Age-Related Macular Degeneration

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Alimera, C/SH, H; Allergan, I, G; Apellis, I, G; AstraZeneca, I, G; Bausch & Lomb, C, H; Eli Lilly, I, G; Genentech / Hoffman-LaRoche, I, G; Gilead, O, H; Merck Sharp & Dohme, I, G; Opthea, I, G; Ophthotech, I, G; Regeneron, I, G; Spark, SH
Objectives

• Review Characteristics of Age-Related Macular Degeneration
• Identify Risk Factors
• Discuss Modifiable Risk Factors that can Lead to Prevention of Disease

Introduction

• Age-Related Macular Degeneration
  • ARMD
  • AMD
### Epidemiology

Most common cause of irreversible visual loss in the developed world in individuals over 50 years of age

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### Epidemiology

AMD is estimated to affect as many as 15 million individuals in the USA
Epidemiology

30% of patients age 75 or older have some evidence of AMD

Anatomy

https://www.flickr.com/photos/nationaleyinstitute/37469598112/
# Age-Related Macular Degeneration

## Risk Factors

1. Age
2. Cigarette Smoking
3. Caucasian
Risk Factors

1. Family History of AMD
2. Higher Body Mass Index
3. Diet High in Saturated Fat
4. Cardiovascular Disease
5. High Cholesterol
6. UV Exposure

Pathophysiology
Pathophysiology

Source: Cogan Collection, NEI/NIH.
Source: Cogan Collection, NEI/NIH.
Pathophysiology

- Drusen
- Focal Yellow Deposits of acellular debris that can be seen with ophthalmoscopy

Source: Cogan Collection, NEI/NIH.

Anatomy
Anatomy
Anatomy

AMD

Dry

Wet
### Symptoms (Dry AMD)

1. Gradual onset of blurred vision
2. Difficulties with tasks requiring fine vision such as driving or reading
3. Need more light to read
4. Scotoma

### Symptoms (Wet AMD)

1. Acute loss of vision
   - Sudden vision loss (1 day to 1 week)
2. Metamorphopsia (Straight lines appear bent)
3. Macular Hemorrhage on ophthalmoscopy
## Screening

1. Visual Acuity
2. AMSLER Grid

### AMSLER Grid

[AMSLER Grid Image](https://www.flickr.com/photos/nationaleyeinstitute/7544605572/)
AMSLER Grid

https://www.flickr.com/photos/nationaleyinstitute/7544605572/
No definitive treatment for Dry AMD other than modifiable risk factor management
## Prevention

AREDS vitamins were shown to slow the progression of the disease by 25% over 5 years

## AREDS 2

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Lutein (10 mg)
- Zeaxanthin (2 mg)
- Zinc (80 mg)
- Copper (2 mg)
AREDS 2

- Vitamin E (400 IU)
  - Conflicting data on the relationship between vitamin E and prostate Cancer
  - In the AREDS trial, high-dose vitamin E had no effect on prostate cancer among male participants

Prevention

Smoking is the most consistently identified modifiable risk factor
Recommendations

1. AREDS Vitamins
2. Smoking Cessation

Recommendations

1. Wearing Sunglasses with UV protection
2. Weight Loss
3. Dietary Considerations
# Quality of Life

- Visual loss from AMD
- Diminished quality of life
- Worse self-reported general health
- More difficulty with ADLs

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# Quality of Life

- Visual loss from AMD
- Greater emotional stress
- Associated with higher rate of depression
Neovascular Age Related Macular Degeneration

Fatoumata Yanoga, MD
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The Ohio State University Wexner Medical Center
Neovascular Age Related Macular Degeneration

- Also called “Exudative AMD” or “Wet AMD”
- Affects about 10 percent of those diagnosed with AMD
- Historically this type of AMD caused irreversible devastating vision loss
- Accounts for the majority of people with severe vision loss (20/200 or worse in either eye) from AMD

Progression of AMD
Neovascular AMD

The stimulus for vascular ingrowth of choroidal vessels remains poorly understood.

Soft drusen have been associated histopathologically with CNV.

Breaks in Bruch’s membrane permit ingrowth of new vessels from the choriocapillaris.

Evidence of inflammatory cells and various growth factors involvement.

Targeting these growth factors is the basis of current pharmacotherapy.

