Optic Nerve Head and Retinal Nerve Fiber Layer Analysis in Glaucoma

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I. Overview of Diagnostic Technology in Glaucoma
   a. Glaucoma Diagnosis – an optic neuropathy characterized by retinal ganglion cell death and corresponding nerve fiber layer loss.
      i. Visual Field: the detection of preperimetric glaucoma may lead to early treatment and prevention of future field loss.
         1. Quigley et al demonstrated that there may be significant optic nerve damage before the appearance of VF loss on Goldmann perimetry.
         2. More than half of study subjects reaching an end point (glaucoma) in the Ocular Hypertension Treatment Study were diagnosed based on optic nerve progression.
      ii. Optic Disc Photography and Stereophotography
         1. Advantages:
            a. Similar to clinical exam; comfort and easy interpretation for some clinicians
            b. Full color helps to distinguish between cupping and pallor
            c. Better detection of disc hemorrhages
            d. Aids in detection of peripapillary atrophy
            e. Stable technology
            f. Less expensive compared to other imaging devices
         2. Disadvantages
            a. Qualitative, not quantitative description
            b. Inter-observer variability
            c. High quality of photographs required for accurate interpretation
            d. May be difficult to detect subtle changes with a photograph
            e. Requires special hand held lenses for viewing and interpretation
      iii. Optic Nerve Analysis
1. A useful technological development in recent years that provides additional documentation of nerve fiber layer status

b. Available Imaging Modalities

i. Confocal Scanning Laser Ophthalmoscopy (Heidelberg Retina Tomograph, Heidelberg Engineering)

1. A 670-nm diode laser generates up to 64 transaxial laser scans through the ONH and peripapillary retina. The reflected image is captured as a 2-dimensional scan. The sections are combined to form a 3-D construct of the ONH, allowing for calculation of the cup-to-disc ratio, rim area, and other optic disc parameters.

ii. Scanning Laser Polarimetry (GDx Nerve Fiber Analyzer, Carl Zeiss Meditec)

1. Measures peripapillary RNFL thickness by sending a laser beam to the posterior retina and assessing the change in polarization (retardation) of the reflected beam. The retardation results from the birefringent properties of the ganglion cell axon neurotubules (updated GDx devices include variable corneal compensation [VCC] that incorporates individualized compensation for the corneal component of birefringence).

iii. Optical Coherence Tomography

1. First described in 1991

2. A non-contact, non-invasive imaging technique that reveals layers of the retina by analyzing the interference patterns of reflected laser light. Involves axial cross-sectional imaging of tissues based on the optical backscattering of low-coherence infrared laser light (850 nm) as it passes through layers of differing optical density, similar to the physical principles of ultrasound. Requires pupil dilation in most cases.

3. Primary mode of imaging utilized today:
   a. OCT data is cross-sectional and not interpolated. The HRT uses floor to ceiling patterns to extrapolate optic nerve rim thickness and GDx generates data by measuring polarization. OCT provides a true structural measure of the actual tissue thickness.
   b. OCT provides information about multiple structures including optic nerve head, macula, and the nerve
fiber layer. GDx = nerve fiber layer. HRT = optic nerve head.


5. Spectral-Domain (AKA Fourier-Domain): Next generation technology 4 years after TD-OCT. Captures more data in less time at a higher axial image resolution (around 5 μm)

   a. 4 Most Common Commercially Available SD-OCT Devices:

      i. Cirrus HD-OCT (Carl Zeiss Meditec)
      ii. RTVue-100 (Optovue Inc.)
      iii. Spectralis OCT (Heidelberg Engineering)
      iv. Topcon 3D-OCT 2000 (Topcon Corporation)

   Cirrus OCT defines the edge of the disc as the termination of Bruch’s membrane and then finds the shortest perpendicular distance to the ILM (minimum band distance) to define the inner cup margin in each slice in a spiral around the optic disc cube data until a center is located. This allows the 3.4mm circle to always be centered in the same spot within the cube. Calculated parameters (except disc area) are compared to a normative database.

