‘Dry’ Age-related Macular Degeneration (AMD)

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Declaration of Interest

Consultant for the following companies
Allergan, Novartis, Bayer, GSK, Neuronsystems, Thrombogenics
Aim

• Overview of the disease
  • Disease Definitions
  • Epidemiology
  • Natural History

• Diagnosis and Management
  • Clinical & Investigations
  • Current standard of care

• Potential parameters that predict visual outcome

• Methods of quantifying lesion growth

Background- Normal Vision

• Normal vision occurs when light is focused on the retina
• The macula is the central part of the retina
• The macula has the highest density of photoreceptors which facilitate central vision and permit high resolution vision
AMD (Dry) Pathogenesis

Neural retina (photoreceptor) produces waste throughout life

With aging, the ability of RPE cells to digest these molecules decreases

Excessive accumulation of intra and extracellular waste (drusen) results in inflammation

Bruch membrane and the RPE cells degenerate and atrophy sets in leading slowly to severe visual loss

Overview-Disease Definitions

Age-related maculopathy
• Progressive disorder of the macula

• Characteristic features
  – Drusen deposits >63 microns
  – Pigmentary changes (hypo- or hyper-) of the RPE
  – Atrophic macular degeneration (=geographic atrophy)
  – Neovascular macular degeneration
The ‘natural’ endpoint for the macula is Geographic Atrophy

<table>
<thead>
<tr>
<th>Normal Vision</th>
<th>Early age-related maculopathy</th>
<th>Late age-related maculopathy = AMD</th>
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<tbody>
<tr>
<td></td>
<td>Early ‘dry’ AMD</td>
<td>Geographic atrophy</td>
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<td></td>
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<td>Neovascular AMD</td>
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Why are we interested in atrophic AMD?
A Major Public Health Issue

Medical Need

- AMD is the most common cause of legal blindness in the developed world
- Atrophic AMD is more prevalent with age, and proportion is probably increasing
  - Under diagnosed
  - Treatment of wet AMD with anti-VEGF may result in increased number of patients with atrophy
  - Iceland 50% late AMD population have GA – high fish oil intake

- NO EFFECTIVE TREATMENT AVAILABLE
Classification of Age-related maculopathy in epidemiological studies

Age-related maculopathy (ARM)
• Different shapes/sizes of drusen used in definitions of various studies – as well as functional changes

Most Epidemiological studies use International Classification or similar (WARMGS) [Bird et al Surv Ophthal 1995]

<table>
<thead>
<tr>
<th>Detection</th>
<th>Grading of colour fundus transparencies using grid 6000 micron diameter</th>
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<tr>
<td>Overall term</td>
<td>Age-related maculopathy</td>
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<tr>
<td>Exclusion</td>
<td>Other diseases mimicking features of ARM e.g. myopia</td>
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<tr>
<td>Early ARM</td>
<td>Drusen&gt;63microns, pigmentary changes</td>
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<tr>
<td>Late ARM=age-related macular degeneration (AMD)</td>
<td>Atrophic or neovascular</td>
</tr>
<tr>
<td>- atrophic AMD=geographic atrophy</td>
<td>Sharply delineated lesion &gt;175 microns diam with apparent absence of RPE in which enhance choroidal vessel visibility</td>
</tr>
<tr>
<td>- exudative AMD</td>
<td>RPE detachment, neovascular membrane, subretinal heam, scar</td>
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</tbody>
</table>

Atrophic AMD will become more common

• The increase in population aged over 80 is expected to be more than five fold by 2050

• One major implication of this demographic change is the emergence of conditions that are directly related to aging
### Risk Factors for development of Late ‘dry’ AMD (GA)

**Only consistent risk factors for incident GA**

#### Systemic

1. Smoking
2. Total serum cholesterol
   
   *(Risk factors for Incident AMD: Pooled findings from 3 continents, Tomany et al. Ophthalmol 2004)*

3. Age (RR, 2.81 [95% CI, 1.33–5.94] for 79 years vs. 50–59 years)

#### Ocular

1. Greater retinal area covered by drusen and pigment change (RR, 5.10 [95% CI, 2.57–10.1] for >25% vs. <10%), RPE depigmentation (RR, 2.64 [95% CI, 1.26–5.53]), RPE hyperpigmentation (RR, 10.4 [95% CI, 4.51–24.0] for >250microns vs. none)
   
   *(CAPT Res Group Ophthalmol 2008)*

### How many people are affected with the Atrophic form of AMD?

**GA exponential increase with age**

**Prevalence over 90 years 22%**

20% of legal blindness from AMD

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Risk factors for Incident AMD: pooled findings from 3 continents
Ophthalmology 2004
What is Happening in Atrophic AMD?

