Navigating the Nerve

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• The not so fine print ……

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Glaucoma

- Optic neuropathy
- Characterized by progressive injury to retinal ganglion cells and their axons
- Specific pattern of optic atrophy (“cupping”)
- Associated visual function deficit

Incidence of Open-Angle Glaucoma

- Affects >2 million over the age of 40 in the US (1.9%); expected to exceed 3 million by 2020
- Average age of onset 54 years of age
- Most patients (63%) have had glaucoma >10 years
- 2nd leading cause of blindness

Glaucoma Diagnosis: An Historical Perspective

- Pre -1980s
  - Elevated intraocular pressure (IOP) → glaucoma
- 1980s - Mid 1990s
  - Elevated IOP + visual field (VF) defect → glaucoma
- Contemporarily . . .
  - Glaucomatous optic disc + retinal nerve fiber layer (RNFL) changes → glaucoma

Underdiagnosis of Open-Angle Glaucoma

- Population studies suggest over half of POAG glaucoma are not diagnosed
- Percentage of patients with undiagnosed glaucoma
  - Baltimore Eye Survey: 36%
  - Beaver Dam Eye Study: 94%
  - Proyecto VER: 63%
  - Thessaloniki eye study
- Many suffer severe VF loss before diagnosis

6. Gallup Eye Health Survey. 2002
Structural Damage Precedes Functional Change

- NFL injury can be observed up to 6 years before VF defects
- Mean number of axons in normal ON ≈ 800,000–1,200,000
- 25-40% of ON fibers can be lost from an eye that retains a normal visual field

Visual Defects Are Associated With ON Damage

- Quadrants with fewer axons correlate with regions of greatest VF loss
- Clinical measurements of disc rim and nerve fiber layer depth correlate quantitatively with visual function in glaucoma

Structure and Function in Glaucoma

- VF loss by SAP does NOT mean early disease
- By the time VF loss is detected by SAP, substantial structural damage may exist
- Functional loss may be detected earlier using selective tests (eg, FDT, SWAP)

First OHTS POAG Endpoint per Participant

<table>
<thead>
<tr>
<th>Medication</th>
<th>Observation</th>
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<tbody>
<tr>
<td>Visual field</td>
<td>15</td>
</tr>
<tr>
<td>Optic disc</td>
<td>18</td>
</tr>
<tr>
<td>Concurrent visual field and optic disc</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>36</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Observation</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual field</td>
<td>29</td>
<td>32.6</td>
</tr>
<tr>
<td>Optic disc</td>
<td>51</td>
<td>57.3</td>
</tr>
<tr>
<td>Concurrent visual field and optic disc</td>
<td>9</td>
<td>10.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>89</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

46-year-old man referred for evaluation
Achromatic visual fields (SAP) (minimal loss OD, normal OS)

HRT: cup-to-disc asymmetry

GDx: inferior RNFL injury OD, confirming glaucoma injury OD

Optic Nerve Abnormality Without Visual Field Loss on SAP

Visual Field Loss on Selective Functional Test: SWAP

Abnormal SWAP

Visual Field Loss on Selective Functional Test: FDT

Abnormal FDT
Is This Early Glaucoma?

- Yes!
  - SWAP can detect visual field loss 3 to 5 years before SAP
  - FDT can detect visual field loss 4 years before SAP

Pathological Change in ON: Early Changes

- Generalized loss of neuroretinal rim (cup enlargement)
- Focal loss of neuroretinal rim (cup enlargement)
- Superficial splinter hemorrhage
- Loss of nerve fibers
- Thinning and translucency of neuroretinal rim
- Baring of vessels
- Cup/disc ratio asymmetry

Periodic ON Exam Advocated in Glaucoma Management Guidelines

- Evidence-based guidelines for glaucoma agree
  - Identification and follow-up of glaucoma requires careful evaluation of ON and RNFL as well as VF
  - Optic disc photographs or detailed drawings to be obtained at initial visit and at regular intervals during follow-up

