AGE-RELATED MACULAR DEGENERATION

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INTRODUCTION

• A common chronic degenerative disorder of unknown pathogenesis that affects individuals over 50yrs and features central visual loss.

• Senile macular degeneration- coined by Haab -1885.

• Age-related macular degeneration named by Professor A C Bird (The International ARM Epidemiological study).
EPIDEMIOLOGY

• The UN estimates the number of people with AMD are about 20-25 million worldwide.

• WHO’s estimate is 8 million people with severe visual impairment due to ARMD.

• Prevalence of AMD in >75 year age group varies from 1.2% to 29.3% in different populations.

• In South India, the prevalence is 1.1% whereas, another study from North India reports the prevalence rate to be 4.7%.
**RISK FACTORS**

Age related condition

**RISK FACTORS**
- Heredity (AD, CFH, single nucleotide polymorphisms on 1q32, 6p21, and 10q26)
- Smoking
- Gender
- Hypertension
- Excessive exposure to sunlight
SYMPTOMS

• Straight lines appear wavy
• Blurry and distorted vision
• Objects may appear as the wrong shape or size
• A dark empty area in the centre of vision (Micropsia, Macropsia, Metamorphopsia)
TYPES

AMD

Early

Non exudative (dry)

Late

Exudative (wet)
DRY AMD

- Accounts for about 90% of all cases
- Also called atrophic, non-exudative or drusenoid macular degeneration

- Clinically, dry AMD may manifest-
  - Stage of drusen and/or hyperpigmentation
  - Stage of incipient atrophy (non geographic atrophy)
  - Stage of geographic atrophy
DRY AMD

Photoreceptors
Retinal Pigment Epithelium
Bruch’s Membrane

Drusen
PATHOGENESIS

Insufficient oxygen and nutrients damages photoreceptor molecules

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

Excessive accumulation of residual metabolic debris and hyaline material (*drusen*)

RPE membrane and cells degenerate and atrophy sets in and central vision is lost
Drusen:

- Drusen are aggregation of hyaline material located between Bruch’s membrane and RPE (Basal Laminar and Basal Linear deposits).

- Drusen are composed of metabolic waste products from photoreceptors.

- Hypo/hyper pigmentation of RPE may be present.
• Types:
  – Small: <63 µ
  – Intermediate: 63-124 µ
  – Large: >125 µ

  – Hard:
    • generally small (<63 µ), bright yellow, solid appearing drusen with well defined margins
    • may be asymptomatic

  – Soft:
    • larger (>63 µ), pale yellow, ill defined, fluffy margins
    • High risk for neovascular AMD(Membranous, Granular, Serous)
Diagnostic criteria

- Degenerative disorder in persons >50 years
  - Soft drusen (>63 μ)
  - RPE abnormalities- areas of hypo/hyperpigmentation
  - Visual acuity (VA) is not a criterion
VISUAL PROGNOSIS

• Patients with only drusen not have much loss of vision

• Presence of large drusen (>63 microns in diameter) is associated with a risk of the late form of the disease like CNV.

• Geographic atrophy- severest form of the dry AMD
EXUDATIVE MACULAR DEGENERATION (WET OR NEOVASCULAR AMD)

• Accounts for about 10%

• The pathology of neovascular AMD is CNVM formation.

• The CNVM lead to haemorrhage and fibrovascular proliferation and subsequent scarring
WET AMD-PATHOGENESIS

Photoreceptors and pigment epithelium send signals to choriocapillaries (VEGF’s)

↓

New vessels grow behind the macula

↓

Breakdown in the Bruch’s membrane

↓

Blood vessels are fragile

↓

Leakage of blood and fluid

↓

Subsequent scarring of macula

Potential for rapid and severe visual impairment
WET AMD

Diagnostic criteria

- persons >50 years, characterized by the presence of any of the following:
  - choroidal neovascularization
  - serous retinal pigment epithelial detachment
  - hemorrhagic retinal pigment epithelial detachment
  - fibrotic scar in the macula
The hallmark of neovascular AMD is CNV & manifestations are-

