AGE-RELATED MACULAR DEGENERATION

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All about the Eye

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ARMD

Definition: It is a chronic bilateral condition of age related degenerative process involving choriocapillaris, Bruch's membrane, RPE and photoreceptors of macular area.

It is a major cause of irreversible loss of central vision in people over the age of 50years.

Characterized by-

Early features	Late features
• Drusen • Hyperpigmentation of the RPE • Sharply demarcated area of the RPE depigmentation.	• Geographic atrophy of the RPE with visible underlying choroidal vessels. • PED with or without neurosensory detachment. • Sub-retinal or sub-RPE neovascularization. • Scar tissue formation, hemorrhage & exudates

Types: This disease has 2 specific presentations -

1. **Dry/ non exudative or atrophic ARMD – comprising 90% cases**
   The dry form occurs when there are
a. pigmentary changes and loss of pigmented cells in the macular area.
b. along with, drusen, the hallmark of macular degeneration.
   Drusen formation is not necessarily the cause of dry ARMD, but it is a fairly good indicator that a person might eventually develop some form of ARMD.

2. **Wet/ exudative or neovascular ARMD – 10% cases**
   The wet form of age-related macular degeneration consists of the changes of dry macular degeneration plus the development of either
a. subretinal choroidal neovascular membranes (subretinal scar tissue),
b. subretinal hemorrhage (bleeding), or
c. an RPE detachment (blister of the retina).

Risk factors: Multifactor etiology-

A. Personal characteristic
1. Age - longer survivors, more incidences
2. Sex - F>M (60%)
3. Hereditary factor – No definite association
4. Iris color – Higher with light colored iris
5. Refraction – Hypermetropic at more risk
6. Smoking – Three times the risk of non-smokers.
7. Race- Common in blacks than whites.

B. Systemic disease
1. CVS disease & Hypertension – Not directly associated
2. But, higher serum cholesterol, ↓HDL, use of H.T medication, ↑parity and elastic degeneration of dermis are at higher risk.
3. Post-menopausal estrogen use - ↓ risk.

C. Environmental factor
Light exposure - ↑risk

D. Nutritional factors
Carotinoids - ↑level → ↓ARMD
Vit E & Selenium – No relation
Zinc – Retard to progression of ARMD

Dry ARMD

Presentation:

1. Gradual loss of central vision
2. Decreased contrast sensitivity and color vision,
3. Difficulty in adaptation to dark
4. When there is disproportionate fall of vision in early cataract.

Signs:

1. One of the difficulties in establishing the pathologic change in AMD is separating the effects of age from those of disease.
2. Focal hyper pigmentation or atrophy of RPE in association with macular drusen.
3. Irregularity of the retinal pigmentation give rise to a fine granularity, and the fundus commonly demonstrate a tigroid, background.
4. Sharply circumscribed, circular atrophic areas of RPE (Geographic atrophy) associated with variable loss of choriocapillaris.
5. Enlargement of atrophic areas within which the larger choroidal vessels may become visible and the pre-existing drusens disappear.

Pathology and pathogenesis

Dry ARMD

1. RPE and photoreceptors:

Malfunction of RPE cells and accumulation of drusen between basement membrane of RPE cells and Bruch's membrane.

Engulfment of debris of photoreceptors by RPE→ Lysosomal enzyme Digestion.
↓
Undigested part
↓
Accumulation of lipofuscin
↓
Morphological change of RPE cells
↓
Gradual separation of its basement membrane
↓
Loss of ability to phagocytose the photoreceptors
↓
Shedding of degenerated cells
↓
Dropout of photoreceptor

2. Bruch's membrane & choroid

1. Hyalinization and thickening of Bruch's' membrane occur which extend down the intercapillary pillars to the level of the choriocapillaries.
2. The choroidal capillaries are separated by widening of the intercapillary pillars and become narrowed by retraction away from Bruch's membrane accompanied by loss of fenestration.

3. Basal linear deposits

Basal linear deposits are phospholipid vesicles and electron-dense granules within the inner collagenous zone of the Bruch membrane.

4. Basal laminar deposit (BLD)

1. Basal laminar deposits are granular, lipid-rich material and widely spaced collagen fibers between the plasma membrane and basement membrane of the RPE cell
2. Histologically, these are pale staining, eosinophilic material with faint striations
3. It is a secretory product of RPE.
4. Late BLD – amorphous, nodular in appearance and appear on the surface of the earlier form.