Optic Disc Evaluation

- WGC
  - Detailed drawing
  - Disc photography

- Best technique to detect early changes
  - Examination of ONH by high magnification, high intensity light, stereo view

Five Rules for Assessment of the Optic Disc in Glaucoma

- Observe the scleral ring to identify the limits of the optic disc and its size

Optic Disc/RNFL Examination

“The 5Rs”
Five Rules for Assessment of the Optic Disc in Glaucoma

1. Observe the scleral ring to identify the limits of the optic disc and its size.
2. Identify the size of the rim.
3. Examine the retinal nerve fiber layer.
4. Examine the region of parapapillary atrophy.
5. Look for retinal and optic disc hemorrhages.

Rule #1

Observe the scleral ring to identify the limits and the size of the optic disc.

Optic Disc Size

- Horizontal disc diameter
- Vertical disc diameter
- Scleral ring
Optic Disc Size

Measurement of optic disc size with direct ophthalmoscope

Small aperture (5 degree) of Welch-Allen direct ophthalmoscope

Size of light spot ~ size of average optic disc

Optic Disc Size

Measurement of optic disc size with biomicroscopy

Volk lens
Measure length of slit beam

Correction factors
Volk 60D – x 1.0
Volk 78D – x 1.1
Volk 90D – x 1.3

Avg vertical diameter: 1.8 mm
Avg horizontal diameter: 1.7 mm

Optic Disc 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

Optic Disc Size

Small discs with glaucoma may have small cups

Rule #2

Identify the size of the neuroretinal Rim

Be cautious with myopic discs
ISNT RULE

Rim width
Distance between border of disc and position of blood vessel bending

ISNT rule
Inferior > Superior
Nasal > Temporal

Localized Rim Thinning/Notching

Observe the color of the rim to identify pallor
A pale rim increases the likelihood for a non-glaucomatous optic neuropathy

Localized Rim Notching

• Localized Rim Notching

Rule # 3

Examine the Retinal nerve fiber layer (RNFL)

Pallor

Diffuse pallor
Pallor > cup
Non-glaucomatous neuropathy
**RNFL Examination**

• Best performed using red-free light (red-free photographs or green light)*

• Look for
  - Brightness
  - Visibility of parapapillary retinal vessels

• Look for diffuse and localized RNFL loss

**RNFL Red-Free Photographs**

**Diffuse RNFL Loss**

Diffuse RNFL loss
Diffuse loss of striate pattern + increased visibility of retinal vessel borders

**Localized RNFL Loss**

Localized RNFL defect
Wedge-shaped dark area

**Rule #4**

Examine the Region of parapapillary atrophy (PPA)
Parapapillary Atrophy

**Alpha zone**
- Hypo- and hyper-pigmented areas
- Present in normal as well as in glaucomatous eyes

**Beta zone**
- Atrophy of the retinal pigment epithelium (RPE) & choriocapillaris
  - Large choroidal vessels become visible
- More common in glaucomatous eyes

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**Rule #5**

Look for Retinal and optic disc hemorrhages

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**Optic Disc Hemorrhage**

Indicative of glaucoma progression

Flame-shaped hemorrhage normally disappears within 2-3 months.

Detection of disc hemorrhages requires careful optic disc examination.
CASE EXAMPLES

