  
  → The model learns patients' unique disease-progression dynamics over time.

- **Be flexible**: Providers can tailor monitoring on the basis of individual patient characteristics
  
  ▫ 90-year-old pt. with mild glaucoma
  ▫ 40-year-old pt. with advanced glaucoma in her only seeing eye

- **Be easily integrated in busy clinical practices**

- **Help guide providers in determining a safe interval between tests** so as to not miss significant disease progression
Kalman Filtering

- Forecasting and noise reduction technique; useful for modeling complex, large systems
  - Used by NASA for space flights
  - Pulmonary blood flow
  - Glucose levels in pts. with diabetes
  - PSA levels in pts. with prostate cancer

- Combines a population-based understanding of disease evolution with the individual patients’ characteristics to forecast future values of key clinical parameters
Developing and Validating the Model

- Participants from CIGTS and AGIS trials who were treated with medications or laser trabeculoplasty

- Total eligible: 571 eyes
  (286 in training, 285 in testing set)
  - No significant difference between training and testing sets

- Pts. followed for ≤10 y (mean, 6.31 y)

- Perimetric (MD, PSD) and tonometric (IOP) data collected every 6 mo after initial intervention
Results

*Example:* AGIS Patient with No Disease Progression

![Graph showing MD over time with periods labeled (6 month)](image-url)
Results

Example: AGIS Patient with Disease Progression

![Graph with data points labeled as Observed, Filtered, and Predicted.](graph.png)
Nerve Fiber Layer Analysis
Relationship C/D to VF Grade – Community Setting
Key Questions for the Future

• “Is this going to get the nerve evaluated?”
• “How sensitive to change is this system?”
• “Who / what is going to interpret the result?”
• “Is it better than what we have today?”
• “What do we get for the money?”