5. Membranous debris

1. This material has the bilayered structure of phospholipid.
2. In AMD these are found due to selective failure of degradative enzyme with respect to lipid metabolism.
3. These are found in three locations

i. Internal to RPE basement membrane : The debris forms basal mounts →stippling.
ii. External to RPE basement membrane →soft drusen.
iii. At the apex of RPE : These debris represents outer segment material of the rod that has been phagocytosed.

Drusens

Drusen are multiple, small, yellow white excrescence deposits of extracellular material, lying typically between the basement membrane of the RPE cells and the inner collagenous zone of Bruch's membrane mostly in the postequatorial retina
Drusens are not uncommon between 45 and 60yrs of age and almost universal thereafter.

Hard drusen	Soft drusen
Small, round, discrete, yellow-white abnormal materials with distinct borders	Larger with less sharply defined edges.
< 50µm in length, < 63µm in diameter. less than one vein width (aprx .125 m) (abt. 63 m)	Diameter- > or equal to 125µm two to four vein width
Represents lipidization of few RPE cells and a localized accumulation of hyaline material in bruch's membrane	soft drusen represent diffuse thickening of the inner aspect of Bruch's membrane throughout the macula; basal linear deposits
Do not ↓ in size with age	They tend to become confluent and hence show greater variation in shape and size Changes with age. They evolve and fade more rapidly than hard exudate
Tends to occur in clusters and usually on temporal side of fovea. Sometime, along major vessels & nasal side	Soft drusens may be distributed around fixation in a petaloid pattern.
Presence of many small drusen may be a precursor for development of AMD	The occurrences of soft confluent drusen are most commonly considered to be a feature of AMD
small hard drusen hyperfluoresce early in FA studies because of a window defect	larger soft and confluent drusen and drusenoid PEDs slowly and homogenously stain late because of pooling of the fluorescein dye in the sub-PED compartment

- **Drusenoid PEDs** are confluent large drusen that coalesce into a PED (>350 µm diameter)
- An additional type of drusen deposition is referred to as reticular pseudodrusen, also known as **subretinal drusenoid deposits,** because of the reticular-like network appreciated on fundus autofluorescence.
- These lesions are smaller than soft drusen and distribute typically in the superior macular region; they have been associated with progressive atrophy of the photoreceptor layer, GA, and a greater risk of CNV.
- Reticular pseudodrusen are identified above the RPE and beneath the inner segment ellipsoid layer and are graded according to their degree of elevation
- Enhanced depth imaging (EDI) of the choroid using OCT has permitted more detailed analysis of the choroid in AMD. Choroidal thickness values are typically normal or reduced in nonneovascular AMD.
- Clincopathologically, **Classified**:
  1. Discrete small hard drusen
  2. Larger drusens derived from clusters of small hard drusen
  3. Soft drusen that appear to develop de novo
  4. Fading/Regressing drusen
- Clinically, the extent of fundus involvement can be assessed by –
  i.. Number of drusen - <20 or >20
  ii Density- can be graded as **scattered** if they are distinct from one another, **sub-confluent** if the boarders are just touching, and **confluent** if the boarders are overlapping.

Abnormalities of the RPE

- Several patterns of RPE abnormalities characterize nonneovascular AMD, including focal hyperpigmentation, nongeographic atrophy, and geographic atrophy.
- **Increased pigmentation** at the level of the outer retina corresponds to focal hyperpigmentation of the RPE.
- On FA, these areas typically show blockage, and on SD-OCT, show hyperreflective outer retinal foci.
- The incidence of focal hyperpigmentations increases with age, and their presence indicates greater risk of progression to the more advanced forms of AMD.
- **Nongeographic atrophy** refers to atrophy that does not cover a contiguous area and may appear as an area of mottling or depigmentation.
- When the area of absent or attenuated RPE is contiguous, the condition is termed **geographic atrophy** of the RPE.
- In areas of GA, the unmasked choroidal vessels are more readily visible, the overlying outer retina may appear thin, and the choriocapillaris is attenuated or atrophied.
- On FA, GA shows well-circumscribed round to oval window defects, whereas on SD-OCT, loss of the RPE and the overlying inner segment ellipsoid and photoreceptor layer can be seen.
- Dense hypoautofluorescence occurs in areas of GA.
- Fundus autofluorescence is a practical and noninvasive tool to monitor progression of GA
- Geographic atrophy often spares the fovea until late in the course of the disease.
- It may first present as one or more noncontiguous patches of atrophy around the fovea.
- These patches enlarge and coalesce and may be associated with a dense paracentral scotoma, thereby limiting tasks such as reading.

