Glaucoma

- Glaucoma is a family of chronic, progressive optic neuropathies characterized by distinctive structural changes to the optic nerve head and retinal nerve fiber layer associated with changes in visual function.

- Functional change can indicate a disturbance of any test of visual function:
  - Visual field
  - Visual evoked potential
  - Electroretinography
  - Color vision
  - Pupillary light reflexes

Measuring Structure and Function

- Clinical measurements of structure and function are attempts to quantify the integrity of the anatomical neural pathway subserving vision.

- Retinocortical pathways for vision are composed of retinal ganglion cells and their axons.

- Clinical measurements of structure and function, at any stage of glaucoma, exhibit a wide variability between individuals and on repeated measurements, so the true extent of glaucoma-induced damage to the visual system is often difficult to ascertain.

Structure-Function Relationship

- In progressive glaucoma, a structure-function relationship exists between optic disc cupping and changes in the visual field.

- For most people with glaucoma, minimal visual field change occurred when the vertical cup-to-disc ratio enlarged from 0.30 to 0.60.

- More marked field changes occurred when the cup-to-disc ratio enlarged from 0.60 to 1.0.

- In these patients, there is a functional latency period where structural damage occurs without measurable visual field loss.

Structure-Function Relationships

- The functional latency period seen in most patients indicates a curvilinear structure-function relationship between optic disc cupping and changes in the visual field.

- What about the nature of the structure-function relationships between optic disc cupping and other tests of visual function?
  - Visual evoked potential
  - Electroretinography
  - Color vision
  - Pupillary light reflex

Optic Nerve Examination – 2013

42-year-old black male suspected of developing glaucoma

- Cup-to-disc ratio = 0.70/0.70
  IOP = 26 mmHg

- Cup-to-disc ratio = 0.70/0.65
  IOP = 23 mmHg

Pupillary Light Reflex Testing

- The pupillary light reflex is an objective sign of visual pathway function
- Relative afferent pupillary defect (RAPD) is an asymmetry in the pupillary light response
- Automated pupillography is the computer-assisted assessment of differential amplitudes and latencies

RAPDx pupillographer is designed to detect a relative afferent pupillary defect.

Pupillary Light Reflex Testing – 2013

- Index-of-defect number is within the “normal” range for each eye
  Number is calculated by determining the log of the difference in amplitude between the pupillary responses

Diagnostic Sensitivity for Glaucoma

- Cup-to-disc ratio = 56%
- Intraocular pressure = 65%
- Retinal nerve fiber layer analysis = 67%
- Ganglion cell complex analysis = 68%
- RAPDx pupillary testing = 81%
- Combination of RNFL, GCC, CD Ratio = 86%


Structural Exam with OCT – 2013

- Loss of retinal ganglion cells and their axons
- Large optic cup with vertical elongation
- Mild asymmetry between the eyes
- OCT test results are consistent with early glaucoma*

60-4 Visual Field – 2013
Some studies suggest that glaucoma must not be considered as a disease exclusively including ocular structures, but is a pathology in which brain structures are also damaged.

- VEP test is normal.


VEP testing evaluates the integrity of the afferent visual sensory system by measuring the speed and strength of the evoked response.

Fallout of the retinal nerve fiber layer, both eyes
- Sector plot analysis demonstrates asymmetry, with more damage on the left eye
- Both eyes show progression from two years earlier

Ganglion cell complex analysis, both eyes
- No perifoveal thinning
- No clinically significant asymmetry
- Ganglion cell complex analysis is normal
- Results do not correlate with RNFL

Results do not correlate with RNFL.

Normal visual field examination, right eye
Small paracentral scotoma, left eye

Extended color vision testing evaluates the integrity of the afferent visual sensory system
- Examination methods determine the severity and axis of the defect:
  - Farnsworth D-15 or D-100
  - ColorDx
  - Robin Cone Contrast Test
  - Anomaloscope
- No color vision defect noted in the patient.

