Assessing Glaucoma Risk Factors and Identifying Glaucoma Progression

Joseph Sowka, OD
Michael Chaglasian, OD

- Outline
- Diagnosing Glaucoma
- Risk Factors
- Ocular Perfusion Pressure
- Optic Nerve Examination
- The 5R’s

Glaucoma Treatment Decisions: Risk Assessment
- Risk Calculator
- Guide to Patient Management
- OHTS – EGPS Limitations?
- RF’s for Glaucoma:

- **OHTS Study and Corneal Thickness**
  - Thin: <555 µ High Risk
  - Average: 555-588 µ No change in Risk
  - Thick: >588 µ Low Risk

Ocular Perfusion Pressure: New Evidence
- Ocular Perfusion Pressure and Glaucoma Progression
- Definition and Calculation
- Lower IOP improves OPP
- Remains number 1 goal !!
- Measure blood pressure on your patients
- Higher systemic BP improves OPP, but you do not necessarily want to raise BP:
- Nocturnal Hypotension and OPP
- Avoiding IOP meds that LOWER systemic BP at night (beta blockers, alpha agonists) makes sense.
- Glaucoma Medications and Their Effects on OPP

Optic Disc Hemorrhages
- Appearance may precede NFL loss, notching, VF defect
- Associated with progressive VF defects in glaucoma or OHT (up to 20X greater risk); especially among females [Drance et al. AJO 2001]
- More frequent in NTG than COAG or OHT
Examples
Clinical Studies and Results

**Corneal Hysteresis**
- Corneal Hysteresis is the difference in the inward and outward pressure values obtained during the dynamic bi-directional applanation process employed in the Ocular Response Analyzer, as a result of viscous damping in the cornea.
- Corneal and Glaucoma
- Numerous studies, such as the Ocular Hypertension Treatment Study (OHTS) have found that corneal thickness is an independent indicator of glaucoma risk.
- More recent research has indicated that the Corneal Hysteresis measurement appears to be even more powerful in this regard.
  - Evidence from the literature.
  - Examples

**Glaucoma Progression Possibilities: Event Analysis vs. Trend Analysis**
- Progression can be categorized as event analysis or trend analysis
  - Event analysis- compares baseline to most recent data; change as dictated by criteria has occurred or not
  - Trend analysis looks at the significance of rate of change over time.
    - Identifies progression by looking at patient behavior over time.
    - Uses all data points and a linear regression formula
    - Weakness- progression is not necessarily linear
- Glaucoma progression rate is the most important determinant of therapy and future visual impairment
- Past progression rate is the most influential determiner of future progression rate
- Measuring rate of progression is difficult as it is hard to differentiate true change from variation in testing.

**Risk Factors for Progression:**
- IOP level
  - The most significant modifiable risk factor for glaucoma development and progression
- IOP fluctuation
  - Possibly indicates changing perfusion pressure and decreased autoregulatory ability
- Exfoliation
  - Higher IOP, worse disease, more difficult to control, noted in numerous studies in association with progression
- Central Corneal Thickness (CCT)
  - OHTS and many others point out that thin cornea a risk factor
- Disc hemorrhages
  - Patients with normal tension glaucoma, primary open angle glaucoma, ocular hypertension
- Anemia, posterior vitreous detachment, vascular occlusion can cause hemorrhages of the disc that are mistaken for glaucomatous disc hemorrhages
  - Ischemic or mechanical
  - Probable infarction of the blood supply to the ONH
  - Inferior, inferior temporal, superior, superior temporal regions of the disc most susceptible and account for virtually all true disc hemorrhages
    - Hemorrhages at other areas of the disc (nasal and temporal) tend to not be associated with glaucoma
  - Typically occurs where notches occur
  - Resides in the retinal nerve fiber layer
    - Not in the cup!
  - Small and contiguous with the neuroretinal rim
  - Can be recurrent and, if it recurs, it typically is in the same place on the disc each time
  - Precedes notching, NFL defect, field loss. Perhaps the earliest change in glaucoma (if it happens)
  - More common in patients with large IOP variations
  - Meaning is unclear – possibly indicates poor control of IOP?
  - Disc hemorrhages do not constitute a diagnosis of glaucoma nor a progression or conversion to glaucoma or an endpoint for any major glaucoma