- Patients with GA may demonstrate good visual acuity (VA) until late in the course of the disease, when the fovea becomes progressively atrophic, leading to severe visual acuity decline from central blindness and forcing the patient to use noncentral retina and eccentric fixation to read and perform other visual tasks.

Geographic atrophy:

1. Also called "areolar atrophy"
2. Represents the most advanced form of non-neovascular AMD. This is the end result of atrophic form of AMD
3. Consist of one or several circumscribed areas, (<175 µm) of discrete absence or attenuation of RPE, exposing the underlying choriocapillaris.
4. Evolution: Three patterns may be recognized that leads to GA-
   i. **Drusen related** - Large, soft, confluent drusen regress leading to multiple atrophic areas of RPE. But, when other changes of AMD affects the intervening RPE, the patches enlarges and coalesce → GA
   ii. **Drusen unrelated, pigmentary** – Central macula may contain tiny areas of reticulated hypo and hyper pigmentation, which may progress to one large area of GA
   iii. **Spontaneous flattening of RPE detachment**- especially those detachment formed by the confluence of soft drusen can give rise to GA.

Clinicopathology-

Replacement of soft drusen with fibrous tissue/Dystrophic calcification.
↓
The attenuated RPE overlying it progressively disappear
↓
Small areas of GA accompanied by loss of overlying photoreceptors

FFA – Early & discrete hyperfluorescence of atrophic areas, presumably resulting from increased transmission of choroidal fluorescence because of lack of RPE.

Wet/exudative ARMD

- Approximately 10% of AMD patients manifest the exudative form of ARMD.
- Associated with rapidly progressive marked loss of vision.
- Involves the ingrowth of fibrovascular tissue into the sub RPE and sub retinal spaces.
- It occurs when new vessels forms, to improve the blood supply to oxygen deprived retinal tissue.
- These newly formed vessels are very delicate and easily breaks causing bleeding and damage to surrounding tissue.
- Typically, the course of exudative AMD rapidly passes through many stages. These includes –
  → Stage of drusen formation
  → Stage of RPE detachment
  → Stage of CNV
  → Stage of hemorrhagic detachment
  → Stage of detachment of neurosensory retina
  → Stage of disciform (scarring) macular degeneration

Risk factors: Same as Dry ARMD + Drusen formation

Pathogenesis of Choroidal neovascularization:

Presence of diffuse thickening in the inner aspect of Bruch's membrane
↓
Development of cracks in basement membrane
↓
Ingrowth of new vessels from the
Choriocapillaris through the cracks (CNV)
↓
Which extends to sub RPE (type 1) space
Or sub retinal space (type 2)

- The endothelial cells of the new vessels lack the barrier function.
- Hence, leaks fluid in the neurosensory, sub sensory and RPE layers of retina.
- These vessels are very fragile and break easily leading to vascular membrane and scar tissue formation.

- These new vessels are accompanied by fibroblasts, resulting in a fibrovascular complex that can leak and bleed and may disrupt and destroy the normal architecture of the RPE–photoreceptor complex, ultimately leading to the formation of a hypertrophic fibrotic disciform scar.

Hemodynamic theory:

Atherosclerosis in ocular vasculatures
↓
↑ Ocular rigidity
↓
↓ Blood flow in vortex veins
↓
Relative choroidal ischemia
↓
Induces angiogenic stimulus
↓
↑ Level of VEGF
↓
Neovascular ingrowth

Presentations:

CNV should be suspected if any elderly patient (>50 years) with large, soft drusen complains –

- Sudden blurring of central vision
- Metamorphopsia (distortion of image)
- Central or paracentral scotoma
- Any sudden, non-specific change in central vision
- Asymptomatic sometime

Signs:

- Visualization of choroidal neovascularization as yellow- green discoloration surrounded by pigment ring
- Presence of sub retinal and sub RPE BLOOD – may be extensive as to obscure all other signs of CNV
- Elevation of RPE
- Sensory retinal detachment
- Sea fan pattern of subretinal vessels.
- Intraretinal blood and cystoid macular edema (CME) may indicate the presence of type 3 neovascularization, which originates from the deep capillary plexus of the retinal circulation.