- Subretinal fluid
- Macular edema
- Retinal, subretinal, or sub-RPE hemorrhage
- Retinal or subretinal lipid exudate
- Plaque like membrane or grey or yellow green discrete discoloration
- RPE detachment
- RPE tear
- Sub-retinal fibrosis or disciform scar
• CNV lesion is well demarcated & its location may be determined by closest point to the FAZ.
• Lesion location is classified angiographically as follows:-
  1. Subfoveal: under the centre of FAZ
  2. Juxtafoveal: 1-199 µm from the centre of FAZ
  3. Extrafoveal: >200 µm & <2500 µm from the centre of FAZ

• Types:
  – Type I: CNV beneath RPE
  – Type II: CNV above RPE
Pattern of CNV Hyper fluorescence

Classic CNV
- Well demarcated boundaries.
- Early hyper fluorescence with peak in mid phase
- Late leakage often obscure boundaries

Occult CNV

Type 1
- Fibro vascular PED
- Irregular elevation RPE.
- Boundaries may be well demarcated or poorly demarcated.
- Persistent staining or leakage of dye at 10 min

Type 2
- Late leakage of undetermined of source
- Boundaries always poorly demarcated
- Source of late leakage cannot be determined from earlier frames of angiograms
OCCULT CNV (TYPE-I)  OCCULT CNV (TYPE-II)
• Leakage of blood or serum in CNV may occur and is associated with the abrupt loss of vision.

• Patients with CNV shows rapid decline in vision (20/200) within weeks.

• Once CNV has developed in one eye, the other eye is at relatively high risk for the same change.

• More frequently, visual acuity deteriorates more slowly and stabilizes within 3 years.
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<th>Non-Exudative (DRY)</th>
<th>Exudative (WET)</th>
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<tr>
<td><strong>Severity</strong></td>
<td>Less severe</td>
<td>more</td>
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<tr>
<td><strong>Pathogenesis</strong></td>
<td>Thinning of macula &amp; deposits and pigmentation of macula</td>
<td>Choroidal neo-vascularisation; friable $\rightarrow$ leak blood and fluid</td>
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<td><strong>Symptoms</strong></td>
<td>Gradual loss of vision</td>
<td>Sudden painless loss of vision</td>
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<td><strong>Signs</strong></td>
<td>Drusen and loss of pigments in retina</td>
<td>Elevation in neurosensory retina or pigment epithelium beneath which abnormal blood, fluid and haemorrhage</td>
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<td><strong>Treatment</strong></td>
<td>Zn supplemetation and antioxidant vitamins</td>
<td>Laser  Photo coagulation Photodynamic therapy Macular translocation surgery, Anti-VEGF’s</td>
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AMD: INVESTIGATIONS

- **Visual acuity**

- **Amsler grid test**: Assesses distorted or reduced vision in the central field of vision.

- **Ophthalmoscopy**: to detect drusen, as well as neovascularization

- **Fluorescein and ICG angiography**: Determines the presence and location of neovascularization.

- **Optical coherence tomography**.
AMD: TREATMENT

• Role of Antioxidants:

• AREDS-1 study (Age related eye disease study) - use of high dose of multivitamins & antioxidants decreases the risk of progression of ARM in those with high risk characteristics.

• Combination of antioxidants and zinc (AREDS-1 Formula) -
  – Vitamin C: 500 milligrams (mg)
  – Vitamin E: 400 international units (IU)
  – Beta carotene: 15 mg (equivalent to Vit.A 25000 IU)
  – Zinc: 80 mg
  – Copper (cupric oxide): 2 mg
AMD: TREATMENT

• AREDS-2 Study:
  – Lutein & zeaxanthin antioxidants micronutrients
  – omega-3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have also been shown to help with AMD.

  – AREDS-2 Formula-
    • Vitamin C - 500 mg
    • Vitamin E - 400 IU
    • Beta-Carotene - 15 mg
    • Zinc - 80 mg
    • Copper - 2 mg
    • Lutein - 10 mg
    • Zeaxanthin - 2 mg
    • DHA - 350 mg
    • EPA - 650 mg
AMD: TREATMENT

• Current treatment –

1. Antiangiogenic drugs
2. Photodynamic therapy
3. Laser photocoagulation
ANTI ANGIOGENICS

- Intra vitreal Anti-VEGFs:
  - reduce new vessel growth and leakage

- Bevacizumab (Avastin)
- Ranibizumab (Lucentis)
- Pegaptanib sodium (Macugen)
- Afliibercept (VEGF Trap-Eye)
• Bevacizumab (Avastin)-
  – Full-length non selective monoclonal antibody (150 Kd)
  – Dose- 1-1.25 mg, repeated 6-8 weekly.