- Normal visual field examination, right eye
- Small paracentral scotoma, left eye

- Color vision testing results and methods.
- No color vision defect noted in the patient.
Acquired Defects in Glaucoma

- Color vision defects may precede visual field loss in patients with glaucoma.
- Most common glaucoma-induced color vision defects are a Tritan type of color vision deficiency.
- Some patients with glaucoma only develop loss of chromatic discrimination in advanced disease.
- Some patients with glaucoma have elevated color contrast levels.

Neural Response of the Visual Pathway

- **Receptors**
  - Photosensitive rods and cones in the retina are neurons specialized to detect light and they encode the initial neural response.
  - Circuitry for color coding begins with the parallel ganglion cell systems that are organized throughout the subcortical pathway.

Parallel Ganglion Cell Systems

- **Transmitters**
  - Optic nerve, optic chiasm, optic tract, lateral geniculate nucleus, optic radiations.
    - Parvocellular division: high-spatial and low temporal frequencies, red-green color vision (64% red cones / 34% green cones), 80% of fibers with high redundancy.
    - Magnocellular division: low-spatial and high temporal frequencies, achromatic vision information that is sensitive to motion, 5-10% of fibers with low redundancy.
    - Koniocellular division: blue-yellow color vision (2% cones), 5-10% of fibers with low redundancy.

Neural Response of the Visual Pathway

- **Primary Visual Cortex**
  - Receives axonal projections from the lateral geniculate nucleus.
  - Uses neural circuits to process the following:
    - Color
    - Form
    - Movement
    - Direction
    - Stereopsis

Lateral Geniculate Nucleus

Reorganizes the parallel ganglion cell systems into separate layers where the axons project to specific layers in the visual cortex.

Fourier transform software in EvokeDx converts the waveform from the Time Domain to the Frequency Domain.

Sophisticated Signal Processing:
- T2 circ
- Signal-to-Noise Ratio (SNR)
- Magnitude-Squared Coherence

Isolated-check VEP Testing

2nd generation VEP+ERG technology allows the testing device to measure other waveform variables in addition to measuring amplitude and latency.

Sophisticated Signal Processing:
- 72 deg Polar Plot
- Signal-to-Noise Ratio (SNR)
- Magnitude-Squared Coherence
- VEP Waveform
Isolated-Check VEP Testing

- Technology uses an isolated-check stimulus pattern to generate the VEP waveform
- Test strategy includes a low-contrast, isolated bright or dark-check pattern that is sinusoidally modulated, on and off, against a uniform gray (50cd/m2) background, producing an appearance-disappearance phenomena
- The high temporal frequency pattern, “icVEP”, is designed to assess the low-contrast processing in the central vision system thought to be affected early in the development of glaucoma

icVEP Testing – Right Eye

T2 circ Polar Plot
- Large spread of “run” points
- 95% Confidence Interval includes the origin (0,0)
- Mean of the runs is virtually at the origin (0,0)
- All variables are abnormal

Signal-to-Noise Ratio (SNR)
- Ratios below 1.00 are considered to be “in the noise” and therefore a SNR of 0.47 is abnormal

Magnitude-Squared Coherence (MSC)
- Fundamental response (1st harmonic) is below the critical level for significance

VEP Waveform
- The waveform shape is non-sinusoidal, an abnormality known as wave shape perturbation

The test results indicate there is no significant response at the stimulus frequency – a clinical finding associated with early glaucoma*

icVEP Testing – Left Eye

T2 circ Polar Plot
- Scattered “run” pattern
- 95% Confidence Interval includes the origin (0,0)
- Mean of the runs is virtually at the origin (0,0)
- All variables are abnormal

Signal-to-Noise Ratio (SNR)
- Ratios below 1.00 are considered to be “in the noise” and therefore a SNR of 0.49 is abnormal

Magnitude-Squared Coherence (MSC)
- Fundamental response (1st harmonic) is below the critical level for significance

VEP Waveform
- The waveform shape is non-sinusoidal, an abnormality known as wave shape perturbation