Anatomical classification

	Type 1	Type 2	Type 3
Location	New vessels originating from the choriocapillaris grow through a defect in the Bruch's membrane into the sub–pigment epithelial space. Leakage and bleeding can lead to the development of a vascularized serous or fibrovascular PED. PCV is a variant of choroidal neovascularization (type 1)	CNV occupies the subneurosensory compartment between the RPE and the outer segments of the retina. On examination, the membrane will appear as a lacy or gray-green lesion; in AMD, this finding is less common than is type 1 neovascularization.	Results from new blood vessels sprouting from the deep capillary plexus of the retina and growing downward toward the RPE. Because of their intraretinal growth, these lesions were originally termed retinal angiomatous proliferations (RAP). On examination, they appear as a small area of red discoloration, often associated with retinal exudate.
FFA	occult CNV may be anatomically related to type 1 neovascularization	classic CNV may be related to type 2 neovascularization	Type 3 or RAP, may be signaled by the presence of a spot of retinal hemorrhage in the macula. FA and ICG angiography may demonstrate a focal hot spot and late CME; associated pooling into a PED may also be present

SD-OCT	Type 1 neovascular membranes demonstrate elevation of the RPE and a PED on SD-OCT	Type 2 neovascular membranes appear as a hyperreflective band or plaque in the subneurosensory	Type 3 neovascular membranes are best appreciated with SD-OCT as a hyperreflective focus from the deep capillary plexus of the retina, with or without associated CME and PED.

FFA classification

a) **Classic CNV** :

In the early phase of the angiogram: An area of well demarcated choroidal hyperfluorescence membrane seen.
In late phase: Borders may be obscured by leakage of dye. Also, progressive dye leakage into overlying sub retinal space seen.
Classification: In relation to the centre of FAZ (Foveolar avascular zone)

- Extrafoveal: CNV >200µm from the centre of FAZ.
- Subfoveal : In the centre, carries poor visual prognosis.
- Juxtafoveal: < 200µm from the centre of FAZ.

a) Occult CNV :

Early phase: A poorly defined membrane in the form of multiple punctate hyperfluorescent dots.
Late phase: Choroidal leakage apparent.
Types : i. Type I – PED either fibrovascular PED or vascularized serous PED
ii. Type II –Late leakage of undetermined source refers to regions of fluorescence at the level of the flat RPE that are ill defined early and best appreciated in the late phases of the angiographic study

Choroidal new vessels are directly associated with clinical findings such as –

I. RPE detachment
II. RPE tear
III. Disciform scar
IV. Breakout vitreous hemorrhage
V. Subretinal hard exudates and subretinal hemorrhage, sub pigment epithelial hemorrhage.

I. RPE detachment: Clinically, sharply demarcated, dome shaped elevation of RPE at posterior pole.
Sensory retinal detachment may be present.
AMD with serous RPED always raises suspicion of CNV.
II. RPE tear: Acute tear occurs spontaneously in association with RPED or during laser photocoagulation. Tear occurs at the junction of attached and detached RPE by fluid in the subretinal space.
III. DISCIFORM SCAR:
→ End stage manifestation of exudative AMD
→ Present with in the central portion of choroidal neovascular lesion.
→ Appears as yellow- white lesion because of fibrous tissue contents and pigmentary component.
→ Continued signs of active CNV at the periphery including subretinal fluid, hemorrhage or lipid.
IV. VITREOUS HAEMORRHAGE: When bleeding breaks through the retina into vitreous cavity. Patients may complain severe and sudden vision loss.
V. SUB RETINAL EXUDATION: Massive subretinal and intraretinal exudation occurs due to chronic leakage from CNV.

DIFFERENTIAL DIAGNOSIS:

Pathological myopia	Posterior scleritis
Angioid streaks	Ocular histoplasmosis
Macro aneurysm	Vitelliform lesions of Best's macular dystrophy
Traumatic choroidal rupture	Vitreous hemorrhage due to retinal vascular disease and retinal tear formation
Choroidal tumours	bull's-eye macular atrophy similar to GA
Central retinal choroidopathy	

TREATMENT OF WET ARMD:

Different modalities of treatment available are –

1) Pharmacological therapy
2) Laser/thermal therapy
3) Macular surgery
4) Low vision rehabilitation therapy

1) Pharmacological therapy:
    a. Antioxidant and micronutrients: As in dry ARMD.
    b. Antiangiogenic drugs: To inhibits the growth of new vessels.

