Insights on Pathogenesis, Structure and Function in AMD

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Course Goals

- To present new insights on the pathogenesis of and risk factors for AMD.
- To review the relationship between structure and function in AMD prevention and assessment.
- To discuss new technologies designed to assess risk, detect progression and early choroidal neovascularization (CNV).
- Case examples
- Interactive!

Associated Factors

- Age
  - AMD is the #1 cause of legal blindness in persons > 65, #2 for 45-64.
  - Brings about degenerative change in retinal tissue after age 45-50, including:
    - Loss of _________________.
    - Decrease in cellular _________________.
    - Drusen, RPE ________________ and _________________.

AMD Is Directly Related To Age

Beaver Dam Study
AMD

• Age Related Eye Disease Study estimated a prevalence of 8 million in the US with at least “intermediate” AMD in one eye who are at risk for “advanced” AMD

• AMD has a genetic component but the disease is “multifactorial”

• Environmental, dietary, medical and lifestyle are influential

Age-Beaver Dam Eye Study

• 5 yr. results: 3,583 whites, 43-84 y/o
  ○ Used Wisc. AMD Grading System (photos)
  ○ >75 y/o
  ○ 30% had early signs of AMD
  ○ Another 23% within 5 yrs
  ○ Incidence was 2.2X more likely in women
  ○ Soft drusen, RPE abnormalities increase risk of GA or CINVM

Progression

○ 33% of patients > 70 yrs will have AMD lesions over a 5-year period

○ Greatest risks
  ○ Soft, indistinct drusen
  ○ Pigmentary abnormality

Genetics and AMD

○ Inherited variation in the complement factor H gene is a major risk factor for drusen.

○ A single-nucleotide polymorphism in the promoter region of HTRA1 (a serine protease gene on chromosome 10q26) is a major risk factor for wet AMD.
  ○ DeWan, A. Science, November 2006:Vol. 314. no. 5801, pp. 989 - 992

Complement Factor H

○ In this tissue section of human retina, bright green demonstrates the protein product of CFH gene.

○ A variant form of the CFH gene increases the risk for age-related macular degeneration.
Parallel Worlds: Heart Disease and AMD

- Diet – Low fruit/vegetable consumption increases risk of AMD and CVD
- Obesity and Physical inactivity
- C-reactive protein (elevated)
  - Inflammatory marker
- Homocysteine (elevated)
- Omega-3 EFA may be beneficial for AMD patients
- Cholesterol (elevated)
- Serum Iron – Increased amounts may increase AMD and CVD

AMD Risks (NEI)

- Smoking
- Nutrition
  - High-fat diet
  - Low Anti-oxidant intake: (C, E, carotenoids - lutein, zeaxanthin, β-carotene), zinc
- Hypertension
- Sun Exposure
- Age
- Increased C-reactive protein

AMD Risks (NEI con’t)

- Genetics
- Gender
- Post menopausal women not taking estrogen are at higher risk
- Light skin or eye color
- Severe hyperopia
- Aphakia/pseudophakia
- High levels of LDL and low levels of HDL cholesterol

Macular Degeneration

Risk Factors:

- Obesity (higher body mass index)
- Race: Whites > Hispanics > Blacks
What is Obesity?

- Increased body weight caused by excessive accumulation of fat.
- BMI defined as patient’s weight (kg) divided by height (m²).
- BMI categories of obesity:
  - Obesity: 30-34.9
  - Moderate obesity: 35-39.9
  - Extreme obesity: over 40

BMI = Weight in Kg
     -----------------
      (Height in Meters)²

BMI 25 - 29.9 = Overweight
BMI > 30 = Obese
BMI > 40 = Morbidly Obese
BMI > 50 = Super Morbidly Obese
Obesity Trends* Among U.S. Adults
BRFSS, 1985

*BMI ≥ 30, or ~ 30 lbs overweight for 5’ 4” person

Early Studies
- Dietary “Ancillary Study” within the multi-center “Eye Disease Case-Control Study”
- Evaluated the relationships between the intake of carotenoids and Vitamins A, C and E and the risk of ARMD
- Results showed that a higher dietary intake of carotenoids was associated with a lower risk for ARMD
- Also showed that the carotenoids, lutein and zeaxanthin, were most strongly associated with this reduced risk

Macular Degeneration

The Beaver Dam Eye Study
- 1,709 patients followed for five years
- No significant relationship found between antioxidants and zinc and the incidence of early age-related maculopathy (ARM)
- Could not determine whether there was any effect on the progression of early ARM to late-stage ARMD
The Blue Mountains Eye Study (Sydney, Australia)

