ACQUIRED RETINAL DEGENERATIONS

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of acquired retinal degenerations via developing:

- A protocol for assessing the signs of acquired retinal degenerations
- A framework for making a differential diagnosis of acquired retinal degenerations
- Management guidelines for acquired retinal degenerations

LEARNING OBJECTIVES

After completing this unit, fellows should be able to:

1. Understand the diversity of presentations of inherited and acquired retinal degenerations
2. Appreciate the complex nature of the aetiology of inherited and acquired retinal degenerations
3. Develop a plan for clinical investigation of these conditions
4. Know that the treatment options are complex and often still in early phase of development

INTRODUCTION

This unit examines retinal degenerations/retinopathies that are either inherited e.g. retinitis pigmentosa, achromatopsia, juvenile macular degeneration, or acquired e.g. age-related macular degeneration (AMD), autoimmune retinopathies.

Diabetic and hypertensive retinopathies are considered as acquired conditions.

Discussion will include, where applicable, a review of gross and cellular anatomy of the retina/choroid complex and also a review of how to clinically assess the retina/choroid structure and function.

AGE-RELATED MACULAR DEGENERATION (AMD)

AMD in Australia is predicted to cost approximately $2.6 billion/year and is projected to grow to $6.5 billion per year by 2025. The projection amounts to a total cost of $59 billion over the next 20 years.

The condition is the most common cause of blindness in those aged over 40 years. (Access Economics, 2009)