The test results indicate there is no significant response at the stimulus frequency – a clinical finding associated with early glaucoma*

PERG Testing – Both Eyes

T2 circ Polar Plot
- 95% Confidence Interval does not include the origin (0,0)
- Mean of runs is away from the origin (0,0)
- Scattered plot grouped tightly in one or two quadrants

Signal-to-Noise Ratio (SNR)
- Ratios above 1.00 are considered to be “out of the noise” and therefore both eyes can be considered normal

Magnitude-Squared Coherence (MSC)
- Step five also has an SNR value below 1.00, which would indicate some parvocellular damage or abnormality

PERG Waveform
- The waveform shape is somewhat sinusoidal

The electrodiagnostic test results indicate there is a significant response*

VEP Testing – 2015

- Pattern-reversal visual evoked potential testing
- Normal statistical analysis of the VEP waveform in both eyes
- Normal N75-P100 wave complex in both eyes
- Normal VEP waveform shape in both eyes*

NOVA-LX PERG Fixed Testing Protocols

Concentric Stimulus Fields
- Protocol aids in the diagnosis of diseases that affect the retina in specific topographic patterns
- Age-related macular degeneration
- Diabetic macular edema
- Toxic maculopathies

Contrast Sensitivity
- Protocol aids in the diagnosis of diseases that affect the retina in a diffuse pattern
- Helps to detect the depth of macular dysfunction in diseases like glaucoma or diabetic retinopathy
Three equally-spaced sinusoidal-shaped wave peaks represents a normal response pERG waveform on the NOVA-ERG

Signal strength above 1.2 microvolts represents a normal response pERG waveform

No clinically significant asymmetry between the eyes represents a normal response pERG

Flattened wave peaks on the left eye's pERG waveform represent an abnormal response

The wave peaks are not equally-spaced and sinusoidally shaped

Normal signal strength on both eyes (above 1.2 microvolts)

Clinically significant asymmetry – a finding common in early glaucoma

Medical Decision-Making

Review all of the diagnostic test results

- Progressive loss of retinal ganglion cells with OCT imaging
- Abnormal intraocular pressures
- Abnormal pERG test results on NOVA-LX (contrast sensitivity)
- Normal OCT scan of the ganglion cell complex
- Normal threshold visual field examination
- Normal pERG test results on EvokeDx
- Normal VEP test results on NOVA-LX (2013 and 2015)
- Normal extended color vision examination
- Normal pupillary reflex testing
- Normal anterior chamber examination

Diagnose and treat primary open-angle glaucoma

Optic Nerve Examination

62-year-old black male suspected of developing glaucoma

Cup-to-Disc ratio = 0.70/0.65
IOP = 29 mmHg

Cup-to-disc ratio = 0.70/0.65
IOP = 26 mmHg

Pupillary Light Reflex Testing

62-year-old black male suspected of developing glaucoma

Index-of-defect number is within the “normal” range in each eye
Mild asymmetry with a slight delay in the latency in the left eye’s response

Retinal Nerve Fiber Layer

Mild loss of retinal ganglion cells in the left eye

TSNIT Curve Profile reveals flattening of the inferior RNFL bundle in the left eye

Clinically significant asymmetry – a clinical finding associated with early glaucoma
Macula Thickness Analysis

- Retinal atrophy revealed on both eyes, slight asymmetry R < L

Ganglion Cell Complex

- Clinically significant perifoveal retinal thinning in both eyes
- Sector plot analysis demonstrates asymmetry with the left eye having more damage

Biomicroscopy

**Anterior Chamber Examination**

- The anatomical configuration of the iris and angle structure is important in the pathogenesis of certain forms of glaucoma.
- This patient appears to have a normal iris configuration with open angles in all quadrants

Gonioscopy

**Goals of Performing Gonioscopic Examination of the Angle**

- Determine the functioning status of the angle
- Determine the degree of angle closure
- Determine the risk of future closure of the iridocorneal angle
- There is no apparent obstruction of the angle or outflow mechanism

Visual Field Examination

- No definite glaucomatous visual field defects

Color Vision

**Dyschromatopsia of glaucoma**

- Mild Tritan color vision defect in both eyes
- In many patients, color vision test results correlate with the mean deviation in threshold visual field tests and OCT measurements of the ganglion cell complex
Isolated-Check VEP Testing

The test results indicate there is no significant response at the stimulus frequency – a clinical finding associated with early glaucoma.

