“Psychophysical Testing of Retinal Structure and Function Using the Preferential Hyperacuity Perimeter”

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Forest Grove, Oregon
June 3, 2011

Disclaimer:

Dr. Yudcovitch does not hold proprietary financial interest in any of the products or companies mentioned in this presentation.

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AMD...

...is the leading cause of blindness in people age 65 or older in:
  - US
  - Europe
  - Australia
  - Japan

...is the leading cause of visual loss in Americans over the age of 50 years.


AMD Forecast from 2010 to 2050

Can We Do Better?

“Early detection of CNV could be one of the most important factors contributing to the reduction of blindness from AMD over the next several years.”

– Neil Bressler MD, Wilmer Eye Institute, Johns Hopkins

Age-Related Macular Degeneration (AMD, ARMD)

AMD is a disorder of the macula and is characterized by one or more of the following:

- Drusen formation (drusen = waste material)
- Retinal pigment epithelium (RPE) abnormalities such as hypopigmentation or hyperpigmentation
- Geographic atrophy of the RPE and choriocapillaris involving the center of the fovea
- Choroidal neovascularization (CNV)
**AMD stages**

**Pre-AMD (AREDS category 1)**
- Consists of less than 5 small drusen (63µ in diameter), with trace to no RPE abnormalities

**Early AMD (AREDS category 2)**
- Consists of a combination of multiple small drusen, few intermediate drusen (63-124µ in diameter), or RPE abnormalities

**Intermediate AMD (AREDS category 3)**
- Consists of extensive intermediate drusen (63-124µ in diameter), at least one large druse (>125µ in diameter), or geographic atrophy not involving the center of the fovea

**Advanced AMD (AREDS category 4)**
- Consists of one or more of the following:
  - Neovascular maculopathy such as
    - Choroidal neovascularization (CNV)
    - Serous and/or hemorrhagic detachment of the sensory retina or RPE
    - Lipid exudates
    - Subretinal & sub-RPE fibrovascular proliferation
    - Disciform scar
- Geographic atrophy (GA) of the RPE & choriocapillaris involving the center of the fovea

**AMD on OCT (Ocular coherence tomography)**
- Normal OCT – note the foveal depression
- Dry AMD – note lack of foveal depression
- Wet AMD – note CNV, hemorrhage, and shadowing

**Important Point:**
- Up to 90% of advanced AMD cases are due to CNV
Limitations of Current Diagnostic Methods for Early Detection of “Wet” AMD

Recent onset choroidal neovascularization is often difficult to diagnose

- No symptoms ~ 20/25
- Any sign of conversion?
- Fluorescein angiogram shows early CNV

Currently 80% of “wet” AMD patients arrive Too Late for most effective treatment

- Normal Fundus
- Fluid and Lipid
- Hemorrhage

Therapeutic Window

When a patient notices symptoms or Amsler Grid changes irreversible vision loss often has already occurred

Why is early diagnosis so important?

- Early Diagnosis Means Better Final Visual Acuity

Lesion size was a more significant factor affecting treatment benefit than either:
1. Lesion composition
2. Baseline visual acuity

TAP and VIP Report 1, AJO, Sept., 2003

Average CNV detection - today

- Average lesion size: 3300μ
- Location:
  - 80% Subfoveal
  - 20% Extrafoveal
- Initial Vision:
  - 20% ≥ 20/40
  - 40% 20/50 – 20/200
  - 40% < 20/200

Olsen, TW Ophthalmology Feb. 2004
AMD Diagnostic/Management Tests

- Dilated fundus examination
- Amsler Grid
- Fundus Photography
- Visual Fields (10-2, macula threshold, microperimetry)
- Preferential Hyperacuity Perimetry (PHP)
- Macula Pigment Density Measurement (Macuscope)
- Computerized Retinal Tomography (OCT, HRT, RTA)
- Angiography (fluorescein, indocyanine green)
- Fundus autofluorescence (confocal SLO)
- Multifocal ERG

Early Detection of CNV
Why Is It So Difficult?

AMD patients fail to notice their macular pathology

The Fundamental Reason:

- We do not see the image formed on our retina; we see an image created by the brain
- This brain image often ignores retinal defects! (e.g., the Blind Spot)

Limitations of the Amsler Grid

- Completion
  - The Amsler Grid does not overcome cortical completion
- Central Fixation
  - The Amsler Grid does not force fixation
- Crowding
  - Inhibition by neighboring peripheral lines reduces detection
- Compliance
  - Few patients use as directed

A subjective test for AMD monitoring & early detection of “wet” AMD

Preferential Hyperacuity Perimetry

- PHP
  - Automated central 14 degree test
    - ~4 minutes/eye
    - Hyperacuity stimuli
    - Detection/Quantification of hyperacuity defects
    - Detects progression of intermediate Dry AMD to early Wet AMD

Foresee PHP Technology
Vernier Acuity

- The human ability to perceive minute differences in the relative spatial localization of two objects in space
- The brain is exceptionally sensitized to the detection of small shifts in the co-linear arrangement of photoreceptors

2 sec arc
Hyperacuity Perimetry

- Combines Vernier Acuity with Central Visual Field testing
- Resistant to retinal image degradation by:
  - Opaque media
  - Age
  - Pupil size

Enoch, 1984

Hyperacuity

- Snellen 20/20 Resolution
  - 1 minute of arc
  - 0.017 degrees
- Vernier Resolution
  - Two seconds of arc
  - ≈ 0.03 minutes of arc
  - 0.00051 degrees
  - The width of a pencil viewed at 300 m !