57 W/M -5.50 (20/20) -9.50 (5/350)

75 W/F -3.50 (20/20) -3.50 (20/20)
56 W/M 20/200 (OD & OS)
55W/M; IOP 19,20 (on 3 meds); 600u CCT

28 B/F; Normal IOP; no VF
64 W/M 20/20 (OD, OS)

29 A/M 20/20 (-7.50 OD, OS) vs
Glaucoma

Diagnosis vs. Progression

› Assessments

› Factors

Progression

Progression

Progression
Recent Developments in predicting Risk of progression in Glaucoma

**TABLE 1. Baseline Demographic and Co-factor Factors in Eyes With and Without Glaucomatous Change**

<table>
<thead>
<tr>
<th>Co-factor Factor</th>
<th>N = 20</th>
<th>N = 29</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (n/m)</td>
<td>54%</td>
<td>54%</td>
<td>0.8</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td>91%</td>
<td>91%</td>
<td>0.90</td>
</tr>
<tr>
<td>Glaucoma Medication in Follow-up</td>
<td>80%</td>
<td>20%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at baseline (years)</td>
<td>65 ± 5.3</td>
<td>65 ± 11</td>
<td>0.42</td>
</tr>
<tr>
<td>NCT at baseline (mm Hg)</td>
<td>4.5 ± 2.0</td>
<td>4.2 ± 1.7</td>
<td>0.62</td>
</tr>
<tr>
<td>SAP Risk at Baseline (dB)</td>
<td>0.0 ± 0.0</td>
<td>1.7 ± 0.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Standard Photograph Assessment</td>
<td>72%</td>
<td>76%</td>
<td>0.12</td>
</tr>
<tr>
<td>Standard (%)</td>
<td>76%</td>
<td>76%</td>
<td>0.12</td>
</tr>
</tbody>
</table>

**DIGS (diagnostic innovations in glaucoma study) data – OCT**

- 4.2 year mean FU, 20% of 114 eyes progressed

**RNFL defects in pre-perimetric glaucoma**

- Study design
  - 49 eyes with RNFL defects (red-free fundus photos)
  - 49 age-matched controls
  - RNFL thickness on OCT (Stratus©)

- Results
  - All 46 eyes showed > 1 RNFL defect (R/F)
  - Most defects were ST or IT
  - 40.8% congruence between OCT and R/F (∅ = 1 clock hour involved @ 5% level) [best sensitivity]
  - Better analytical methods are required to distinguish early (pre-perimetric) RNFL defects from normals using TD OCT

**What about precision?**

- Study design
  - 51 stable glaucoma patients
  - Tested and re-tested on 5 different occasions within 2 months (mean RNFL thickness)
- Results (test-retest variability)
  - Range (fast or standard RNFL scan): 6.6 – 20.2 u
- Practical guidance
  - Fast scan variability (stable): < 9.5 u (95%)
  - < 8u DECREASE for stable condition for test-retest (95%)

**Glaucoma diagnosis with digital instrumentation**

*Diagnostic ability of the Heidelberg retina tomograph, optical coherence tomograph, and scanning laser polarimeter in open-angle glaucoma*

Diagnostic capability of digital imaging instruments

- **Background**
  - RNFL and ONH evaluation is essential in glaucoma diagnosis and management.
  - These analyses are subjective, qualitative and may be fraught with variability due to subjective interpretations.

- **Purpose**
  - Diagnostic ability comparison to discriminate between healthy and glaucomatous eyes based on different parameters of 3 instruments

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Diagnostic capability of digital imaging instruments

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Diagnostic capability of digital imaging instruments

- **Methods**
  - **HRT-II**, confocal scanning laser ophthalmoscopy
    - FSM, RB (linear discriminant functions including cup shape measure, rim volume, RNFL height variation; MRA)
  - **Stratus OCT**, optical coherence tomography
    - RNFL thickness (mean, quadrant and clock hour)
  - **GDx VCC**, scanning laser polarimetry
    - NFI, TSNIT average

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Diagnostic capability of digital imaging instruments

- **Results**
  - Glaucoma patients were older than normals
  - ALL parameters of the 3 instruments tested had ROC > 0.8 (@95% specificity)
  - From this and pairwise comparisons, best criteria were selected for each instrument
    - HRT-II – MRA < 0.5% [outside the 95% range of normal]
    - Stratus OCT – RNFL < 77u
    - GDx – NFI > 37