• Ranibizumab (Lucentis )
  – Recombinant humanized immunoglobulin antibody fragment (Fab) (48 kD)
  – Dose- First 3 injections of 0.5 mg (0.05 mL) four weekly
• Pegaptanib sodium (Macugen)
  – Ribonucleotide aptamer
  – Binds to Heparin-binding domain of VEGF-A
  – Given 0.3 mg dose six weekly minimum for two years.

• Afiblercept (VEGF Trap-Eye)
  – a fusion protein of key binding domains of human VEGFR-1 and 2 combined with a human IgG Fc fragment
  – blocks all isoforms of VEGF-A and placental growth factors-1 and 2
COMPLICATIONS

• Common-
  – Raised intra-ocular pressure

• Occasional
  – Cataract Formation
  – Intra-ocular hemorrhage

• Rare
  – Endophthalmitis
  – Retinal Detachment
PHOTODYNAMIC THERAPY (PDT)

- PDT helps to selectively close subretinal new vessels.

- Two stage treatment:
  - Injecting the photosensitiser drug (Verteporfin/Purlytin)
  - Applying cold laser/Diode laser (689 nm/805 nm) to activate the drug
    - Releases the singlet oxygen molecule that damages the endothelium
    - Thrombosis of the capillaries
LASER PHOTOCOAGULATION

• Modality for juxtafoveal & extrafoveal CNV associated with AMD

• New blood vessels identified on the fluorescein angiogram and lasered.

• **Disadvantages**-
  – Immediate significant fall in central vision
  – evolution of central scotoma

• **Complications**-
  – Hemorrhage, perforations of BM, RPE tear & arteriolar narrowing.
  – Persistent or recurrent CNV is common.
LASER PHOTOCOAGULATION

Laser Treatment of Wet Macular Degeneration

Laser beam

Macula

Macular degeneration
The goal of TTT is to create and maintain tissue hyperthermia.

The diode laser (810 nm, near infrared):
- poorly absorbed by haemoglobin and Xanthophyll
- mainly absorbed in the choroid, enabling effective treatment of choroidal lesions.

In ongoing trials: 3 mm spot, 800 mW, 60 sec.
RADIATION THERAPY

- **TELEThERAPY (EBRT):**

- **BRACHYThERAPY (Plaque Radiotherapy):**
  - Use of Palladium-103 (103 Pd), Strontium-90 (90 Sr) and Ruthenium-106 (106 Ru)
SURGICAL OPTIONS

- Submacular excision of CNV
- Macular translocation
- Retinal rotation
- Homologous Iris/Retinal pigment epithelium transplantation
- Autologous RPE transplantation
EMERGING TREATMENTS

- Retaane (Anecortave acetate) - modified steroid
- AdPEDF - Adenovirus-based Pigment Epithelium Derived Factor
- siRNA (Bevasiranib) - silences the genes
- ATG3 (mecamylamine) - inhibits the nicotinic acetylcholine receptors
- EVIZON™ (squalamine lactate) - aminosterol with anti–angiogenic activity
- OT-551 (antioxidant eye drops)
EMERGING TREATMENTS

• Encapsulated Cell Technology- contains retinal cells that produce a vision-preserving protein - Ciliary Neurotrophic Factor (CNTF)
REHABILITATION

• Low vision aids-
  – Individual who experiences untreatable visual loss & effects the daily life.
  – Reading lamps & simple magnifiers
  – Closed circuit television & scanning devices to provide electronic magnification & contrast enhancement.
CONCLUSION

• AMD continues to be one of the leading causes of visual loss in aged people.

• New therapeutic strategies continue to be developed & tested.

• Anti-angiogenic drugs remain the mainstay of current treatment.

• Advancement in pharmacology, genetic engineering and surgical techniques may dramatically change the treatment protocol with better outcome in near future.
THANK YOU