- drugs designed to interfere with VEGF have
### Clinical Presentation

- Metamorphopsia – distortion
  - Especially with near vision
- Scotoma - blind spot
- Micropsia - decreased image size
- Blurred vision
- No symptoms or only vague visual complaints

### Eye Exam

- Complete eye exam
- Visual Acuity
- Amsler grid to map areas of distortion or scotoma
Dilated Fundus Biomicroscopy Findings

- CNV may appear as a gray–green elevation of tissue deep to the retina with:
  - Hemorrhage
  - Exudation
  - Subretinal fluid
  - Intraretinal fluid

“Advanced wet AMD. Retina Image Bank. 2014; 12163. © the American Society of Retina Specialists.”

Dilated Fundus Biomicroscopy Findings

- Pigment epithelial detachment

- Atrophy of photoreceptors and the retinal pigment epithelium (RPE)

Dilated Fundus Biomicroscopy Findings

- Subretinal fibrous or fibrovascular tissue

“This image was originally published in the Retina Image Bank. Mitzy E. Torres Soriano, MD; Centro medico Cagua-Estado Aragua, Venezuela. Active Neovascular AMD With Disciform Scar. Retina Image Bank. 2015; 24986. © the American Society of Retina Specialists.”

Dilated Fundus Biomicroscopy Findings

- Massive subretinal hemorrhage

“This image was originally published in the Retina Image Bank. Jared Watson COT. Wet AMD. Retina Image Bank. 2015; 25440. © the American Society of Retina Specialists.”
Dilated Fundus Biomicroscopy Findings

- Vitreous Hemorrhage


Fluorescein Angiography

- Fluorescein Angiography was the Gold Standard the diagnosis and management of wet AMD for many decades

- Wet AMD – Classification
Fluorescein Angiography Patterns in Wet AMD

<table>
<thead>
<tr>
<th>Classic</th>
<th>Occult</th>
<th>Minimally-Classic</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image of Classic CNV" /></td>
<td><img src="image2" alt="Image of Occult CNV" /></td>
<td><img src="image3" alt="Image of Minimally-Classic CNV" /></td>
</tr>
</tbody>
</table>

Many physicians no longer refer to CNV composition but it has prognostic implication and treatment response and many clinical trial rely on for their inclusion/exclusion criteria.

Optical Coherence Tomography

![Image of OCT scan](image4)
Optical Coherence Tomography (OCT)

- Optical Coherence Tomography has become standard of evaluation of CNV
  - Subretinal fluid
  - Intraretinal fluid
  - Subretinal fibrosis
  - Atrophy to the photoreceptors and RPE
**OCT- Angiography**

This image was originally published in the Retina Image Bank. Sarah Orrich, CNV FA and OCT Angiogram Retina Image bank. 2018.28592. © the American Society of Retina Specialists

<table>
<thead>
<tr>
<th>CNV Response to Intravitreal Aflibercept</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Afibercept</strong></td>
</tr>
<tr>
<td><strong>Before</strong></td>
</tr>
<tr>
<td><strong>2 days</strong></td>
</tr>
<tr>
<td><strong>1 week</strong></td>
</tr>
<tr>
<td><strong>4 weeks</strong></td>
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<tr>
<td><strong>CNV reopens</strong></td>
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<tr>
<td><strong>1 day</strong></td>
</tr>
<tr>
<td><strong>2 weeks</strong></td>
</tr>
<tr>
<td><strong>6 weeks</strong></td>
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<tr>
<td><strong>Maximum response</strong></td>
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</tbody>
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Bruno Lumbroso, MD; Marco Rispoli, MD Centro Oftalmologico Mediterraneo, Rome
Treatment of Wet Macular Degenerations

- Thermal Laser
- Photodynamic Therapy
- Pharmacotherapy

Laser Treatment of Wet AMD

- Historical treatment
- CNV location, type, composition and border are determined by FA
- Laser burn are applied to the entire CNV lesion
- Results permanent blind spot in the treated area

Maurice F. Rabb, M.D. Chicago IL
### Thermal Laser Photocoagulation of CNV

- **Moofields Macular Study** and **Macular Photocoagulation Study**
- Extrafoveal classic CNV derive the most benefit from thermal laser
  - Prevented severe vision loss
- **Cannot use in subfoveal CNV**
- 60 percent had persistent or recurrent CNV


### Photodynamic Therapy

- CNV location, type, composition and border are determined by FA
- Intravenous injection of photosensitizing drug - Verteporfin (Visudyne)
- Followed by a low-intensity laser light is applied to the CNV
- Closure of the CNV without damage to the surrounding tissue
- Can be used in subfoveal CNV
Photodynamic Therapy