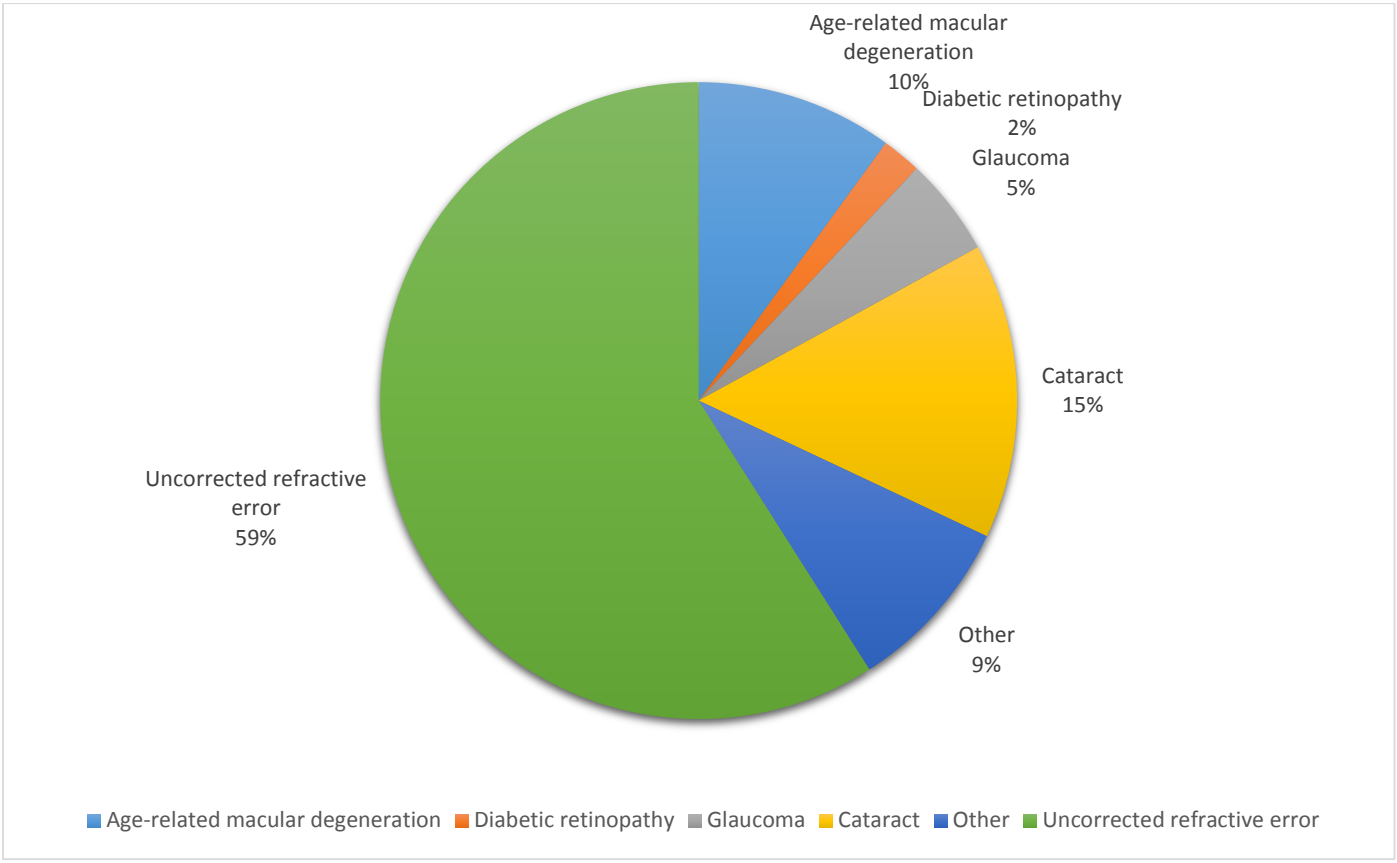

Figure 1a: *Vision impairment by cause among Australians aged 40 or over, 2009*

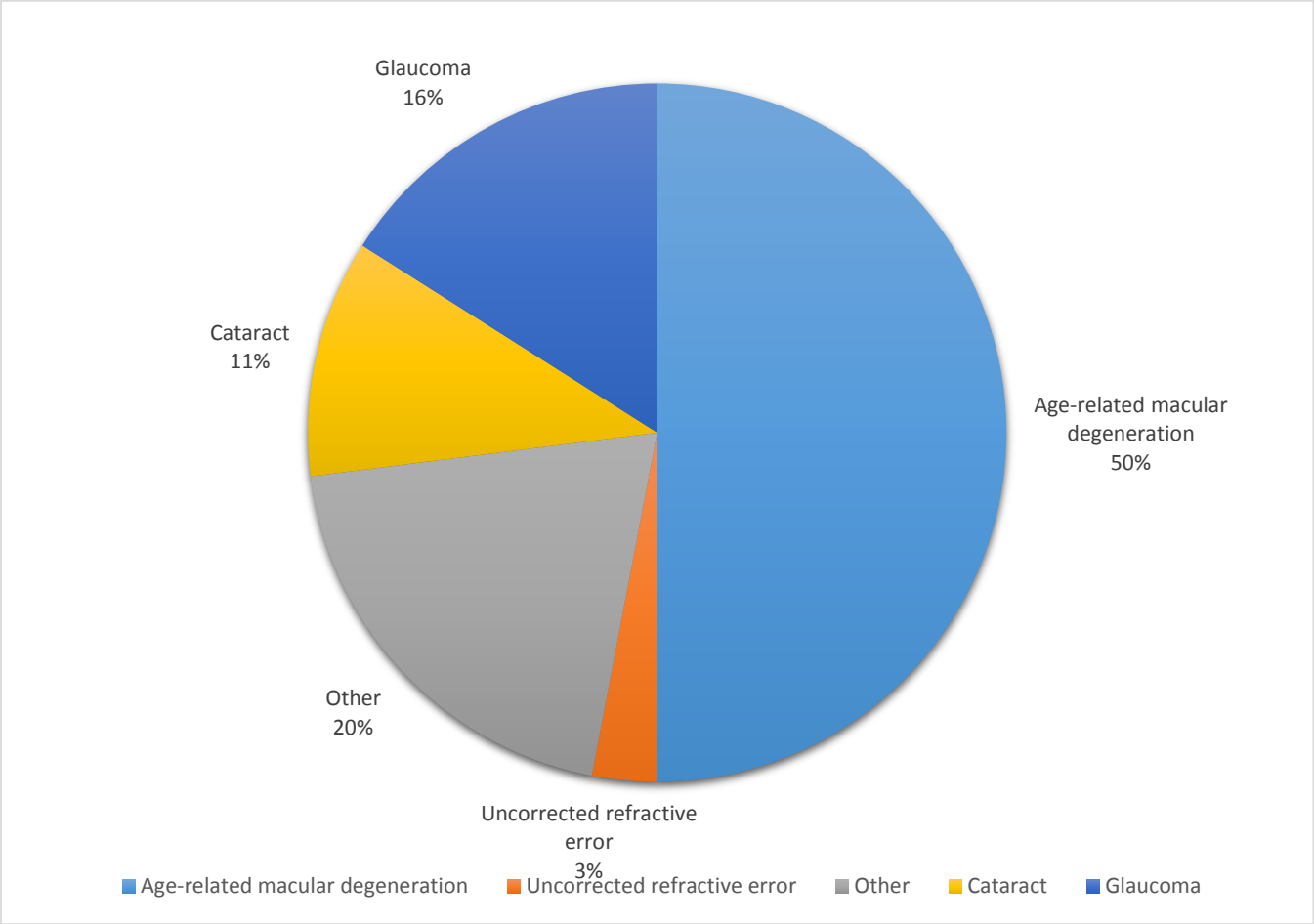

Figure 1b: *Blindness by cause among Australians aged 40 or over, 2009*

Clinically, end-stage AMD is classified as either:

- Non-exudative: "dry" or atrophic (most common, about 90% of AMD cases)
- Exudative: "wet" or neovascular
    - Approximately 66% of the cases of wet AMD accounts for about 90% of all blindness related to AMD (National Eye Institute, 2000b)

AGE-RELATED EYE DISEASE STUDY CLASSIFICATION SYSTEM

Several classification schemes for AMD have been developed with one of the widely used based on the Age-Related Eye Disease Study (AREDS). The classification system below defines four stages of AMD based on lesions falling within a 3mm radius of the fovea, adapted from the standard Early Treatment Diabetic Retinopathy Study (ETDRS) grid.

- **AREDS category 1 – (No AMD)**
    - This was the AREDS control group, consisting of patients with no or a few small drusen (<63 microns in diameter).
- **AREDS category 2 – (Early AMD)**
    - Characterized by a combination of multiple small drusen, a few intermediate drusen (63 to 124 microns in diameter) or RPE abnormalities.
- **AREDS category 3 – (Intermediate AMD)**
    - Characterized by extensive intermediate drusen, at least one large drusen (>125 microns in diameter) or geographic atrophy not involving the center of the fovea.