Hyperacuity

- 2 mm
- Normal Retina

Hyperacuity

- 2 mm
- Large Druse

Vernier Acuity Macular Mapping
Preferential Hyperacuity Perimeter

Artificial distortion

Patient will identify this spot

Graduated Height of Artificial Distortions

- 0.1 deg.
- 0.2 deg.
- 0.3 deg.

During the test, signals containing artificial distortions of various magnitudes are presented to the patient.
Vernier Acuity macular mapping

Patient will preferentially pick this spot when the distortion is larger than the artificial distortion

Preferential Selection

Competition between artificial and pathological distortion
- Present artificial distortions of decreasing magnitude
- Patient selects the distortion that is most prominent
- Algorithm determines the depth of the visual field defect & the quantitative size of the lesion

PHP report
- Results
  - Normative database assessment & reliability indicators
- Examination History
  - Classification of previous PHP test results
- Hyperacuity Deviation Map
  - Metamorphopsia defect assessment
- Hyperacuity Defect Zones
  - Zone analysis of defects, cluster consistency analysis, estimated retinal location
- Comments
  - Recommendation based upon complete analysis
- Test Results Remarks
  - Doctor’s report

How clinically effective is the PHP in identifying early CNV?

PHP Sensitivity/Specificity, Repeatability

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject number</th>
<th>Criteria</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122</td>
<td>CNV</td>
<td>82%</td>
<td>88%</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>CNV</td>
<td>85%</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>Repeatability 15 min apart</td>
<td>81 Kappa agreement</td>
<td>92% defects correspond to lesion</td>
</tr>
</tbody>
</table>

The Amsler chart: absence of evidence is not evidence of absence*

- Metamorphopsia often noted well after CNV development and progression
- “… the sensitivity of Amsler charts in detecting macular disease can be less than 50%, implying that presentation may be delayed in over half of patients with advancing disease relying on the Amsler chart to detect progression.”

PHP Versus Amsler Grid

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject number</th>
<th>Criteria to identify</th>
<th>Sensitivity (PHP)</th>
<th>Sensitivity (Amsler)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>128</td>
<td>CNV</td>
<td>100%</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>AMD</td>
<td>68%</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>Geographic atrophy</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>CNV</td>
<td>90%</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>97</td>
<td>Geographic atrophy</td>
<td>85%</td>
<td>62%</td>
</tr>
</tbody>
</table>


PHP Versus OCT

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient number</th>
<th>Criteria to identify</th>
<th>Sensitivity (PHP)</th>
<th>Sensitivity (OCT)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
<td>CNV</td>
<td>100%</td>
<td>100%</td>
<td>Large drusen → PHP defects</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>Advanced AMD</td>
<td>95%</td>
<td>95%</td>
<td>Good correlation of PHP to OCT</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>CNV</td>
<td>87%</td>
<td>...</td>
<td>PHP defect linked to PED height</td>
</tr>
<tr>
<td>4</td>
<td>19</td>
<td>CNV</td>
<td>95%</td>
<td>...</td>
<td>Good correlation of PHP to OCT</td>
</tr>
</tbody>
</table>


PHP use with Myopia, Other Macular Disorders

- "In 4/5 patients, PHP correlated with FA & VA. PHP may be used to monitor myopic CNV patients following PDT." - A. Lamoureux, S. Osterband, A. D. Divekar et al. (2005). Progression of Age-related Macular Degeneration in Myopic Patients: The Importance of the Preoperative Visual Field. JAMA 2005;293(11):1349-1356.
- "7 patients with myopic CNV diagnosed by FA. All positive for PHP defects. 5 showed location correlation between PHP and FA. PHP defect size and CNV size by OCT was positive correlation. PHP may be used to detect myopic CNV and is beneficial for analyzing functional effect following PDT in myopic CNV patients." - Cho E et al. Prospective study of lutein/zeaxanthin intake and risk of age related macular degeneration. American Journal of Clinical Nutrition 2007;85(3):690-696.
- "74 eyes with various macular diseases underwent PHP, OCT and FA. By disease, 91% DR, 50% CSR and 71% other retinal diseases were positive. Many retinal diseases revealed a PHP defect when lesion was not only in RPE but also in outer retinal layer." - Cho E et al. Prospective study of lutein/zeaxanthin intake and risk of age related macular degeneration. American Journal of Clinical Nutrition 2007;85(3):690-696.

What happens today to a patient suspected to have CNV?

50-90% of the patients that are referred to a retina specialist do not have wet AMD

PHP For Monitoring AMD

- PHP may prevent 90% of unnecessary fluorescein angiograms (FAs) and reduce unnecessary referrals
- PHP may identify wet AMD lesions before a fluorescein angiogram does

Thank you!
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