Technological Advances in the Diagnosis of Patients with Glaucoma

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Key Points
- Glaucoma viewed as CNS disease
- Integration of clinical & research efforts
- Importance of research collaborations
- Innovative diagnostic technologies
- Revolutionary therapies (neuroregeneration)

Glaucoma: Blinding Disease
- Second leading cause of blindness globally (WHO)
- By 2020, nearly 80 million (Quigley HA, BJO 2006)
- Gradual loss of vision; “A thief in the night”
- Treatment does not slow progression of the disease in all cases (EMGT)
- 45% progression at 5 years (Leske MC, Arch Ophth 2002)

Diagnostic Tests for Glaucoma
- IOP
  - Tonometry
- Optic Nerve Damage
  - Ophthalmoscopy
  - Fundus photography
  - Other devices (eg, HRT, GDx, OCT)
- Visual Fields
  - Perimetry (SAP, SWAP)
  - Other technology (FDT)

Once Vision Loss is Detected, Structural Damage Has Already Occurred
- Patients may lose up to 40% of their optic nerve fibers before damage can be detected
- Patients may lose up to 90% of their nerve fibers before they notice symptoms

Most glaucoma patients are likely to show disease progression (modified from Bengtsson & Heijl).

If just followed long enough

If monitored with reasonably sensitive methods

EMGT, median follow-up time: 8 years

Variability issues with Standard Perimetry

Subjective nature of test

- Ability to measure visual function is a benefit & a limitation of perimetry
- Reliable results provide quality of life assessments; however, patients do not always test reliably

Type of defect

Deeper defects vary more than shallow defects

Peripheral defects vary more than central defects

Baseline printout: Baseline

- Summarizes the two earliest exams
- Averages threshold levels to arrive at a "baseline level" of damage
- Includes rate of progression analysis

Follow-up printout: Follow-up

- Summarizes the subsequent exams
- Determines change from baseline

HVF: GPA Overview

GPA analyzes results from multiple exams, and identifies progressing points, as compared to baseline data.
HVF Trend Analysis: Progressor

- Calculates rate of change for individual point
- Linear regression analysis of all visual fields obtained (slope)
- More sensitive to gradual, sustained change (as opposed to event analysis (GPA) which is more sensitive to sudden, stepwise changes)

Selecting Functional Tests

- Isolate one type of visual function (or ganglion cell)
- Detect visual field loss earlier than SAP (achromatic)
- Includes SWAP, FDT perimetry, Motion perimetry, Ring perimetry

HVF: Visual Field Index (VFI)

- replaces MD (dB) with % of a full field
- reduces effects of cataract

VFI: Visual Field Index (VFI)

Concomitant glaucoma and cataract

VFI: 87%
MD: -11.13 dB
(MD≈62%)

Courtesy: Bengtsson & Heijl

VFI and Ganglion Cell Density

A weighting procedure is applied by scaling the test point pattern according to ganglion cell density
The test point pattern is divided into 5 zones
Central zones are weighted more heavily than peripheral zones

Central defects - associated with more ganglion cell loss; influence VFI more than MD
Peripheral defects - associated with less ganglion cell loss; influence VFI less than MD

VFI 68%
MD -15.98 dB

VFI 39%
MD -15.98 dB

VFI 68%
MD -14.69 dB

VFI 39%
MD -15.98 dB

VFI and Ganglion Cell Loss

(Courtesy: Bengtsson & Heijl)

Advantages with VFI

- Scaled according to ganglion cell density
- Less sensitive to cataract than MD
- Comprehensible (%)
- Compact printout - everything on one paper
SITA SWAP Technology

SWAP (blue-on-yellow technology)
- Yellow background desensitizes only red and green cones
- Blue cones, and resulting ganglion cell connections, are tested
- These P-cells thought to be among the first damaged by glaucoma, and sparse population of P-cells inhibits masking of damage due to redundancy

SITA for SWAP
- The proprietary SITA algorithm, when applied to SWAP, reduces test times by incorporating probability functions to estimate threshold levels

Frequency Doubling Technology (FDT)
- Based on an optical illusion created when low spatial frequency grating patterns are contrast modulated at high rates
- Screening and Full threshold modes
- May be more sensitive than SAP for detecting early VF changes
- User friendly
- Allows testing in ambient light without eye patches/trial lenses