- **AREDS category 4 – (Advanced/Late AMD)**
  - Characterized by one or more of the following (in the absence of other causes), in one eye:
    - Geographic atrophy of the RPE and choriocapillaris, including the center of the fovea
    - Neovascular maculopathies, such as the following: Choroidal neovascularization (CNV)
    - Serous and/or haemorrhagic detachment of the sensory retina or the RPE
    - Hard exudates in the retina
    - Subretinal and sub-RPE fibrovascular proliferation
    - Disciform scar

DRY AMD (GEOGRAPHIC ATROPHY)

The dry form of AMD results in a gradual, insidious loss of vision.

It is characterized by sharply delineated roughly round or oval areas of hyperpigmentation or depigmentation or apparent absence of the retinal pigment epithelium (RPE).

The choroidal vessels are more visible than in the surrounding area.

WET AMD (EXUDATIVE)

The wet form of AMD is characterized by any/all of the following:

1. Retinal pigment epithelium (RPE) detachments associated with neurosensory retinal detachment
2. Subretinal or sub-RPE neovascular membranes
3. Retinal scarring
4. Subretinal haemorrhage
5. Hard exudates within macula not related to other retinal vascular diseases

TERMINOLOGY AND FLUORESCEIN ANGIOGRAPHY (FA) TERMS

- Classic: early leakage from edge of the membrane with a lace-like pattern; early transit phase; some late leakage
- Extrafoveal: indicates a distance greater than 200 µm from the foveal avascular zone (FAZ)
- Subfoveal: center of the FAZ is involved
- Juxtafoveal: closer than 200 µm but not involving the FAZ
- Occult: 'hidden', poorly defined membrane, ill-defined leakage on FA (Type I or II); Indocyanine green (ICG) angiography is useful
- PED: pigment epithelial detachment, sharp edges, late fluorescence
- Polypoidal choroidal vasculopathy: is different than wet AMD. Does this respond to Lucentis for example? Requires ICG angiography.

PATHOPHYSIOLOGY OF AMD

The pathophysiology of AMD remains incompletely understood. Drusen, basal laminar deposits (BLamD) and basal linear deposits (BLinD) accumulate within the extracellular environment of the RPE-choroid interface.

- BLamD: fibrous long-spacing collagen and other material between the RPE and RPE-basal laminar
- BLinD: membranous material located between RPE-BLamD and inner collagenous layer

Inflammation and age-related maculopathy (ARM or AMD)

- Drusen contain a number of proteins associated with inflammation or its aftermath – especially proteins associated with complement activation
- Single nucleotide polymorphisms: complement regulatory protein 'Factor H' leads to unregulated activation of 'alternate complement pathway' (i.e. inflammation is involved)
- It is proposed that drusen are a manifestation of chronic, local inflammation at the level of Bruch's membrane

DRUSEN

- Hard drusen: are small, round, discrete yellow spots associated with ageing and dry AMD. They are typically less than 63 µm in size (about half the diameter of a retinal vein, category 1 in the AREDS system)
- Soft drusen: are largish, grey-yellow-white confluent lesions. The coalescence of soft drusen often heralds AMD (dry and wet) and they can affect the RPE significantly
- Size, type, location and number of drusen are critical

IMMUNE DYSREGULATION, AGING AND AMD

Complement Factor H: first gene identified that confers a significant risk for development of AMD.

- CFH Y402H SNP confers about a 60% risk of developing AMD

The uncontrolled regulation of the alternative pathway of complement suggests a central role in AMD pathogenesis.

A possible scenario is as follows: exposure to 'triggering event' in genetically susceptible individuals, coupled with impaired complement regulation, leads to sustained activation of the complement cascade, drusen formation and results in the development of AMD.

RISK FACTORS RELATED TO AMD

- **Age**
  - Is the main risk factor
- **Smoking**
  - Beaver Dam Study, Blue Mountains Eye Study and others: the development of exudative AMD is associated with a history of current cigarette smoking
- **Nutrition**
  - Age-Related Eye Disease Study (AREDS, AREDS2)
- **Genotype**
  - CFH polymorphisms, plus others
- **Positive Family History**
  - Genetic factors: siblings have a 20X higher risk
- **Cardiovascular Risk factors**
  - Hypertension
- **Light**
  - Blue Mountains Eye Study disclosed no relationship between light and ARM (?)
- **Cataract**
  - Nuclear cataract in particular
- **Gender**
  - Studies are inconclusive but there may be a possible female predilection
- **Race**
  - Less common among more pigmented races
- **Atherosclerosis**
  - Increased risk among people with evidence of atherosclerosis
- **Blood lipids**
  - May be an association with increasing levels of total cholesterol
- **Antioxidants**
  - May play a role in preventing cellular damage to retina by acting against free radicals. Combination of anti-oxidants and Zinc may be beneficial in moderate AMD; Omega-3 fatty acids appear to be beneficial in AMD

WHY THE MACULAR REGION?

There are a number of suggestions for why the disease has a predilection for the macula.

- Bruch's membrane is approximately 1/4 the thickness and more porous than other regions of the retina (Curcio et al; also Chong et al Am J Pathol)
- There may be differences in the photoreceptors (?)

- Density of the choriocapillaris / vascular supply in the region
- Inflammation and macrophages are involved

MANAGEMENT OF AMD

Optometrists have many roles to play including early detection of the disease, monitoring, referral when needed, giving advice about health and lifestyle choices, use of sunglasses and the need for low vision devices in the late stages of the disease.