- What do we see when we examine the eye?
- What is happening to the structures of the eye?
- What do we think is happening at a microscopic and cellular level?
- How should we measure disease progression in clinical studies?
- What are the potential therapeutic approaches?

What do we see when we examine the eye?

- hyperpigmentation
- Hypopigmentation & drusen regression
- 'refractile' drusen
- Geographic atrophy

45% unifocal, 18% multifocal, 37% merged lesion Klein et al AJO 2008
Lipofuscin Autofluorescence Precedes Death of Photoreceptor and RPE Cells in Patients With Age-related Macular Degeneration

Typical expansion rate 1.5 to 2 mm sq/year

What is happening to the structures of the eye?
- Neural retina (photoreceptor) produces waste throughout life
- With aging, the ability of RPE cells to digest these molecules decreases
- Excessive accumulation of intra(residual bodies) and extracellular waste (drusen) results in inflammation
- Bruch membrane and the RPE cells degenerate and atrophy sets in, associated with choroicapillaris atrophy and photoreceptor loss leading slowly to severe visual loss
What is happening to the structures of the eye?

- Rods cells lost with age (30% by age 90)
- Cone cells relatively well preserved with age
- In patients with GA, rod cells lost before cones, but cones seem structurally abnormal

What does the patient experience?

**Extrafoveal GA**
- Poor vision in dim light
- Difficulty reading
- Impaired Contrast
- Reasonable central VA
- 50% loose 3+ lines vision within 2 years

**Subfoveal GA**
- Severe central vision loss
- Eccentric fixation

Visual Function Abnormalities and Prognosis in Eyes with Age-related Geographic Atrophy of the Macula and Good Visual Acuity

- Josep M. Amengual, MD, PhD, Greg J. Hafez, MD, Olga V. Aragona, MD
- Mary V. Greenstein, MD
- Maria J. March, MD
- Barbara B. Weecher, MD, PhD
- and David K. Harmon, MD
Diagnosis and Management

Clinical & Investigations
- Diagnosis usually made clinically
- Atrophy in the presence of drusen/rpe change with the exclusion of other mimicking disorders

Current standard of care
- No proven intervention halts progression of GA
- Smoking cessation?
- AREDS vitamins may prevent nAMD but theoretically may worsen atrophy
- Removing drusen (laser etc) increased risk of nAMD

More than one cause of Atrophic AMD
Different therapeutic approaches

cf: age-related choroidal atrophy Spaide AJO 2008
Natural History of Geographic Atrophy
(Sunness et al. Ophthalmol 2007)
Atrophy expands at median 2.1mm²/yr

- Digitised colour photos
- Median time to develop central GA (after GA diagnosis) 2.5yrs [95% CI 2-3]
- Av VA decrease after ‘central’ GA development 3.7 letters initially then 22 letters at 5 years

Change in Area of Geographic Atrophy in the Age-Related Eye Disease Study
AREDS Report Number 26
The AREDS Research Group

Figure 5. Mean visual acuity over time following development of central geographic atrophy. The small dots indicate 95% confidence intervals.
Potential biomarkers affecting progression of GA

- **Genetics** - none proven for CFH, C2, C3, APOE, or TLR3 genes. There was a nominally significant association with the LOC387715/ARMS2/HTRA1 (Progression of geographic atrophy and genotype in AMD Klein et al Ophthalmol 2010)
- **Rate of progression** - 1.52 mm(2)/year (IQR, 0.81 to 2.33) (Holz et al AJO 2007)
- **Autofluoresence Pattern** – yes - banded (median 1.81 mm(2)/year) diffuse FAF pattern (1.77 mm(2)/year) were significantly higher compared to eyes without FAF abnormalities (0.38 mm(2)/year) and focal FAF patterns (0.81 mm(2)/year, P < .0001).