- Time
  - Glaucoma is by nature a progressive disease and treatment likely only slows the progression
  - Given enough time, most will demonstrate progression and this is not a sign of treatment failure

- Ocular Perfusion Pressure (OPP)
  - The difference between systemic blood pressure and intraocular pressure.
    - A measure of retinal and optic nerve perfusion
  - Systolic Perfusion Pressure (SPP)
    - SPP = Systolic Blood Pressure – IOP
  - Diastolic Perfusion Pressure (DPP)
    - DPP = Diastolic Blood Pressure – IOP
  - Mean Perfusion Pressure (MPP)
    - MPP = Mean arterial pressure – IOP
      - Mean Arterial Pressure = 2/3 DBP + 1/3 SBP

- Baltimore Eye Survey
  - Lower OPP strongly associated with prevalence of POAG
  - Six-fold excess risk of having glaucomatous optic nerve damage in persons with lowest category of OPP

- The Egna-Neumarkt Study
  - Lower DPP associated with a higher risk of having glaucomatous optic nerve damage

- Proyecto Ver Study
- Persons with Diastolic Perfusion Pressure < 50 mmHg had a four-fold higher risk of having POAG compared to those with Diastolic Perfusion Pressure of 80 mmHg
- Los Angeles Latino Eye Study
  - Persons with Low Diastolic and Systolic perfusion pressures had a higher risk of having POAG
- Barbados Incidence Study
  - 4-year risk of developing glaucomatous optic nerve damage increased dramatically at lower
    - Systolic Perfusion Pressure 2.6 fold
    - Diastolic Perfusion Pressure 3.2 fold
    - Mean Perfusion Pressure 3.1 fold
  - 9-year risk of developing glaucomatous optic nerve damage increased at lower
    - Systolic Perfusion Pressure 2.0 fold
    - Diastolic Perfusion Pressure 2.1 fold
    - Mean Perfusion Pressure 2.6 fold

Patient Compliance
- Nearly 50% of patients show non-continuous use by 6 months after start of therapy
- Communication Skills and Information Exchange
  - How well the Doctor communicates the importance of compliance
- Choice of Medications and the treatment regimen
  - Managing side effects
  - Impact the diagnosis and medication has on one’s quality of life
- Situational and Environmental factors
  - Other diseases
  - Life events
  - Social support
- Assorted other factors
  - Cost
  - Insurance and formulary issues
  - Physical barriers
    - Drop instillation difficulties due to arthritis

Risk Factors for Progression: Summarizing What the Major Studies Tell Us
- Disc hemorrhage (NTGS, OHTS, EMGT)
  - NTGS, EMGT saw no difference with IOP reduction
- Fluctuation of IOP (AGIS)
  - Technically reported, but not accurate or accepted
- Thin cornea (EMGT, OHTS)
- Higher baseline IOP (EMGT, OHTS, AGIS)
  - Not CNTGS
- Exfoliation (EMGT)
- Cardiovascular disease (EMGT, NTGS)
- Lower OPP (EMGT)
- Older age (EMGT, AGIS)
  - not CNTGS

**Judging progression**

Progression may be measured by

- Functional change as indicated by visual field deterioration
- Structural change in the optic disc or retinal nerve fiber layer
- Progression can be categorized as event analysis or trend analysis
  - Event analysis- compares baseline to most recent data; change as dictated by criteria has occurred or not
  - Trend analysis looks at the significance of rate of change over time.
    - Identifies progression by looking at patient behavior over time.
    - Uses all data points and a linear regression formula
    - Main Weakness- progression is not necessarily linear
- Glaucoma progression rate is the most important determinant of therapy and future visual impairment
- Past progression rate is the most influential determiner of future progression rate
- Measuring rate of progression is difficult as it is hard to differentiate true change from variation in testing.