Other important aspects of management include:

- Routine screening: VA, Amsler grid, visual fields, dilated fundus exam, fundoscopy
- At home monitoring by the patient to check EACH eye with e.g. an Amsler grid
- Imaging: OCT, FA and ICGA, FAF as required
- Mild, low risk disease can be managed by the optometrist
- Referrals for patients with recent onset of distortion on the Amsler grid and visual loss (as soon as possible) in order to preserve the quality of vision
- If a 'neovascular net' is suspected, then an urgent referral is recommended; diagnosis to treatment should be less than 2 weeks
- The elderly population with AMD often have concurrent eye problems e.g. cataract and glaucoma. Such conditions may occur frequently and therefore need to be identified and treated appropriately.
- Good control of hypertension may favourably influence surgical treatment of neovascular membranes

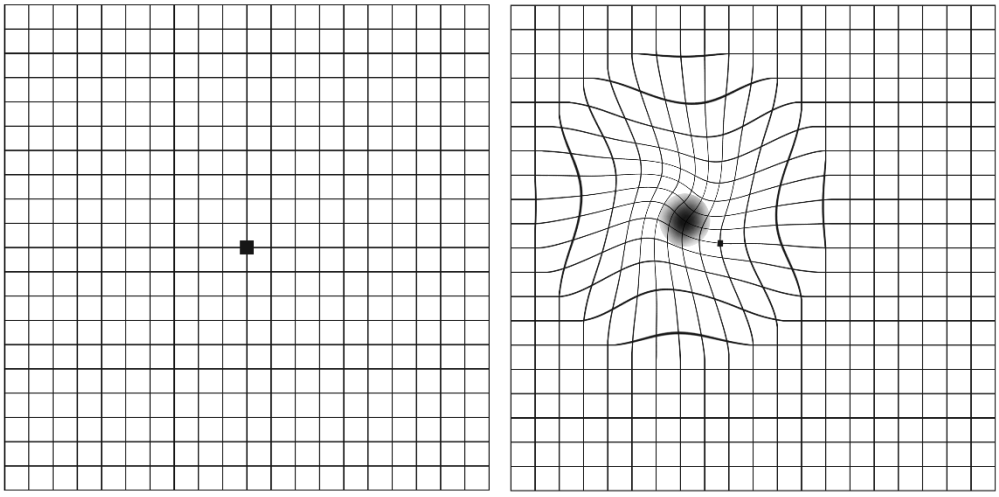

Figure 2: *Example of Amsler grid distortion*

AMD AND LOW VISION

The provision of low vision aids is a vital part of the management of AMD. Other beneficial strategies include:

- Visual handicap registration
- Training and coping strategies
- Support services in the community
- Macular Degeneration Foundation services and newsletters, etc.

ANTI-VEGF DRUGS

Vascular endothelial growth factor (VEGF) is a signalling protein that is important for the growth of new blood vessels. VEGF is part of a system that restores blood supply to cells and tissues when they are deprived of oxygenated blood due to e.g. inadequate blood circulation.

- Hypoxia is a key upstream factor in the activation of VEGF
- VEGF binds to receptors (VEGF-R1 and R2) leading to new blood vessel growth and increased vessel leakiness
- Lucentis and Avastin: inactivates VEGF, antibody-based therapy (reviewed Marquest et al, 2013)
- Eylea (aflibercept; VEGF Trap): consists of VEGF-R1 and R2 – binds all forms of VEGF and Placenta-derived growth factor (PlGF) (trial for wet AMD only) (VIEW1 and 2 Studies; Bakall et al, 2013)