- 2,335 participants followed for five years
- Looked at dietary intake, some antioxidant vitamin supplementation and zinc
- Did not find that the nutrients provided protection against early ARMD
- They reported an association of an increased risk of early ARMD with increased Vitamin C intake

Modify-able Risk Factors

- Cigarette smoking
- Lifetime blue-light exposure
- Decreased dietary/plasma presence of antioxidant vitamins and Zn**
- High-lipid diet

Systemic Health Factors

- Cardiovascular Disease (HTN, AS)*
  - AMD Study Group showed that nutrients which are important in CV health were low in veterans w/AMD
- Smoking (Men > Women)
  - There is an smoking frequency.
- Alcohol (BDES): beer - RPE, Wet/red wine may help
- Nutritional factors
  - Decreased vit B, E, zinc, magnesium intake

Parallel Worlds of Heart Disease and AMD

- Diet – Low fruit/vegetable consumption increases risk of AMD and CVD
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Nutritional Factors

AREDS
AREDS 2

AREDS 1 and 2 Formulations
- Vitamin C: 500 mg*
- Vitamin E: 400 IU*
- Beta-carotene: 15 mg (May be listed on the label as “25,000 IU vitamin A as beta-carotene”) (eliminated)
- Why?
- Zinc oxide: 80 mg (40 mg)
- Copper: 2 mg (needed to prevent Cu deficiency caused by high dosage of zinc)*
- Lutein & Zeaxanthin (10 mg & 2 mg)
- Omega-3 fatty acids (1 gram)

Retina Quiz
- The AREDS 1 study found that in subjects with intermediate AMD, or advanced AMD in one eye (but not the other):
  a. Zinc alone lowered risk of advanced AMD by about 25 percent.
  b. Lutein alone lowered risk of advanced AMD by about 25 percent.
  c. Antioxidants increased risk of advanced AMD by about 25 percent.
  d. Antioxidants + zinc lowered risk of advanced AMD by about 25 percent.

AREDS Grading Scale
1. No drusen or a few small drusen.
2. Pigment abnormalities or non-extensive small or intermediate drusen.
3. Extensive intermediate drusen or any large drusen or non-central atrophy.
4. Good acuity and no advanced AMD in the study eye. Advanced AMD in the fellow eye (choroidal neovascularization or geographic atrophy).
Macular Pigment Optical Density
HFP

Risk assessment, early detection and monitoring of AMD
- Macular Pigment Optical Density
- MPOD
- QuantIFEye™ (ZeaVision)

Macular Pigment
- Lutein and zeaxanthin (L and Z)
- C________ that comprise the MP
- L and Z are in sub-class xanthophylls
- What is the other subclass?
- Low dietary and serum levels of L and Z associated w/increased risk of AMD
- Diets rich in L and Z are inversely correlated w/prevalence of AMD

Xanthophylls and AMD
- Lutein and zeaxanthin form the macular pigment
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants or light screening compounds

Macular Pigment & AMD
- Filters b____ light
- Acts as an antioxidant by quenching f____ r____
- Provides support to sensory retina

DOCTOR FUN
- How Macular Pigments Work

Auntie Oxidant leeks out the Free Radicals.
National Health and Nutrition Examination Survey

NHANES
* Found that higher levels of Lutein and Zeaxanthin were related to lower odds for pigment abnormalities (an early sign of AMD)

Macula “Lutea”

Lutein and Zeaxanthin

2 mm

Photomicrograph courtesy of Dr. Joanne Curtin-Celentano.

Macular Pigment

How can we quantitatively measure it?

How can we determine influence of dietary or supplemental intervention on MP?

Methods of measuring MP in vivo

- Reflectance
- Scattering
- Absorbance
- Heterochromatic Flicker Photometry (HFP)
  - HFP measures absorbance of light by MP
  - Absorbance of MP = Optical Density

Heterochromatic Flicker Photometry (HFP)

How it works
- Patient views small circular stimulus that alternates between test WL absorbed by MP (blue-460nm) and reference WL (white or green-540nm).
- Flicker reduced to null point by adjusting intensity of test WL while viewing centrally, then again peripherally.
- Difference indicates MP
Heterochromatic Flicker Photometry (HFP)

- A higher intensity of test stimulus is required centrally due to attenuation of BL by MP.

\[ \text{MPOD (du)} = \log \frac{I_{\text{central}}}{I_{\text{peripheral}}} \]

Blue light is absorbed by (yellow) macular protective pigment while green light is not

