Structure-Function In Early Glaucoma

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Glaucoma

- Chronic, progressive and potentially blinding optic neuropathy characterized by distinctive morphological ('structural') changes of the optic nerve head and RNFL associated with visual field changes ('functional').
- Both structural and functional changes result from loss of the retinal ganglion cells (RGC's) and their axons.

Historical Thinking: Structural Damage Precedes Functional Change

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

How much loss before detection?

- **Structural:**
  - Recognition of RGC loss by disc or nerve fiber layer examinations would ideally be possible with a loss of 5% of RGC, but under average circumstances, it requires a loss of 15-40% of RGC.
- **Functional:**
  - loss occurs with variable RGC loss, depending on method and retinal eccentricity, with a greater loss required centrally. Visual field damage by probability values on the Humphrey requires a 25-35% loss in a local area.
  - H. Quigley

Structural Damage Precedes Functional Change (cont.)

- 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 (e.g., FDT, SWAP)

Clinical Reality Truths

1. Patients with the same degree of neuroretinal rim loss can have different and variable amounts of VF loss.
2. Some patients have evidence of glaucomatous optic neuropathy without a detectable VF abnormality.
3. Some patients have classic glaucomatous VF defects without detectable structural abnormalities.

Why is there variability of functional loss of vision in patients with same degree of rim loss?

- There are different types and size of RGC
- The function of these variable RGC will cause variable functional loss.
- Different types of RGC respond to different stimuli

Why Structural Change and No Functional Change?

AIGS Consensus Paper on Structure-Function:
- Evidence suggest that RGC’s with larger cell bodies and larger axons die first in glaucoma
  - Smaller axons and cell bodies die first in ischemic optic neuropathies (AION).
- The RGC may “shrink” and change in morphology before dying
- RGC become “dysfunctional” in early glaucoma before they die.
- There is a “functional reserve” period where ONH gets worse before the VF.

Why Structural Change and No Functional Change?

- There is “functional latency” where structural change occurs early in the disease without functional vision loss.
- In early glaucoma, more glaucoma induced structural damage relative to the amount of glaucoma-induced functional damage.
- In moderate-late glaucoma, functional loss is greater than structural loss.
Why Do Some Glaucoma Patients have Functional Loss Prior to Structural Loss?

- RGC become “dysfunctional” in early glaucoma before they die.
  - Dysfunction causes reduced VF sensitivity that does not correlate with RNFL loss of ganglion cell complex loss.
- Quigley:
  - The translation of anatomical selectivity into psychophysical testing depends upon the sensitivity with which the loss of RGCs of particular types can be detected by functional testing.

Can damage to the Retina Ganglion Cells (RGC) be assessed clinically?

- Indirectly and directly through imaging
  - OCT

- The ganglion cells in the area outside the paramacular region are not multilayered
- Early losses in these regions are more readily detected by visual field testing.
  - Nasal steps, arcuate scotomas

Is VF testing sensitive enough to detect Early Glaucoma?

- Multiple layers of ganglion cells in the paramacular region
- A stimulus from a VF stimulus can be detected as long as there is one remaining layer of ganglion cells.
  - This means that we can lose 5 layers of these cells (each with a thickness of 30 microns) before the visual fields may show an abnormality in the central area.
- Flicker, Motion, Pulsar Perimetry, VEP, mERG as optional functional assessment?

- Remember: losses of RGCs occurs both the within paramacular region and outside the paramacular region.

1. Why Measure the paramacular RGC?
2. How do we measure RGC loss within the paramacular region?
Why Measure the Paramacular RGC?

- Due to the large variation amongst normals in optic nerve size, shape and total axonal count (and thus width of neuroretinal rim), it is difficult to differentiate early glaucoma from normal.
- A majority of ganglion cells reside in the macula and that their numbers are relatively constant amongst normals.
- The multi-layered retinal ganglion cells along with the RNFL, constitute 40% of the retinal thickness in the paramacular region.

How do we measure RGC loss within the paramacular region?

Retinal Layers with OCT & Histology

-measuring the ganglion cells

Inner retinal layer provides:
Ganglion cell complex assessment:
- Axons = nerve fiber layer
- Cell Body = ganglion cell layer
- Dendrites = inner plexiform layer

GCC

OD: 94.93
OS: 95.96
Ganglion-Cell Analysis (GCA)

What is the advantage of measuring only the GC-IPL?

- The measurement of GC-IPL thickness alone may increase diagnostic accuracy.
- Less variability among normal individuals compared with RNFL measurements.

GCA=GC-IPL

Case Example 1

Cirrus-SD OCT

Glaucoma Diagnostic Accuracy of Ganglion Cell–Inner Plexiform Layer Thickness: Comparison with Nerve Fiber Layer and Optic Nerve Head

What is the advantage of measuring only the GC-IPL?
**Cirrus Example 1**

- Measure retinal thickness in the posterior pole using 61 lines (30° x 25° OCT volume scan) for each eye in a central 20 degree area.
- Covering a larger area that corresponds more to the 24-2 visual field.

**Spectralis**

- Measure retinal thickness in the posterior pole using 61 lines (30° x 25° OCT volume scan) for each eye in a central 20 degree area.
- Covering a larger area that corresponds more to the 24-2 visual field.

**Posterior Pole Asymmetry Analysis of the Paramacula**
Macular Thickness Map

Which is Better?

<table>
<thead>
<tr>
<th>OCT Device</th>
<th>Macular Imaging Protocol</th>
<th>Standard Area of Analysis</th>
<th>Standard Layer Thickness</th>
<th>Normalized Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTVue 100-OCT</td>
<td>Ganglion cell complex analysis</td>
<td>7 mm, centered 1 mm temporal to fovea</td>
<td>RNFL, RGC-PE</td>
<td>Yes</td>
</tr>
<tr>
<td>Spectralis HD-OCT</td>
<td>Proximal pole symmetry study</td>
<td>5 mm, centered on fovea</td>
<td>All macular layers</td>
<td>Yes</td>
</tr>
<tr>
<td>Cirrus HD-OCT</td>
<td>Ganglion cell analysis</td>
<td>Elliptical annulus, vertical radius of 2 mm, horizontal radius of 4 mm, compared to ILM</td>
<td>CC/RL</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; RGC, retinal ganglion cell; RL, superficial retina; CC, ganglion cell and inner plexiform layers.