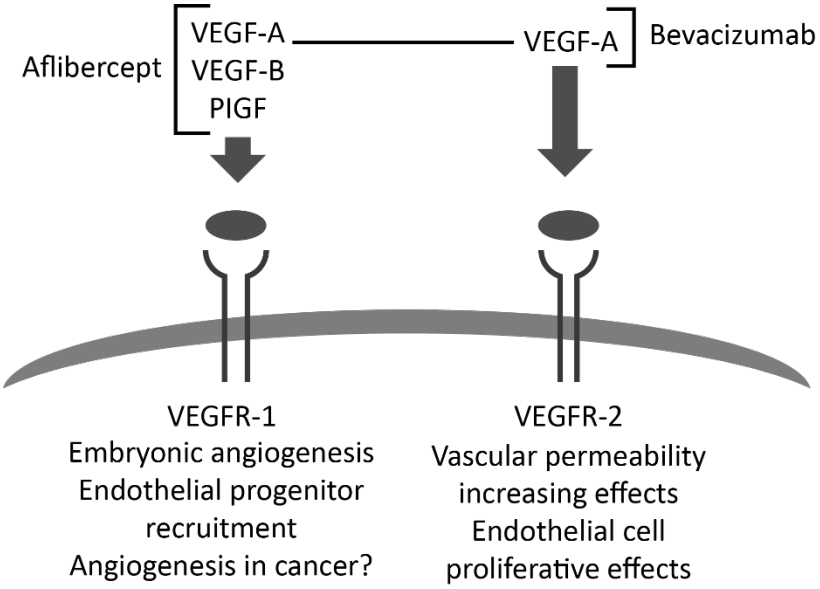

Figure 3: *VEGF binding to receptors*

TREATMENT FOR DRY AMD

- No proven treatment at this stage
- Nutritional supplements show potential – AREDS/AREDS2
- Original formulation for AREDS1 included:
    - 500 milligrams (mg) of vitamin C
    - 400 international units of vitamin E
    - 15 mg beta-carotene
    - 80 mg zinc as zinc oxide
    - 2 mg copper as cupric oxide
        - To prevent anaemia with high zinc intake
- AREDS/AREDS2 formulation appears to help
    - Intermediate AMD in one or both eyes
    - With advanced AMD (dry or wet) in one eye but not the other eye, the use of the formulation will not prevent the formation of dry AMD
- AREDS2 study: designed to determine if removal of beta-carotene and/or reducing dose of zinc provided any benefit
- AREDS study group recommended continued use of original AREDS formulation but with beta-carotene removed and replaced by lutein/zeaxanthin
- The formulation for AREDS2 includes:
    - 500 milligrams (mg) of vitamin C
    - 400 international units of vitamin E
    - 80 mg zinc as zinc oxide
    - 2 mg copper as cupric oxide
        - To prevent anaemia with high zinc intake
    - 10 mg lutein
    - 2 mg zeaxanthin

ROCHE PHASE II CLINICAL TRIAL

Mid-stage study of lampalizumab: slowed progression of dry AMD in patients with advanced disease, shrinking the area of geographic atrophy by 20.4%.

Lampalizumab is a monoclonal antibody that binds CFD (complement factor D, Adipsin, C3 convertase activator, properdin factor D) – alternative complement pathway.

TREATMENT FOR WET AMD

Haemorrhages associated with new vessels and macular oedema, fibrovascular lesions, macrophages, inflammatory mediators. Treatment options include:

1. Laser photocoagulation therapy (to reduce vessel leakage)
2. Photodynamic therapy with Visudyne, PDT (to decrease new vessels)
3. Intravitreal steroids (to reduce leakage and inflammation)
4. Intravitreal injection anti-VEGF drugs such as Lucentis, Avastin, Eylea (to stop new vessels)
5. Adjuvant therapies

AMD: SUMMARY

Dry or atrophic AMD

- Develops slowly
- Vision loss happens gradually
- End stage of Dry AMD: geographic atrophy; loss of RPE and photoreceptors

Wet or exudative AMD

- Develops more quickly
- Dramatic effect on vision
- Drusen (yellowish deposits include different types of proteins)
- Choroidal neovascularization (CNV)
- Occult versus classical
- Progression in other eye
    - New vessels in one eye
    - Large drusen, close to fovea (within 1500 µm)
    - RPE hyperplasia/pigmentary disturbance
    - Confluent drusen (size is approximately the area of the optic disc)
    - Systemic hypertension

POLYPOIDAL CHOROIDAL VASCULOPATHY

Polypoidal choroidal vasculopathy (PCV) is an exudative maculopathy that affects vision. Some of the clinical features of PCV are very distinct from neovascular age-related macular degeneration.

- PCV is observed as a branching inner choroidal vascular network with polypoidal lesions
- The lesions are reddish-orange spheroidal aneurysms (polyp-like) at the end of branching vessels
- Yannuzzi et al (1982) described choroidal new vessels in the peripapillary retina as “idiopathic polypoidal choroidal vasculopathy”

WHO IS AFFECTED BY PCV?

Ethnic background plays a role in the development of PCV. The incidence seems to be higher in people of Asian background. This is especially so in Japan (Byeon et al, 2008).

- Caucasians are also affected (Ciardella et al, 2004, Uyama et al, 2002)
- Age of onset: usually between 50 and 65 years, but reported between 20 to 80 years of age (Ciardella et al, 2004)
- PCV occurrence may be unilateral or bilateral, but mostly it is asymmetric affecting one eye first, then the other (Imamura et al, 2010)

CLINICAL FEATURES OF PCV

The main features of PCV are as follows:

- Polypoidal lesions from choroidal vessels
- Detachment of retina and RPE around optic nerve or in central macula
- Subretinal haemorrhage
- Atrophy of the retinal pigment epithelium (RPE)
- Branching network of choroidal blood vessels
- Multiple, recurrent haemorrhagic pigment epithelium detachments (PEDs) from ‘grape-like’ structures