II. Use in Glaucoma Diagnosis and Detection of Progression
   a. Optic Nerve
      i. Parameters

         1. Retinal Nerve Fiber Layer Analysis

            a. RNFL thickness can be directly measured and quantified via OCT because the technology allows for the quantification of light reflectance signal from the retina.

            b. RNFL axon bundles are thickest superiorly and inferiorly, hence the increased reflectivity (also seen on red-free illumination).

            c. Color coding with green, yellow, and red signifies a 5% - 95%, a 1% - 5%, and a <1% chance that the measured RNFL thickness is within normal range for an age-matched population, respectively. White = Thicker than 95% of controls.
2. Optic Nerve Head Analysis
   a. A topographic image is obtained using the same 200 x 200 A-scan data cube as that for RNFL Analysis. Automated software defines the margin of the disc as the termination of Bruch’s membrane.
   b. Parameters measured by SD-OCT include optic rim area, optic disc area, average cup-disc-ratio (average of 180 radial line measurements around the cup), vertical cup-disc ratio, and optic cup volume.

3. Ganglion Cell Complex Analysis (see below)
   ii. Diagnostic Capability
      1. A study by Chang et al suggested that an increasing number of abnormal clock hours on the RNFL thickness map is both more sensitive and specific for diagnosing early and moderate glaucomatous damage than average RNFL thickness and that the diagnostic capability for both SD-OCT and TD-OCT technologies were similar.
      2. Tan et al concluded that GCC and RNFL parameters may be complementary in the diagnosis of glaucoma. In this study, abnormalities in 3 GCC parameters were found to detect an additional 9% of perimetric glaucoma and 11% of preperimetric glaucoma cases with normal TD-OCT average and RNFL values.
      3. Reproducibility of SD-OCT was investigated by Leung et al. Repeated scans on non-glaucomatous eyes were compared. It was concluded that that SD-OCT demonstrates sufficiently low variability to detect glaucomatous progression. This was superior to TD-OCT thought secondary to the automatic, technician-independent rendering of the peripapillary circle employed for RNFL map analysis.

   iii. Progression Patterns
      1. Widening of an existing RNFL defect
      2. Deepening without widening of an existing RNFL defect
      3. Development of a new RNFL defect

b. Macula
   i. The ganglion cell layer is thickest in the perimacular region and loss from glaucoma results in decreased total macular thickness.
Cirrus’ Ganglion Cell Analysis (GCA) consists of the combined ganglion cell layer and inner plexiform layer. A similar color-coded scale is used dividing sections around the fovea. The sector calculations are compared to a normative database.

III. The Role of OCT in Clinical Practice
   a. Many physicians utilize the OCT to help confirm VF defects as true and not artifact, or conversely, reveal that the nerve tissue is undamaged and that the defect may be more consistent with artifact.
   b. Although a useful adjunct, should not be relied upon alone as the means of glaucoma diagnosis.
   c. Tips on Obtaining and Interpreting OCT (Aggarwal, N., AAO 2013)
      i. Choose the Right Scan Protocol
         1. Fast protocols are important in the evaluation of glaucoma/optic nerve as they minimize motion artifact.
      ii. Adjust Scan Position Carefully
          1. Proper patient fixation is required (focus on the green light or yellow light in patients with cataracts). The operator may manually adjust the scan ring around the grey-scale image of the disc to ensure it is centered.
      iii. Check Signal Strength
          1. A reliable test has a signal strength >7. Superior and nasal quadrants are more susceptible to changes in image quality when SS is low.
          2. Maximize Signal Strength:
             a. Adequate dilation
             b. Focus the adjustment knob to match the patient’s refractive error
             c. Use artificial tears and have the patient blink frequently
      iv. Do Signal-Profile Analysis
          1. Look at the TSINT “double hump” profile. Quality? Compared to age-matched controls?
2. Look for asymmetry between the 2 eyes
3. Look at the RNFL thickness measurements (especially superior and inferior), however keep in mind that these may be “normal” in the setting of focal depressions.