Glaucoma Consult: A.B.
- 64 y/o female dx borderline glaucoma x 4 yrs
- ?Borderline IOP ?Change in disc cupping
- Cc: vision more blurry OD
- OcularHx: phaco/IOL OD 1999
- PMHx: HTN, DM Type II (diet & exercise)
- FHx: glaucoma (mother)
- ROS: Hx of migraine HA, vasospasm

Initial Examination
- Va: 20/20 OU
- Ta: 21 OD, 18 OS (11:15 AM)
- K pachymetry: 534 OD, 536 OS
- Slit lamp: PCL OD (?PC opacity), trace NSC OS
- Gonio: Grade IV OU; No PAS
- Fundus: C/D ratios of 0.75 OD, 0.70 OS (intact disc rim 360 degr.); macula & periphery WNL

FDT and Matrix Clinical Examples

Limitations of FDT
- Still an emerging technology
- Less suitable for widespread use
- VF defects need repeat testing for validation
- Lack of long-term data
- Only 17 locations tested with initial FDT (Humphrey Matrix with 24-2 pattern)
- Caution should exercised when used for
- Definitive diagnosis
- Detecting disease progression

Nonlinear Response
1 cycle/degree or less
\{ greater than 15 Hz counterphase flicker
**Diagnosis and Management**
- Pre-perimetric glaucoma (as evidenced by normal SAP & abnormal SWAP)
- Ta: 24 OD, 20 OS (10:40 AM) on repeat visit
- Dx: early stage POAG OU
- Start IOP lowering medical therapy

**Pattern ERG**
- Predictive potential for assessing RGC function in glaucoma suspect & early OAG
- Circular black-white grating of 25 degrees visual angle, reversing 16.28 times per sec.
- Skin cup electrodes over lower eyelids & reference electrodes on ipsilateral temples
- Pilot study: PERG improvement with IOP lowering in high tension OAG and NTG

**Multifocal VEP**
- Promising research area in glaucoma
- Reduced response to high-flicker VEPs corresponds to degree of glaucoma damage
- May be abnormal when standard automated perimetry is normal (the reverse is also true)
- Selectively tests M cells on response

SAP=standard automated perimetry.

**icVEP - Overview**
- Objective (M)
- Selective

**icVEP - Theory**
- Isolated Check VEP (icVEP)
Stimuli

Isolated Check VEP Instrument

Electrode Placements

Three standard EEG electrodes will be placed along the midline of the head with water-soluble paste: one is connected to the scalp at Oz (active site); one is connected to the top of the head (vertex) at Cz (reference site); and the third one is placed midway between Oz and Cz at Pz (floating ground site).

Appearance-Disappearance

Fixation Screen Temporal Modulation

Stimulates On-pathway M cells

Low contrast, Bright pattern

Stimulates Off-pathway M cells

Low contrast, Dark pattern

icVEP – Current Modifications

<table>
<thead>
<tr>
<th>Frequency of Reversal</th>
<th>Contrasts</th>
<th># / Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original</td>
<td>10 Hz</td>
<td>10% 15%</td>
</tr>
<tr>
<td>Modification</td>
<td>10 Hz</td>
<td>16% 32% 100%</td>
</tr>
</tbody>
</table>

Can icVEP Technology

- Detect early RGC functional damage in the wide spectrum of glaucoma diagnosis?
  - 16:32 MAR shows promise
- Monitor RGC functional changes due to intraocular pressure (IOP) lowering?
  - To be continued...
- Establish moderate test-retest reliability?
  - r=0.975 for 16% SDR in control
- Detect functional asymmetry in interocular comparison?
  - 32:100 MAR and other measures show promise

Limitations

- Co-morbid conditions may lead to false-positive results
- Requires intact central vision
- Our clinical research studies (to date)
- Numerous exclusion criteria limit external validity
- Small sample size
- Intent to treat analysis

Current Glaucoma Treatment

Medication:
- α-adrenergic agonists
- Beta-blockers
- CAIs (topical & oral)
- Prostaglandins
- Miotic agents
- Combination agents

Surgery:
- Laser trabeculoplasty
- Laser iridotomy
- trabeculectomy
- Glaucoma implants
- Cyclodestruction
- Trabecular-based
- Schlemm’s canal
- Suprachoroidal

Clinical Outcome: Variable
Future Treatment Strategies

- Neuroprotection
  - Drugs
  - Gene Therapy
  - Stem Cell Therapy

Drugs / Biotechnology:
- Brimonidine
- Memantine (Namenda, Forest Labs)
- BDNF & CNTF (Phase 1: Sieving et al., PNAS 2006)
- Anti-NgR proteins