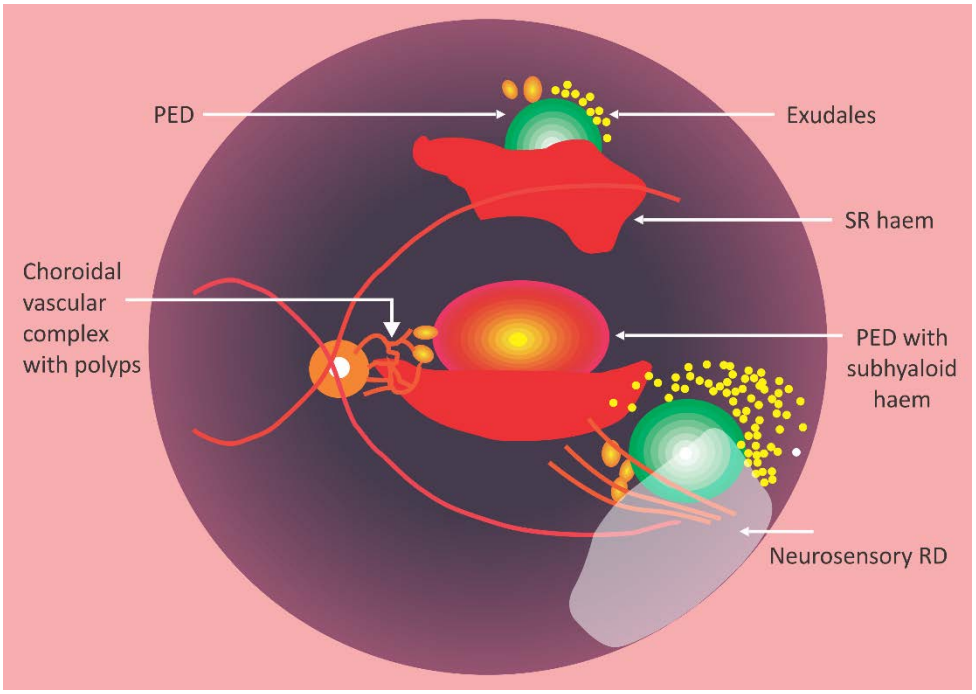

Figure 5: *Polypoidal choroidal vasculopathy*

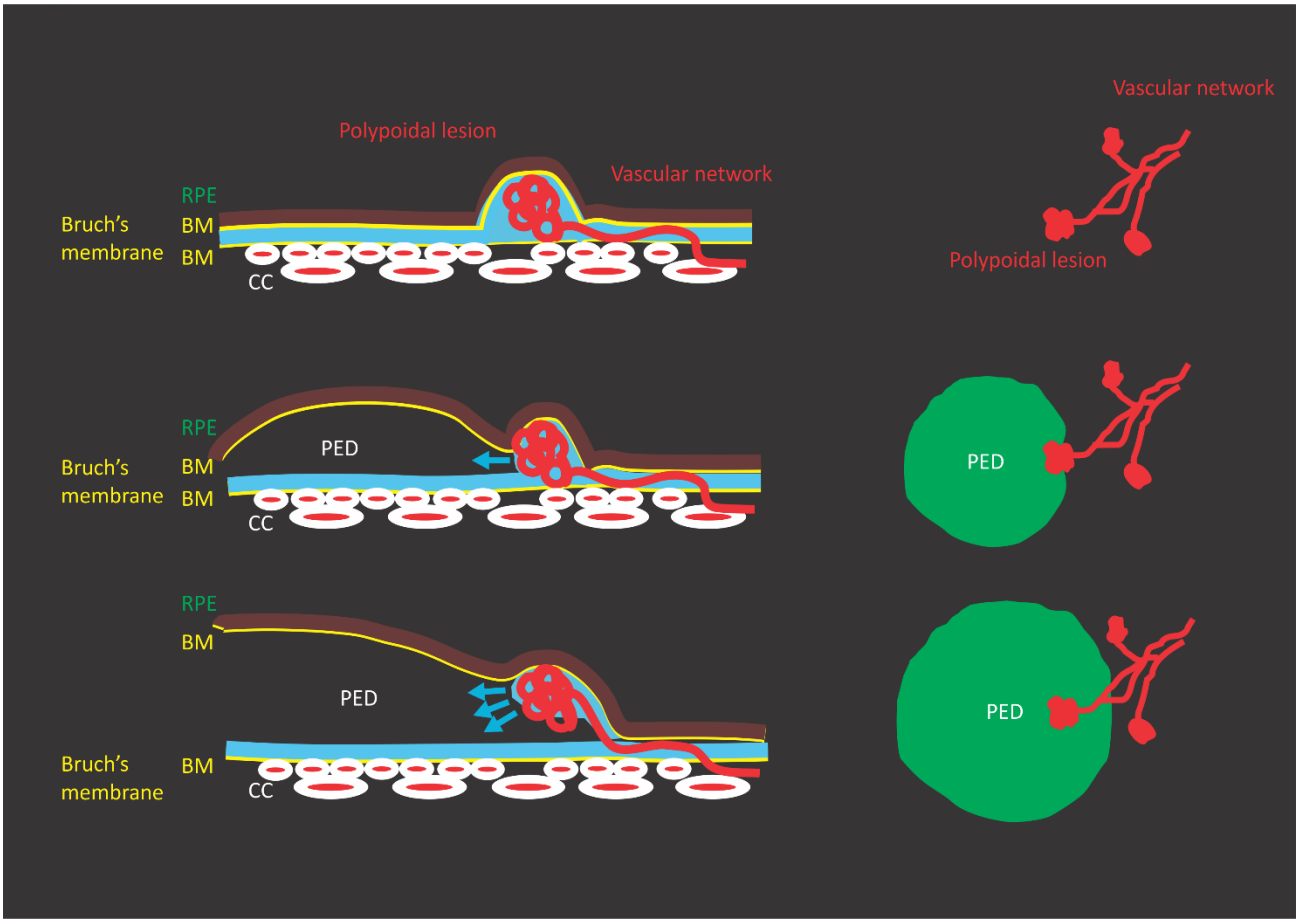

***Figure 6**: Development of PED with polypoidal lesion in PCV (Tsujikawa et al., 2007)*

DIAGNOSIS OF PCV

The two main methods for assisting in the diagnosis of PCV are:

1. **Optical Coherence Tomography (OCT)**
   - Detects abnormalities surrounding polypoidal lesions
   - High quality OCT images show that the polypoidal structures are under the RPE and are attached to the RPE basal surface (Imamura et al, 2010)
2. **Indocyanine green angiography (ICGA)**
   - The technique is the best way to diagnose PCV
     - Abnormal vessels and small lesions detected (Ciardella et al, 2002; 2004).
   - Best clinical way to initially differentiate between wet AMD and PCV

DIFFERENTIATION BETWEEN WET AMD AND PCV

Some clinical features of wet AMD and PCV are common. Distinctive features of branching vascular networks and polypoidal structures are seen in PCV (Ciardella et al, 2004, Uyama et al., 2012).