v. Conduct Sector Analysis – the “pie charts”
vi. Check Correlation to VF – important! Periodically go back looking for new VF defects when preperimetric glaucoma is evident.

vii. Compare to the Normative Database with Discretion
1. Stratus OCT Fast Protocol: 328 control subjects (11 Asian, 3 Indian, 27 Black, 79 Hispanic, 205 White, 3 Other). No myopic discs, peripapillary atrophy, or ON drusen.

viii. Remember Your Pros and Cons
1. Cons
   a. Pupil dilation required
   b. Cataracts/cornea/retina pathology affect results
   c. Small normative database
   d. No progression software
   e. Only a sampling of points along a circle

2. Pros
   a. No reference plane required
   b. Most paths can be corrected for
   c. Fast and easy to interpret
   d. Most versatile
   e. RNFL and ONH scanning data

ix. Involve the Patient – Show them the printouts

x. Consider Cost/Compliance
1. Document interpretation and assessment, even if unreliable
2. One test per year is usually sufficient
3. Rarely useful in advanced glaucoma because of the “floor effect.” VF testing is more appropriate.

IV. Potential Artifacts and Interpretation Errors
a. “Red and Green Disease” – a diagnosis of glaucoma based on mistaken identification of an area as abnormal vs. a missed glaucoma diagnosis because the OCT appeared normal.
   i. Red Disease: Refractive extremes, especially high myopia, in comparison to normative databases. High myopes’ measurements tend to fall outside of the normal range and will show up as red.
   ii. Green Disease: Small focal areas of damage in any eye often show up as green because the instrument averages the thickness in a particular sector.
An example of “green disease” with focal loss corresponding to a VF defect mistakenly read as normal (left). “Red disease” in a high myope (above). Asrani, S., Rev of Ophth 2013.

b. Types of Artifacts
   i. Acquisition-Dependent Artifacts: caused by the person acquiring the images
      1. Ring measurement is not placed concentric with the ONH (look at the raw data to avoid)
   ii. Disease-Related Artifacts
      1. Peripapillary atrophy may result in a failure to identify the nerve fiber layer in those regions
      2. Epiretinal membranes – may appear as a double edge to the nerve fiber layer or as wrinkling
      3. The posterior vitreous face may be mistakenly identified as the upper edge of the retina
   iii. Instrument-Related Artifacts
      1. Patient head tilt
         a. A variation in head position as little as 8 degrees between scans can result in a major difference in the thickness reading. Some machines will now compensate for this.
      2. Micro-saccades
         a. Image quality numbers and areas of “black out” on the print out may indicate a poor quality scan from microsaccades. Newer machines now have eye tracking available.

V. The Future of Optic Nerve Head Imaging in Glaucoma
   a. The paradigm is shifting from macroscopic to microscopic measurements.
i. Higher-resolution SD-OCT devices (27,000 A-scans per second) have been developed with shorter acquisition times and 3-dimensional imaging of posterior segment structures that enable measurement of the RGC thickness.

ii. Higher-speed technology (such as swept-source OCT with 100,000 A-scans per second) may allow for imaging of deeper structures including choroid, sclera, and lamina cribrosa.

1. Looking directly at the lamina cribrosa, the hypothesized site of glaucoma damage, is an area of increasing interest in glaucoma research.

"View with the DRI OCT-1, Atlantis swept source OCT (Topcon)"

b. Technology to measure RGC dysfunction and imaging of cellular and sub-cellular structures may be a possibility thereafter.

c. Progression detection may be enhanced by improvements in eye tracking, image registration, and refinement in software algorithms that differentiate test-retest variability from true biological changes.

d. A combined structure function index that allows for an estimation of the rate of RGC loss may provide improved change detection.

References