**Structure change vs. Function change: Which comes first?**

- Ocular Hypertension Treatment Study (OHTS)
  - Patients who converted to glaucoma
    - 55% had optic disc changes only
    - 35% had Visual field changes only
    - 10% had both
- Early Manifest Glaucoma Trial (EMGT)
  - Of the 136 patients who showed evidence of progression
    - 86% reached endpoint by Visual Field changes alone
    - 13% showed optic disc and visual field changes together
    - 1 patient showed optic disc change
- Structure and Function Evaluation Study (SAFE)
  - 479 eyes of 295 subjects
    - Ocular hypertension patients with normal visual fields
    - Followed for 4 or more years
    - Optic discs that appeared glaucomatous at baseline were more likely to show visual field progression
      - Suggests that structural change preceded functional change
      - These findings support the premise that a glaucomatous optic disk is predictive of the subsequent development of glaucomatous visual field loss

**Combining Functional and Structural Measurement for Glaucoma Diagnosis and Determining Progression**
• In reality, there are patients that show structural changes first in glaucoma (likely the majority) and others that show functional changes first.
• The combination of a functional test (visual field analysis) and a structural measurement (disc photograph or imaging device) allows for most accurate diagnosis as one alone is likely not enough.
• Importance and limitations of clinical assessment
  o Wide diversity of normal appearance
  o Potential overlap of non-glaucomatous and glaucomatous
• Clinical application of imaging
  o Diagnosis
    ▪ Normal vs. abnormal
  o Determination of progression or stability

Limitations of Functional Measurement
• Reliability and reproducibility biggest limiting factor
  o In the OHTS, an attempt was made to identify the occurrence of normal visual field test results following 2 vs. 3 consecutive, abnormal, reliable test results in the OHTS study
    ▪ A VF endpoint confirmed by 3 consecutive abnormal, reliable VF test results appears to have greater specificity and sensitivity than either 1 or 2 consecutive abnormal, reliable VF test results.
  • However, some eyes whose VF POAG endpoint was confirmed by 3 consecutive abnormal, reliable VF test results nonetheless had 1 or more normal tests on follow-up.
  o AGIS: In patients with advanced glaucoma, a single confirmatory test 6 months after a VF worsening indicates with at least 72% probability a persistent defect when the worsening is defined by at least 2 decibels of MD.
    ▪ When the number of confirmatory tests is increased from 1 to 2, the percentage of eyes that show a persistent defect increases from 72% to 84%.

• Ability to understand test
• Patient physical limitations to sit through long tests
• Significant damage must occur prior to measurable functional loss
• Subjective interpretation of results

Limitations of Structural Measurement
• Artifact in acquisition
  o motion, media, placement of measurement, operator skill
• Anatomy not consistent with normative database to which patient is being compared
  o severely tilted discs, extreme variations in disc size, high myopia
  o Very early damage
    ▪ acquired change has occurred but does not exceed the range of normal values
Advanced damage
- little value obtained from images from clearly end extensively abnormal optic nerves and retinal nerve fiber layer
- dynamic range of device is exceeded, abnormality is clear, values too low to be able to determine progression

Subjective interpretation of results

When to do each and when to repeat?
- Visual fields more often due to long term fluctuation and learning curve
- Annually if stable, more often if unstable
- Photographs and imaging at time of initial diagnosis and then annually thereafter

When not to do each and when not to repeat?
- Poor initial quality
- Photographs and imaging not helpful in very advanced disease
  - No information to be gained