Thalidomide platelets factor K 16 Growth factor blockers K factor of prolactin	Anti VEGF (pegaptanib sodium, Bevacizumab, Ranibizumab) Interferon Steroid (Triamcinolone acetate, Anecortane acetate),

2) Laser /Thermal therapy:

a. Laser photocoagulation:

- Aim: to reduce the risk of severe vision loss.
- Indications: Well demarcated extrafoveal or juxtafoveal CNV, Classic CNV, Recurrent CNV.
- Laser used: Argon green, Krypton red.
- Treatment protocol: After taking the consent from the patient and a recent FFA (<72 hours) (Since it is estimated that the CNV can grow at an average of 10 to 18 microns a day), 200µm laser is applied for 0.2-0.5 seconds to a well localized CNV.
- The use of thermal laser treatment is now rare except to treat extrafoveal lesions that are sufficiently far from the foveal center to have minimal risk of iatrogenic foveal laser damage and a lower rate of recurrence.

b. Photodynamic therapy (PDT):

Here tissues are treated with photosensitizers and then exposed to low intensity light exposure to produce photochemical effects. It causes selective destruction of CNV with preservation of the overlying neurosensory retina by proper localization of CNV.

- Laser used: Diode laser
- Drug used: Verteporfin
- Technique: Vertiporfin (6mg/kg BW) is infused intravenously over 10 minutes. Five minutes later, laser is applied to the selected CNV for 83 seconds.
- Use of PDT in the management of exudative AMD is now rare except in recalcitrant cases or eyes with PCV

c. Transpupillary Thermotherapy (TTT):

It is a recent modality of treatment of neovascular AMD. Here, large spot size, low irradiation, long pulse modified diode laser irradiation (810nm), for the management of occult and classic CNV, is applied to the choroids and the RPE through the pupil.

3) **Macular surgery**: An alternative means of removing choroidal neovascular membrane (CNVM). Modalities are –

i. **Surgical removal of submacular hemorrhage:** as it causes irreversible photoreceptor damage due to barrier, toxic and tractional effect.
ii. **Thrombolytic agent such as, tissue plasminogen activator (TPA)** is used to dissolve clots. Dose: 10-20µgm in 0.1ml.
iii. **Pneumatic displacement of subfoveal blood** with or without TPA is also carried out.
iv. **Surgical removal of CNV membrane (submacular surgery)** through a retinotomy site made by a sharp 130 degree angled needle.
v. **Subretinal endophotocoagulation:** carried out with the help of a 31 gauge endolaser probe in previously lasered case, pre RPE CNV.
vi. **Macular translocation**: Here, retina is shifted away from the underlying subfoveal CNV.
    a. Indication: Subfoveal CNVM.
    b. Procedure: Involves vitrectomy+ lensectomy+ total RD created by fluid infusion under the retina+ Retinotomy +Removal of sub retinal blood and membranes+ Retinal rotation +Reattachment.
vii. **RPE transplantation**: As the main pathology is the dysfunction of RPE cells, so efforts have been made to transplant RPE cells in subretinal space.
Routes: External (anterior transvitreal), Internal (posterior transscleral)
viii. Retinal Transplants and Implants
ix. Regeneration of Retinal Cells
x. Rheopheresis
xi. Feeder Vessel treatment

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CHOROIDAL NEOVASCULAR MEMBRANE: DISEASES ASSOCIATED WITH CNVM FORMATION:

Degenerative conditions	Inflammatory and infectious conditions	Hereditary
❖ Wet ARMD ❖ Degenerative myopia ❖ Angioid streaks ❖ ONH drusen ❖ ICSC and RPE detachment	❖ POHS ❖ Toxoplasmosis ❖ Tuberculosis ❖ Sarcoidosis ❖ Syphilis ❖ Rubella ❖ Choroidopathies (serpiginous, birdshot, punctate inner) ❖ Behçet's syndrome ❖ VKH Syndrome	❖ Best's disease ❖ Dominant drusen ❖ Fundus Flavimaculatus ❖ Choroideremia ❖ RP
Tumors	**Trauma**	**Miscellaneous**
❖ Malignant melanoma ❖ Choroidal hemangioma ❖ Metastatic tumors	❖ Excessive PRP ❖ Choroidal rupture	❖ Idiopathic CNVM ❖ Radiation retinopathy ❖ Retinal detachment ❖ Tilted disc syndrome