Gene: Bcl-2, p53
Stem cells (e.g. with encoded peptides)

Neuroprotection

- Drugs / Biotechnology:
  - Brimonidine
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  - Anti-NgR proteins

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Structural Assessment of Change

- Essential for early detection of glaucoma progression
- Provides an opportunity to prevent or minimize optic disc/RNFL damage with anti-glaucoma therapy
- Correlate with functional assessment of progression (e.g. visual fields)

Advantages: Stereophotography

- Permanent / reproducible & allows tracking of change over time
- Quantitative and objective measure of ONH changes
- Shown to assist in early Dx of glaucoma, prior to VF loss
- Useful in detection of disc hemorrhage

Which Instrument To Use?

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Hardware</th>
<th>Software</th>
<th>Database Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSLO</td>
<td>Stable</td>
<td>Refined</td>
<td>Database need input</td>
</tr>
<tr>
<td>SLP VCC</td>
<td>Stable</td>
<td>Evolving</td>
<td>Good theoretical potential for glaucoma diagnosis/monitoring</td>
</tr>
<tr>
<td>OCT</td>
<td>Evolving</td>
<td>Evolving</td>
<td>Good theoretical potential</td>
</tr>
</tbody>
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HRT for Progression: Reports

- Chauhan BC et al. Arch Ophthalmol 2001:
  - HRT1 for glaucoma progression

  - OHTS: HRT1 at certain sites
  - PPV = 14% BUT NPV = 92-95%
  - 92-95% of OHT w/ nl MRA & HRT classification did not develop OAG (5 years)
### Progression Rates: HRT / Perimetry

- **No progression (27%)**
- **HRT only (40%)**
- **Perimetry only (4%)**
- **Both, HRT and perimetry (29%)**

Chauhan et al., Arch Ophthalmol 2001;119:1492-1499

### Limitations: HRT

- **Normative database still expanding:**
  - Caucasian >700; African descent >200; SE Indian >100; Hispanic & Asian coming
- **Ability to detect change needs validation**
- **Progression software**
  - Reliability and validity being tested
  - Further algorithms to determine progression are needed

### Advantages: SLP With VCC

- Measures RNFL thickness by detecting birefringence
- Useful for diagnosing glaucoma
- Individually compensates for corneal birefringence
- GDx with VCC

### GDX VCC: Progression Tools

- Deviation Map
- Nerve fiber index (NFI): global measure (Medeiros FA et al, AJO 2005)
- TSNIT Map / Progression graph
- Newer ECC software

### Limitations of TD-OCT

- Needs reproducibility data
- Ability to detect change needs validation
- Longitudinal data currently not available to track progression
- Evolving platform & software
- Schuman et al. paper (AGS 2007)

### Sensitivity and Specificity: TD-OCT vs. SD-OCT

- Early (-3.2 dB) to moderate (-8 dB) OAG
- Cirrus: 83% & 88% (avg RNFL abnl @ 5%)
- Stratus: 80% & 94% (avg RNFL abnl @ 5%)
- Similar values for both in regards to quadrant & clock-hour RNFL thickness
- Cirrus equivalent to Stratus for RNFL

Comparison of GDx, HRT, OCT

Models: GDx VCC, HRT II, Stratus OCT
- 75 w/ glaucoma, 66 age-matched controls
- MD of glaucoma VF: approx. –5 dB
- AUC: GDx 0.91, OCT 0.92, HRT 0.86
- AUC & sensitivities at high specificities (80% and 95%) were similar


Optic Nerve Imaging

- Imaging instruments used to complement our clinical evaluation & disc photos
- Longitudinal assessment will likely improve our ability to monitor & follow glaucoma
- None of devices detect disc hemorrhages
- HRT3 promising for progression: disc size
- Spectral domain OCT & GDx ECC: clinical assessment underway

Key Points

- Glaucoma viewed as CNS disease
- Integration of clinical & research efforts
- Importance of research collaborations
- Innovative diagnostic technologies
- Revolutionary therapies (neuroregeneration)

Glucoma Translational Research at Yale School of Medicine

- Understanding pathophysiology of disease:
  - Trabecular meshwork
  - RGC development & alteration
  - Genetics
  - Immunobiology
- Neuroprotection therapies (preserve vision)
- Future:
  - Neuroregeneration (restore vision)
  - Nanotechnology drug delivery systems

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Thank You