Functional Testing: Visual Fields

New Technologies for Measuring Progression: Visual Field Guided Progression Analysis (GPA)
- *Glaucoma Progression Analysis*
- Used with Humphrey HFA II-i perimeter
- Uses algorithm developed for Early Manifest Glaucoma Trial
- Designed to help identify clinically significant progression of visual field loss in patients with glaucoma
- Highlights changes from selected baseline examinations that are larger than typical clinical variability in patients with similar degrees of glaucoma.
- Identifies consistent and repeated patterns of loss
- Corrects for ocular media effects
- Analysis based upon detailed empirical knowledge of variability found at all stages of glucomatous visual field loss
- Can be used on full threshold (baseline only), SITA Standard, and SITA Fast strategies
- Visual fields that repeatedly and consistently show changes exceeding what is known to represent typical variability are identified as having “possible” or “likely” progression

GPA: Clinical Considerations
- Baseline is established
  - Either by machine or by operator
  - Machine picks two earliest similar strategies
- Small triangles on printout (following baseline) identify statistically significant change
- Open triangles
  - Denotes a point that has progressed at least one time
  - Identifies any point that has worsened by an amount that exceeds the variability expected in all but the most variable 5% (p<0.05) of glaucoma patients having
similar visual fields status. This symbol is shown if the change is greater than 95% of the variability seen in that exact test location in fields having a similar mean threshold deviation from normal values. This can occur on the first follow-up (after baseline) exam

- Half-filled triangle
  - Identifies points changing as described above (p<0.05) in two consecutive follow-up (after baseline) exams. (Possible Progression)

- Filled triangle
  - Identifies points changing as described above (p<0.05) in three consecutive follow-up (after baseline) exams. (Likely Progression)

**GPA Alert: Possible progression, Likely Progression, and No Progression Detected**

- Combines the knowledge of clinical variability with the demand that the change be consistent and repeatable.
- Judging progression should involve all clinical data
  - However, if solely using perimetric data, the significant change should be present in at least two follow-up tests and must be found consistently in the same area of the visual field
  - Before changing therapy based upon this information, care should be made to ensure that the baseline exams are appropriate and the follow-up exams are reliable.
- When significant degradation is present in the same three or more points (on the same side of the horizontal meridian) on two consecutive follow-up exams, the GPA software will alert you to “Possible Progression”. If this trend is present on three consecutive follow-up exams, the GPA software with alert you to “Likely Progression”
- On newest version, if none of the above criteria are met, the message “No Progression Detected” will be displayed. (The term, “Definite Progression” will never be displayed).

**Visual Field Index (VFI)** is a new summary measurement of the visual field status as a percent of a normal age-adjusted visual field.
- VFI is optimized for progression analysis
- It is less affected by cataract or media changes than earlier indices
- VFI is used to quantify the rate of progression where it is plotted relative to the patient age to calculate the rate of functional loss
- The VFI plot provides a linear regression analysis of the VFI over time
  - Minimum of 5 exams over 3 years is required to have VFI plot
  - This is the trend analysis
- An outstanding concept, but it ignores the fact that progression isn’t necessarily linear.

- Slope of Mean Deviation from all exams is determined using a regression analysis. This allows one to determine the rate of progression

In general, a total minimum of 4 exams (2 baseline and 2 follow-up exams) is required in order to judge “Possible Progression”. In order to get a message of “Likely Progression”, 5 exams (2 baseline and 3 follow-up) are necessary
Structural Testing: Photographs and Imaging Devices

- Using photographs to judge progression can be difficult with a steep learning curve.
- Subject to errors based upon observer as well as artifacts of camera and equipment
- Newer approaches use imaging devices and statistical analyses (HRT, GDx, OCT)
  - Two possible reasons for change on imaging devices
    - Error in acquisition, error in image registration, poor image quality/signal strength, cataract, inherent variability in measurement
    - True biological change
  - Differentiating one from the other is difficult

New Technologies for Measuring Progression: Guided Progression Analysis (GPA) for Structural Tests