Modified from Snodderly DM, Auran JD, Delori FC (1984). IOVS 25, 674-685

QuantifEYE™ MPOD

- Non-invasive
- Non-mydriatic
- 2-3 min test time
- Only 1 eye needs to be tested in non-AMD, early and intermediate AMD patients
- Test better eye if asymmetric w/one advanced AMD eye

Two Psychometric Functions

QuantifEYE™ Test Results:
Macular Pigment Optical Density (du)

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<thead>
<tr>
<th></th>
<th>Low</th>
<th>Average</th>
<th>High</th>
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<tbody>
<tr>
<td>Value</td>
<td>0.1-0.25</td>
<td>0.25-0.45</td>
<td>&gt;0.45</td>
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“Superfoods”

- Lutein

Zeaxanthin

Essential Fatty Acids (AMD, CVD, Stroke)

Anti-oxidants, CA Fighters

- Walnuts favorably affect cholesterol levels, reduce risk of heart disease.
- Dark chocolate, red wine are rich in antioxidants.
- Resveratrol enhances circulatory health and may have benefits in certain types of cancer.

Not-so-guilty Pleasures
Folic Acid, $B_6$, $B_{12}$

- Folic Acid, Pyridoxine, and Cyanocobalamin Combination Treatment and Age-Related Macular Degeneration in Women The Women’s Antioxidant and Folic Acid Cardiovascular Study
  - William G. Christen, ScD; Robert J. Glynn, ScD; Emily Y. Chew, MD; Christine M. Albert, MD; JoAnn E. Manson, MD

Advantages in Foods

- 5442 female health care professionals 40 years or older with pre-existing CV disease
- Randomly assigned to receive a combination of folic acid (2.5 mg/d), pyridoxine hydrochloride (50 mg/d), and cyanocobalamin (1 mg/d) or placebo.
- After an average of 7.3 years of treatment and follow-up, there were 55 cases of AMD in the combination treatment group and 82 in the placebo group (relative risk, 0.66; 95% confidence interval, 0.47-0.93 ($P = .02$)).

Normal Retinal Metabolism

- Outer seg discs of rods and cones are transported to RPE for metabolism
- Discs are engulfed into RPE and fuse with lysosomes, where they are digested
- Undigested residual bodies remain as lipofuscin
- These are the real troublemakers

Advanced AMD starts out like this:
Reactive Oxygen Species

- ROS are the byproducts of oxygen metabolism.
  - free radicals
  - hydrogen peroxide
  - singlet oxygen
- The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen and its exposure to visible light.

Functional Anatomy

Metabolism in AMD

- Abnormal Metabolism in Non-exudative AMD
  - Free Radical Formation
    - From radiation or O2 metabolism, damages photoreceptors, altering outer segments
    - RPE unable to recognize and digest altered outer segs
    - Lipofuscin build-up causes RPE cell degradation or cell bursting

The 4 Horsemen

- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization
Lipofuscin accumulates in aging RPE

Retinal Metabolism

Result of RPE Cell Bursting
- Extrusion of Aberrant Materials
- Accumulate in Bruch’s Membrane
- Aggregation
  - Drusen
  - Basal laminar deposits

Soft confluent drusen

Geographic Atrophy
- Progression of Dry AMD
  - Atrophy of RPE, photoreceptors, choroid
  - Coalescence of choroidal atrophy
  - Geographic Atrophy *
  - Macrophages replace drusen with fibrous tissue or dystrophic calcification
  - Once this occurs, no further risk for CNVM at that site

Geographic Atrophy
- GA w/dystrophic calcification of drusen which appears as glistening, bright yellow specks.

Atrophic (Non-exudative) AMD
- Clinical Features
  - Drusen
  - Basal Laminar Deposits
  - RPE Atrophy
  - Focal RPE ________
  - G____ A____ of RPE, PRs, Choroid
- ______% will progress to exudative! *
Macular Degeneration

Pathobiology of AMD
- Aging of the photoreceptor and RPE
- Genetic component
- Environmental stress

Soft Drusen
- Histopathology
  - Amorphous material between inner and outer Bruch’s
  - Soft, confluent more inclined to lead to __________ AMD *
- Ophthalmoscopic Appearance *
  - Large, ill-defined
  - May become confluent

Retina Quiz
- Approximately what percentage of dry (non-exudative) AMD eyes progress to wet (exudative) AMD?
  - a. 37 %
  - b. 50 %
  - c. 2 %
  - d. 20 %

Choroidal Neovascularization
- Ophthalmoscopic Appearance
  - Round/oval green-gray elevation--
- Associated findings
  - Lipid
  - Blood
  - Sensory RD
- Location
  - Subfoveal, juxtafoveal, extrafoveal