How should we measure disease progression in clinical studies?

- **Structural**
  - Colour
  - AF
  - OCT
  - IR reflectance

- **Functional**
  - microperimetery
  - VA – standard or low luminance
  - Reading
  - Dark adaptation
  - Contrast sensitivity

Colour Topcon AF HRA-AF
Schmitz-Valckenberg et al IOVS 2009
Why is the standard endpoint of high contrast visual acuity problematic?

Alternatives

- Low-luminance visual acuity
  Sunness JS et al. Low-luminance visual dysfunction as a predictor of subsequent visual acuity loss from geographic atrophy in age-related macular degeneration. Ophthalmology. 2008 Sep;115(9):1480-8

- Reading Speed

Reading Speed

What is the best parameter to take?
- Maximal reading speed
- Critical print size

Lesion position may affect reading speed – language dependent

Repeatability in AMD for MNread: The 95% coefficient of repeatability (CR) was 0.30 logMAR for reading acuity. The CR for critical print size and maximum reading speed varied depending on the analysis method applied.

Test-Retest Variability of Microperimetry Using the Nidek MP1 in Patients with Macular Disease

Fred K. Chen,1,2 Praveen J. Patel,1 Wen Xing,1 Gylies Ramee,1 Catherine Egam,1 Adam T. Tufail,2 Peter J. Coffey,2 Gary S. Rubin,2 and Lyndon Da Cruz1,2

Chen FK, Patel PJ, Webster AR, Coffey PJ, Tufail A, Da Cruz L. Nidek MP1 is able to detect subtle decline in function in inherited and age-related atrophic macular disease with stable visual acuity. Retina. 2011 Feb;31(2):371-9

Other Functional tests

• Coeff of repeatability of Pointwise sensitivity 5.56db
  Av sensitivity of central Macula 2.13db for MP-1

• Still has potential to detect Decline in function with Stable VA

• How do the different micro perimeters compare and which is best suited to measuring change?

- Dark Adaptation

- Contrast Sensitivity

- Quality of Life Questionnaires
95% limits of agreement for 2 readers of colour images: -1.54 to 1.25 mmsq
AREDS report 26

Median progression: ca. 1.52 mm²/year (IQR, 0.81 to 2.33) (range 0 to 13.8)
Holz et al. 2007 FAM Study Group

Fovea not involved until the late course of the disease
Maguire et Vine 1986; Schatz and McDonald 1989; Sunness et al. 1999
Lipofuscin Autofluorescence Precedes Death of Photoreceptor and RPE Cells in Patients With Age-related Macular Degeneration

Typical expansion rate 1.5 to 2 mm sq/year


Findings from the FAM study group - implications in clinical trials


- Fleckenstein et al.; FAM Study Group. Concordance of disease progression in bilateral geographic atrophy due to AMD. Invest Ophthalmol Vis Sci. 2010 concordance correlation coefficient between the eyes was 0.310 (95% CI, 0.097–0.495) for visual acuity, 0.706 (95% CI, 0.575–0.801) for GA size, and 0.756 (95% CI, 0.644–0.837) for GA progression rate
Influence of nuclear lens opacities

Optical Coherence Tomography (OCT)

Potential therapeutic Approaches

1-Reduce stop stimuli of continuing damage

2-Protect remaining cells from damaging stimuli/ environment

3- Repair/Regenerate damaged cells
Can we avoid the development of Atrophic AMD?

`Prevention is better than cure`

10-15%

54%

Summary

- The geographic atrophy form of AMD will become an increasingly common cause of severe vision loss
- No proven treatments yet halt progression
- Current outcomes measures in AMD trials (high contrast VA) may not be optimal for GA trial
- Functional testing in low luminance or test that measure parafoveal function may be most suitable, but noisy
- Structural changes can reproducibly measured and may represent a good endpoint for clinical trials