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Diagnostic capability of digital imaging instruments

- **Correct identification based on best criterion for each instrument**
  - 66/73 (90.4%) correctly identified as glaucoma
    - 62/66 HRT-II
    - 45/66 Stratus OCT
    - 35/66 GDx VCC

- **Conclusions / clinical implications / cautions**
  - All instruments perform well in glaucoma diagnosis
  - As has been reported in previous studies, none is superior to the other
  - Best parameter should be looked at most carefully

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Diagnostic capability of digital imaging instruments

- **Conclusions / clinical implications / cautions**
  - None of the instruments could be recommended as a screening tool even based on best parameter and clear differentiation between healthy and glaucoma
  - Based on data acquisition paradigm, an interrelationship between results on the same patient may give improved results
Diagnostic capability of digital imaging instruments

- Conclusions / clinical implications / cautions*
  - RNFL thins with age and the glaucoma patients in the study were slightly older than normals
  - These results confirm another recent report:

First POAG Endpoint (n=125)*
- Optic-disc damage first
- Visual-field defect first
- Concurrent visual-field and optic-disc defects
- Includes all subjects

How often should a VF be done?
- It depends . . .
- Variability
- Fast vs. slow progressors
- How do we know?

![Distribution of intra-individual standard deviation (SD) of MD values in patients followed for up to 12 years](image)

Table 2  Rates of visual field change corresponding to total change in mean deviation (MD) over 2, 3 and 5 years (a) and the number of visual fields per year required to detect the corresponding change with 80% power (b)

<table>
<thead>
<tr>
<th>a) Total MD change (dB)</th>
<th>Progression rate (dB/year)</th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
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</thead>
<tbody>
<tr>
<td>-1.0</td>
<td>-1.0</td>
<td>-0.5</td>
<td>-0.3</td>
<td>-0.2</td>
</tr>
<tr>
<td>-2.0</td>
<td>-1.0</td>
<td>-0.7</td>
<td>-0.4</td>
<td>-0.0</td>
</tr>
<tr>
<td>-4.0</td>
<td>-2.0</td>
<td>-1.3</td>
<td>-0.0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b) Annual examinations</th>
<th>Total MD change (dB)</th>
<th>2 years</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.0</td>
<td>7.0</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>-2.0</td>
<td>7.0</td>
<td></td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>-4.0</td>
<td>7.0</td>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Other Notes on Glaucoma
- Neuroretinal rim loss & mean deviation [MD]
  - “Early” defects (<6 db) may have 60% rim loss

- Ganglion cell loss & visual field results (human histopathologic study)
  - RGC loss averages 35.7% when CPSD <0.5%
  - Individual points significant @ 0.5% probability showed 29% RGC loss

Clinical Practice Today: Diagnosis & Follow-Up of Glaucoma
- Need to evaluate ON, VF, and IOP
- Focus on ON damage in early disease
  - Disc or RNFL changes usually observed prior to functional damage
  - Examination of IOP alone, or IOP plus VF, not sufficient
- VF testing
  - Reproducible VF defects in early disease can confirm glaucoma or progression in cases with an unremarkable or suspicious disc
  - Critical in more advanced disease
To Treat or to Advance Treatment?

- Ocular hypertension
  - Treatment is individualized and is most appropriate for
    - Suspects at high risk of developing glaucoma
    - Patients with pre-achromatic glaucoma

- Glaucoma
  - All patients need to be treated
  - Treatment needs to be advanced if progression is present or highly likely

Conclusions

- Evaluate and document ON to
  - Diagnose glaucoma
  - Determine disease severity
  - Evaluate progression

- Set target pressure based on risk factors and optic nerve appearance
  - Aim for lower targets: every mm Hg counts

- Prescribe therapy with best ability to achieve and maintain target IOP (or lower)

- Re-evaluate structure/function critically as patient is followed

- Readjust target IOP and treat more effectively when subtle progression is noted