Type I CNVM
- CNV beneath RPE (AMD) *
  - Retina
  - RPE
  - Bruch’s
  - CC
**Type II CNVM**

CNV in subsensory space (POHS)

**Pathogenesis of CNVM**

- Breaks in Bruch’s Theory
- Diffuse thickening w/soft drusen predisposes Bruch’s to breaks
- New BV’s from CC grow and proliferate

**Break in Bruch’s**

- Characterized by abnormal growth of blood vessels (Choroidal Neovascularization - "CNV") into the subretinal space
- Poorly formed vessels leak to fill subretinal space and distort macula
- Causes injury to the retina, promotes scarring of the fovea and loss of central vision

**Wet AMD Pathology**

- Characterized by abnormal growth of blood vessels (Choroidal Neovascularization - "CNV") into the subretinal space
- Poorly formed vessels leak to fill subretinal space and distort macula
- Causes injury to the retina, promotes scarring of the fovea and loss of central vision

**Pathophysiology of FV Scar**

- Disciform Scar
  - If untreated, CNVMs progress to this stage
  - Scar replaces most of sensory retina, RPE
  - May continue to grow and invade new areas
  - Results in retinal tissue death, severe visual loss
  - Surgical excision may improve visual function

**Pathogenesis of CNVM**

- Two I’s Theory
  - Reduced choroidal and retinal blood flow
  - Chronic I________ to Bruch’s, RPE, neurosensory retina
  - A higher # of lymphocytes, macrophages, and fibroblasts in Bruch’s of AMD patients
  - I________________ki to Bruch’s
  - Induce CNVM
How do the two I’s induce CNVM?

**Angiogenic Growth Factors**

- Angiogenesis = New BV Invasion
- BV growth triggered by endogenous stimulators (proteins):
  - Fibroblast Growth Factor (FGF)
  - Transforming Growth Factor (TGF)
- Vascular Endo. Growth Factor (VEGF)
- Elevated levels have been demonstrated in association w/ocular angiogenesis.

Angiogenesis

VEGF-A binding and activation of VEGF receptor

Endothelial cell activation

Environmental factors ($\text{hypoxia, pH}$)

Growth factors, hormones

(EGF, bFGF, PDGF, IGF-1, IL-1α, IL-6, estrogen)

VEGF-A

*VEGF-A* is a key mediator of angiogenesis

Endothelial cell activation, proliferation, migration

VASCULAR LEAKAGE

VEGF-A

*VEGF-A* is a key mediator of angiogenesis

Endothelial cell activation, proliferation, migration

VASCULAR LEAKAGE

VEGF-A

*VEGF-A* is a key mediator of angiogenesis

Endothelial cell activation, proliferation, migration

VASCULAR LEAKAGE

VEGF-A
Monitoring Patients with Dry AMD
Preferential Hyperacuity Perimetry

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

Macular Drusen
Fluid and Lipid
Hemorrhage

Therapeutic Window

Are current monitoring methods working?
NO

80% of eyes w/CNV have worse than 20/40 vision at diagnosis

Early Detection of CNV: The Most Important Unmet Need in Eye Care

VA at diagnosis:
- 20/20
- 20/40 - 20/100
- < 20/200

Average size:
- 1500 µm
- 3000 µm
- 3300 µm

Location:
- Subfoveal
- Extrafoveal

Average size CNV lesions @ diagnosis
- 3000-3300 µm
- Growth ~ 10-20 µm/day
- Too large, too late

Hyperacuity Perimetry
Combines Vernier Acuity with Central Visual Field Testing
Resistant to retinal changes
Opaque media
Age
Pupil size

Enoch, 1984

Olsen, TW Ophthalmology Feb. 2004

CNV Size and Progression
How does The Foresee PHP™ work?

Preferential Hyperacuity Perimetry

Hyperacuity Perimetry

- Resistant to retinal image degradation by
  - Opaque media
  - Age
  - Pupil size

Enoch, 1984

Hyperacuity is 10 times more sensitive than resolution (Snellen)!

2 sec arc

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.