- TAP Investigation (Classic CNV)
- Visudyne in Minimally Classic CNV Trial
- VIP Trial (Occult CNV)
- Does not improve vision
- Can reduce the risk of moderate and severe vision loss for at least 2 years
  - subfoveal lesions with a predominantly classic lesion composition
- Photosensitivity reactions

Pharmacotherapy Wet AMD

- CNV strong association with vascular trophic factors
- Vascular Endothelial Growth Factor (VEGF), specifically VEGF-A
- What if something could inhibit VEGF-A?
Pegaptanib

- Pegaptanib a pegylated aptamer that inhibits a specific VEGF isoform (VEGF165 – a type of alternatively spliced VEGF-A)

- VISION study: Pegaptanib vs. PDT with all forms of subfoveal CNV

- Pegaptanib showed less vision loss compared to PDT


Bevacizumab (Avastin Genentech)

- Full-length recombinant humanized antibody that is active against all isoforms of VEGF-A

Bevacizumab

- Used an anti-VEGF medication called bevacizumab to reduce tumor angiogenesis for colorectal cancer
- SANA study at the University of Miami
  - subfoveal CNV received systemic bevacizumab injections
  - Average gain of 14 letters after 2 years
- Intravitreal bevacizumab injection to treat wet AMD
  - Very impressive results
  - Wide spread use “off label” use of bevacizumab worldwide


Ranibizumab (Lucentis, Genentech)

- Ranibizumab is a recombinant humanized antibody Fragment that is active against all isoforms of VEGF-A

Ranibizumab

- MARINA Trial (minimally classic or occult CNV) – relative to Sham Injection
- ANCHOR Trial (classic CNV) – relative to PDT
- Both MARINA and ANCHOR demonstrated a significant gain in vision relative to their respective controls
  - The vision stabilized in about 80% of those treated and it improved significantly in about a third
- Anti-VEGF treatment was more effective than PDT


Aflibercept (Eylea, Regeneron)

- Recombinant Fusion Protein
- Consists of the extracellular components of both VEGF receptors 1 and 2
- Fused to the constant region of an IgG1 molecule
- Inhibits VEGF-A, VEGF-B, and Placental Growth Factor (PGF)
- VIEW-1 and VIEW 2 Studies showed the Aflibercept was on-inferior to monthly ranibizumab
- FDA Approval 2011

Which Anti-VEGF to Use?

- Is one Anti-VEGF is “better”?
  - Clinical trials and follow up studies have shown similar effectiveness among the 3 drugs

- Cost
  - Bevacizumab less than 1/10 the cost of the other two

- Provider dependent
  - Some insurance companies may require using bevacizumab prior to trial the more expensive agents


Are Intravitreal Injections Painful?

- NO!!!

- Topical anesthetics (tetracaine, proparacaine, or lidocaine drops)

- Lidocaine 4% pledges and/or injection subconjunctival lidocaine

- Many times patient don’t realize it when the needle enters the eye
How Many Injections are Required?

- With the current available treatment many wet AMD patients will require treatment for many years with varying frequencies
- Monthly injections initially
  - Drug only last 4-6 weeks
- Treat and observe
- Treat and extend
- As need treatment
- Many ongoing research working on finding long active Anti-VEGF agents or port/reservoir delivery systems

Surgery for Wet AMD

- Submacular Surgery Trials
- Subfoveal CNV
- Equivocal with respect to overall visual acuity
- Small cohort of predominantly hemorrhagic subfoveal CNV did have a reduction in severe vision loss (loss of greater than 6 lines at 2 years)

**Vitreous Hemorrhage**

- Pars plana vitrectomy


**Pneumatic Displacement of Subretinal Hemorrhage**

- In office intravitreal TPA and Gas
- Pars plana vitrectomy subretinal TPA and intravitreal gas

“This image was originally published in the Retina Image Bank. Yusuke Oshima, MD, PhD. Massive Submacular Hemorrhage. Retina Image Bank. 2013; 8641. © the American Society of Retina Specialists.”

“This image was originally published in the Retina Image Bank. Yusuke Oshima, MD, PhD. Pneumatic Displacement of a Massive Submacular Hemorrhage. Retina Image Bank. 2013; 8643. © the American Society of Retina Specialists.”
Wet AMD and Anticoagulation

- Anticoagulation therapy may contribute to massive subretinal hemorrhage

- A large retrospective study showed that 19% of AMD patients with massive subretinal hemorrhage and or vitreous were taking sodium warfarin or aspirin

- Patients with AMD who need anticoagulation therapy should do so but should be aware of an increased risk of extensive subretinal hemorrhage and or vitreous hemorrhage