Progression of PCV is slow, so for most patients the VA remains good (Ciardella et al, 2002; 2004). Patients with wet AMD progress more quickly, with a more dramatic effect on VA (Khandhadia et al, 2012).

Genetic factors are involved in both conditions. Complement Factor H polymorphism reported to be related to an increased risk for both diseases, but more strongly associated as a risk factor in wet AMD (Chen et al, 2012).

A comparison of the clinical features for wet AMD and PCV is shown in Table 1.

Wet AMD	PCV
Drusen	Polypoidal lesions, choroidal circulation
PED	Recurrent haemorrhagic PED
Subretinal haemorrhage, CNV	Subretinal haemorrhage
Atrophy of RPE	Atrophy of RPE
Intraretinal haemorrhage	New blood vessel network
Disciform scar - end stage	Macular / retinal detachment

Table 1: *Features of wet AMD and polypoidal choroidal vasculopathy*

ANTI-VEGF DRUGS (LUCENTIS OR AVASTIN)

Use of the anti-VEGF drugs results in increased fluid absorption that leads to an improvement in visual acuity (VA). The fluid absorption results in a reduction in retinal thickness which is measurable with an OCT.

- These drugs are not effective in diminishing new blood vessels in polypoidal lesions in all cases (Kokame et al, 2010, Cho et al, 2012, Gomi et al, 2008, Hikichi et al, 2013, Lee et al, 2008)
    - Consider the type of study: retrospective or prospective

CURRENT MANAGEMENT FOR PCV: COMBINATION THERAPY

The main option for treatment of PCV involves the use of ICGA-guided photodynamic therapy in conjunction with either Lucentis or Avastin. The benefits of this combination therapy include:

- Faster fluid absorption (reduced retinal thickness measured with OCT)
- VA improvement
- Decreased haemorrhages associated with pigment epithelium detachment (PED)
- Decreased number of injections and Photodynamic therapy (PDT) treatments

PDT alone and in combination increases the risk of subretinal haemorrhage.

- From studies by **Koh et al, 2012, Tomita et al, 2012, Nemoto et al, 2012, Saito et al, 2013, Jeon et al, 2013, Lee et al., 2012;
    - **Prospective randomized clinical trial
- Other studies: retrospective studies, case series

CONCLUSIONS

The use of ICGA and OCT is the best method for diagnosing PCV and to differentiate between wet AMD and PCV.

For PCV treatment there are limited comparative trials of PDT and Lucentis to date.

- EVEREST Study (Koh et al, 2012): 1 PDT (baseline) + Lucentis (1.4 + 3.9 injection) over 6 months

The evidence to date indicates that PDT plus Lucentis results in:

- Polyp regression
- Decreased retinal thickness measured with OCT
- Improved VA
- Decreased vessel leakiness

There is need for further randomized clinical trials (similar to EVEREST) but for a longer period to examine combinations with other anti-VEGF drugs and other medications such as steroids (e.g. triamcinolone).

CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy (CSCR) is a fairly common condition that presents as a neurosensory retinal detachment over localized fluid accumulation. It may occur with or without an associated RPE detachment.

The condition typically manifests with unilateral blurred vision, metamorphopsia and micropsia. It is generally observed in young, or middle-aged adults. It is more frequently observed in males with a Type A personality.

When noted in women the person typically tends to be of older age but CSCR may be induced during pregnancy.

CSCR is often associated with small RPE defects e.g. pigment epithelium detachment (PED)

SIGNS AND SYMPTOMS

The following are signs and symptoms associated with CSCR:

- May be asymptomatic
- VA less than 6/9 to 6/12
- A small plus power correction often improves the VA
- Visual distortions noted
- Abnormal photo-stress test result
- Fundus appearance: Round or oval localized detachment at macula, often outlined by glistening reflex
- Subretinal fluid: clear or turbid, sometimes abnormal RPE (leakage of fluid from choriocapillaris)
- Fluorescein angiography shows a ‘smokestack’ or ‘ink blot’ pattern
- Course: most cases spontaneously resolve over 12 months
    - Can get recurrences in some cases
    - Rarely associated with long-term visual consequences
    - Chronic CSCR associated with RPE changes, may get atrophy, etc.

THE NORMAL MACULA

The integrity of the macula is paramount for vision. Any adverse impact in its structure or function has serious ramifications.

Key features of the macula:

- It is about 4% of the total retinal area, but is responsible for most of the useful photopic vision
- The fovea is approximately 1.5mm in diameter and has the highest density of cone photoreceptors
- It accounts for almost 10% of the entire visual field
- Lesions in this region may occur at any age

WHEN THINGS GO ‘WRONG’ IN THE MACULA

Alteration to the structure and function of the macula can result in:

- Impaired central vision
    - Loss of acuity (obstructing vision compared with a ‘hole’ in the vision)
- Metamorphopsia
    - Distortion
- Micropsia
    - Decreases in image size
- Macropsia
    - Increases in image size

Damage to the macula may occur for a variety of reasons including:

- Idiopathic premacular fibrosis
- Idiopathic choroidal neovascularization
- Traumatic retinopathies
- Solar retinopathy
- Toxic retinopathies, etc.