Foresee PHP Technology:

Preferential Hyperacuity Perimetry

- Automated central 14 deg test
  - 4 minutes/eye

- Hyperacuity stimuli
- Detection/Quantification of hyperacuity defects
- Detects progression of Intermediate Dry to Early Wet AMD

Foresee PHP Hyperacuity Stimulus

- "artificial" distortion or straight line
  - Stationary
  - Flashing

Tests CENTRAL 14° of VF

600 data points tested 3-5x each
Hyperacuity
CNV causing “pathologic” distortion

Vernier Acuity Macular Mapping
Preferential Hyperacuity Perimeter

Vernier Acuity macular mapping

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

Foresee PHP Test Report
The Foresee PHP report includes:
- Results Section – Normative database assessment & reliability indicators
- Hyperacuity Deviation Map – Metamorphopsia defect assessment
- Examination History – Classification of previous PHP test results
- Hyperacuity Defect Zones – Zone analysis of defects, cluster consistency analysis, estimated retinal location
- Comments – Recommendation based upon complete analysis

Foresee PHP Results and Case Examples

The Foresee PHP report includes:
- Results Section – Normative database assessment & reliability indicators
- Hyperacuity Deviation Map – Metamorphopsia defect assessment
- Examination History – Classification of previous PHP test results
- Hyperacuity Defect Zones – Zone analysis of defects, cluster consistency analysis, estimated retinal location
- Comments – Recommendation based upon complete analysis
Glaucoma

AMD

AMD is twice as prevalent as glaucoma!

Case Example: 67 y/o Male

Hemorrhage
Subretinal Fluid

20/25 – No complaints

Vernier Acuity macular mapping Preferential Hyperacuity Perimetry

Hyperacuity disturbance pattern

Case Example: FA Confirming CNV

CNV Tx. W/PDT

84 y/o Male

CC: mild decrease in vision OD
HPI: gradual decreased vision X 2 yrs OS
POHx: Corneal scar OS, 2+ NS OU
Dry AMD
Soft drusen OD
Geographic atrophy OS
PMHx: HTN & hypercholesterolemia

Case Example: 84 y/o Male

BCVA: OD 20/60 OS 20/400
3M ago: 20/50 20/400
Amsler: Unchanged between visits
SLE:
OK: Corneal scar OS
L: 2+ NS OU

84 y/o Male

BCVA: OD 20/60 OS 20/400
3M ago: 20/50 20/400
Amsler: Unchanged between visits
SLE:
OK: Corneal scar OS
L: 2+ NS OU
DFE: No clinical evidence of soft drusen

No clinical evidence of CNV/leakage

OCT of OD

Increased depth of a significant superior VFD OD

A CNVM was confirmed by angiography

Tx was scheduled

59 y/o Female

- RTC for 3 month AMD follow-up evaluation
- No visual complaints
- POHx: Dry AMD OD/OS, lens opac OD/OS
- BCVA: 20/40 OD 20/50 OS
- Amsler: Patient home monitored
  - No change in metamorphopsia OD/OS
- DFE: No clinical evidence of CNV

CNV was confirmed via angiography. Pt was treated with Anti-VEGF
Early Diagnosis
Early Intervention
Improved Visual Outcomes
Enhanced Quality of Life!

- Optical Coherence Tomography
- Principle is similar to ultrasound
- Uses optical reflectivity instead of acoustics
- Captures reflected light from ocular structures to create cross sectional image
- <3 um resolution

Optical Coherence Tomography

Analog to ultrasound

Stratus OCT healthy retina

Time Domain and Spectral Domain

Stratus OCT high-resolution line scan and the Cirrus HD-OCT scan reveal details of retinal structure
Spectral Domain OCT

Coverage for OCT

- Medicare Part B
- Provider should record diagnosis to the greatest level of specificity (ICD-9 codes)
- FL covers OCT for GLC, most retina
- 1-2 times per year
- Private Insurance
- Most cover if medically necessary
- CPT code 92135

Codes and Coverage

- ICD-9 codes
  - 362.50 Macular degeneration, unspecified
  - 362.51 Nonexudative macular degeneration
  - 362.52 Exudative macular degeneration
- Nutritional counseling for AMD is reimbursed as part of the PQRI (2%)
- Exam code (ie. 99201)
- PQRI code
  - Level 2 CPT performance measures 4007F - AMD suggestion of antioxidant prescription documented

Codes and Coverage

- AMD patient codes
  - Extended Exam (Est.) 92014
  - Fundus Photo (1-2x/yr) 92250
  - FANG 92235
  - ICGANG 92240
  - PHP (2-4x/yr) 92882
  - OCT (1-2x/yr) 92135
  - MPOD 59986 (Screening-not covered)

QUESTIONS AND COMMENTS?
Conclusions

- With MPOD and nutritional intervention, PHP, and OCT, clinicians are better equipped than ever gain ground in the war against AMD.
- Proactive maximization of macular wellness may result in improved visual outcomes and quality of life!

Thank you!

For spending your precious time with us!

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