Age-Related Macular Degeneration

Matthew P. Ohr, MD
Interim Chairman
Retina Division Director
Associate Professor
Department of Ophthalmology
The Ohio State University Wexner Medical Center

Financial Disclosures

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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**

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

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

[Image of eye anatomy](https://www.flickr.com/photos/nationaleyeinstitute/37469598112/)
## Anatomy

![Anatomy Image]

## Age-Related Macular Degeneration

![Age-Related Macular Degeneration Image]

## 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

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

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

**Anatomy**

Source: Cogan Collection, NEI/NIH.
**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

https://www.flickr.com/photos/nationaleyeinstitute/7544605572/
**AMSLER Grid**

https://www.flickr.com/photos/nationaleyeinstitute/754460460/in/photostream/

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**Treatment**

No definitive treatment for Dry AMD other than modifiable risk factor management

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**Prevention**

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

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**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

### Quality of Life

- Visual loss from AMD
- Greater emotional stress
- Associated with higher rate of depression

### Neovascular Age Related Macular Degeneration

Fatoumata Yanoga, MD  
Assistant Professor - Clinical  
Department of Ophthalmology  
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

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; 23446. © 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 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>
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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 (OCT)

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

Optical Coherence Tomography (OCT)
OCT- Angiography

This image was originally published in the Retina Image Bank. Sarah Ortlich.CNV FA and OCT Angiogram Retina Image bank.2016.20552.© the American Society of Retina Specialists

CNV Response to Intravitreal Aflibercept

Before | 2 days | 1 week | 4 weeks
---|---|---|---
Aflibercept

1st Treatment

2nd Treatment

3rd Treatment

Before | 1 day | 1 week | Maximum response

1 day | 1 week | Maximum response

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
<table>
<thead>
<tr>
<th>Thermal Laser Photocoagulation of CNV</th>
<th>Photodynamic Therapy</th>
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<tbody>
<tr>
<td>Moofields Macular Study and Macular Photocoagulation Study</td>
<td>CNV location, type, composition and border are determined by FA</td>
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<tr>
<td>Extrafoveal classic CNV derive the most benefit from thermal laser</td>
<td>Intravenous injection of photosensitizing drug - Verteporfin (Visudyne)</td>
</tr>
<tr>
<td>Prevented severe vision loss</td>
<td>Followed by a low-intensity laser light is applied to the CNV</td>
</tr>
<tr>
<td>Cannot use in subfoveal CNV</td>
<td>Closure of the CNV without damage to the surrounding tissue</td>
</tr>
<tr>
<td>60 percent had persistent or recurrent CNV</td>
<td>Can be used in subfoveal CNV</td>
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<tr>
<th>Photodynamic Therapy</th>
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<tr>
<td>TAP Investigation (Classic CNV)</td>
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<tr>
<td>Visudyne in Minimally Classic CNV Trial</td>
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<tr>
<td>VIP Trial (Occult CNV)</td>
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<tr>
<td>Does not improve vision</td>
</tr>
<tr>
<td>Can reduce the risk of moderate and severe vision loss for at least 2 years</td>
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<tr>
<td>subfoveal lesions with a predominantly classic lesion composition</td>
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<td>Photosensitivity reactions</td>
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<th>Pharmacotherapy Wet AMD</th>
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<td>CNV strong association with vascular trophic factors</td>
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<tr>
<td>Vascular Endothelial Growth Factor (VEGF), specifically VEGF-A</td>
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<tr>
<td>What if something could inhibit VEGF-A?</td>
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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 show 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 realized 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 acting 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
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