Pattern-Reversal VEP Testing

- Delayed peak time on the low-contrast response, right eye
- Low amplitude on both low-contrast VEP responses
- Both VEP waveform abnormalities are consistent with early glaucoma*

Reproducibility on Retest – 2 weeks

IOP is 16 mmHg in each eye on Travatan Z at bedtime*

icVEP-CSwp-B (Bright Checks)

- The Magnocellular ON pathway contains the largest cells (M-cells) in the human visual system, and therefore, they are likely to be the most metabolically active and susceptible to disease
- Bright checks are designed to target the Magnocellular ON pathway
- A series of 10 second sweeps create time-domain data packages that are averaged and then Fourier transformed to the frequency domain
- Multi-variant, Fourier transformed, analytic tools are then used to assess frequency domain signal and noise information derived from the entire waveform rather than an assessment based upon just one or two time domain latency values

Steps of Contrast Variation

- The first four steps are thought to test the magnocellular part of the visual pathway
- The last two steps test the Parvocellular part of the visual pathway
- Step four is almost identical to the icVEP-UC test parameter

Signal-to-Noise Ratio (SNR)

- The first four steps have an SNR value below 1.00 (red)
- Steps five and six have an SNR value above 1.00, which would indicate overall Parvocellular function still intact

icVEP-CSwp-D (Dark Checks)

- The Magnocellular OFF pathway contains the smallest cells (P-cells) in the human visual system, and therefore, they are likely to be the least metabolically active and susceptible to disease
- Dark checks provide negative contrast, which is thought to test the magnocellular OFF pathway

Signal-to-Noise Ratio (SNR)

- The first three steps have an SNR value below 1.00 (red); this would indicate damage to the OFF portion of the magnocellular pathway
- Step four, for the right eye, is showing green. However, step five is showing red. This may just be a statistical anomaly or it may indicate possible magnocellular damage or abnormality in the right eye.
icVEP-Cswp-D (Dark Checks)

- Dark checks provide negative contrast, which is thought to test the Magnocellular OFF pathway

Signal-to-Noise Ratio (SNR)
- Steps three and four are green and have an SNR value above 1.00. This would indicate overall Magnocellular function is intact.
- Steps five and six are green and have an SNR value above 1.00. This would indicate overall Parvocellular function is intact.

Medical Decision-Making

- Review all of the diagnostic test results
  - Mild loss of retinal ganglion cells with OCT imaging
  - Abnormal intraocular pressures
  - Abnormal VEP test results (EvokeDx and NOVA-LX)
  - Abnormal OCT scan of the ganglion cell complex
  - Abnormal color vision examination
  - Normal threshold visual field examination
  - Normal pupillary reflex testing*
  - Normal anterior chamber examination

- Diagnose primary open-angle glaucoma
- Prescribe topical medication to treat glaucoma

Discussion

- There are several ways to measure a person’s vision, and glaucoma can produce functional defects in all of them
- Although visual field testing is the standard method of evaluating glaucoma-induced vision loss, only 35% of patients have a visual field defect as their first clinical sign
- New functional testing has proven that in many patients, glaucoma-induced vision loss can be detected with other technologies before visual field loss can be detected on a perimeter

Medical Hypertension Treatment Study

Conclusion

- Combining structural and functional testing improves the ability to diagnose early glaucoma
- We should use measurements in one domain (structure or function) to support the interpretation of clinical measurements in the other domain
- We should remember that every patient with glaucoma is different, every diagnostic test result has the potential to be different, and the relationship between structure and function measurements varies from patient-to-patient