MACULAR HOLES

A small hole that occurs at the macula is most likely due to shrinkage of the vitreous. With aging, the vitreous becomes watery and begins to pull away from the retina. If the vitreous is firmly attached to the retina when it pulls away, a hole can result.

IDIOPATHIC MACULAR HOLES: CLINICAL FEATURES

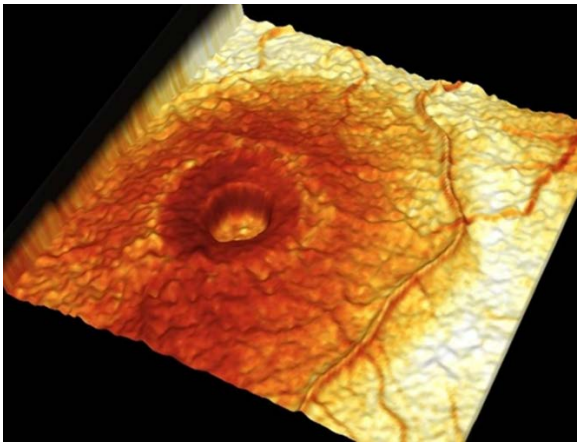

Figure 7: *Macular hole*

The main features of a macular hole include:

- Fairly common; about 3 in 1000 patients
- Typically seen in females over the age of 70 yrs
- Eventually presents as bilateral in about 10% of cases
- VA may be reduced to 6/60
    - Central vision affected (but can be asymptomatic)
- Presentation
    - Hole at fovea that may be full thickness
    - Punched-out appearance
- Signs
    - Surrounding halo of subretinal fluid
    - If a narrow slit is located over the macular hole the patient reports a thinning or a break
        - Watzke-Allen test
- Amsler grid
    - Non-specific distortion, not a scotoma
- OCT
    - Best way to evaluate the condition
- Fluorescein angiography (FA)
    - A full-thickness hole will show a window defect due to the displacement of xanthophyll and RPE atrophy
    - Hyperfluorescence is observed with FA

IDIOPATHIC MACULAR HOLES: POSSIBLE PATHOGENESIS

Possible mechanisms for the formation of a macular hole include:

(1) Antero-posterior traction that is often related to a posterior vitreous detachment (PVD)
(2) Tangential traction especially if epiretinal membrane or a lateral shifting of vitreo-retinal adherence
(3) Intraretinal constraint that weakens the inner retinal surface by inducing cystic changes and thereby contributes to the macular hole

It is important to consider any posterior eye inflammation.

- Inflammation often induces changes that result in vitreous liquefaction and a PVD
- Development of an epiretinal membrane may occur in uveitis
- Chorioretinitis foci or cystoid macular oedema may cause retinal fragility

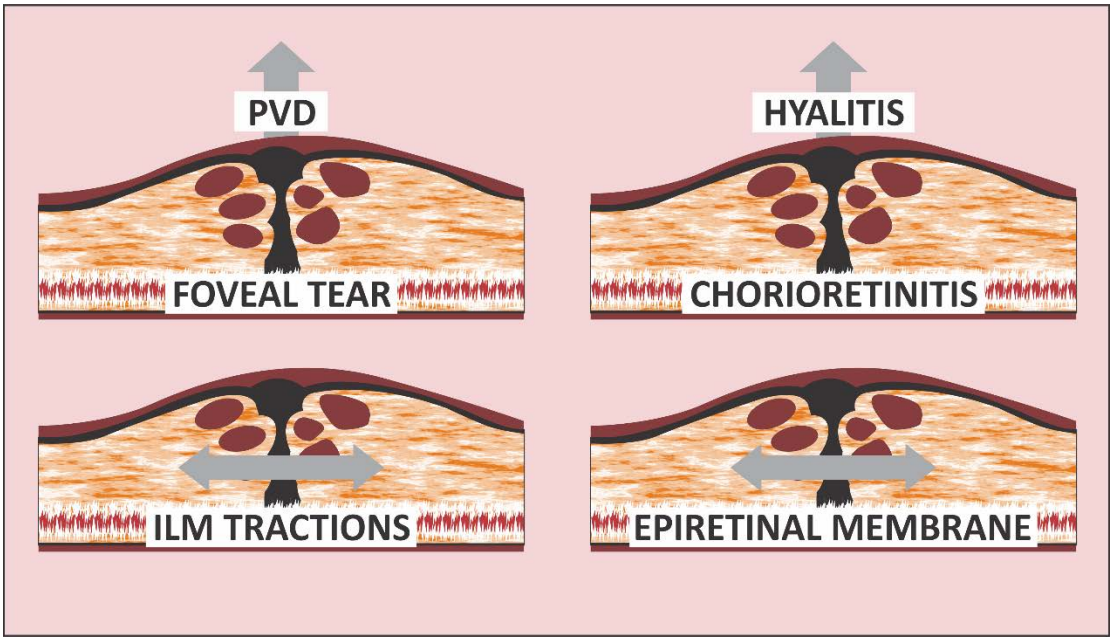

***Figure 8**: Physiopathology of idiopathic macular holes and macular holes in circumstances of inflammation. Bonnin et al., 2013*

The stages of formation of a macular hole, as seen with OCT, are shown in the five images (A-E) below.

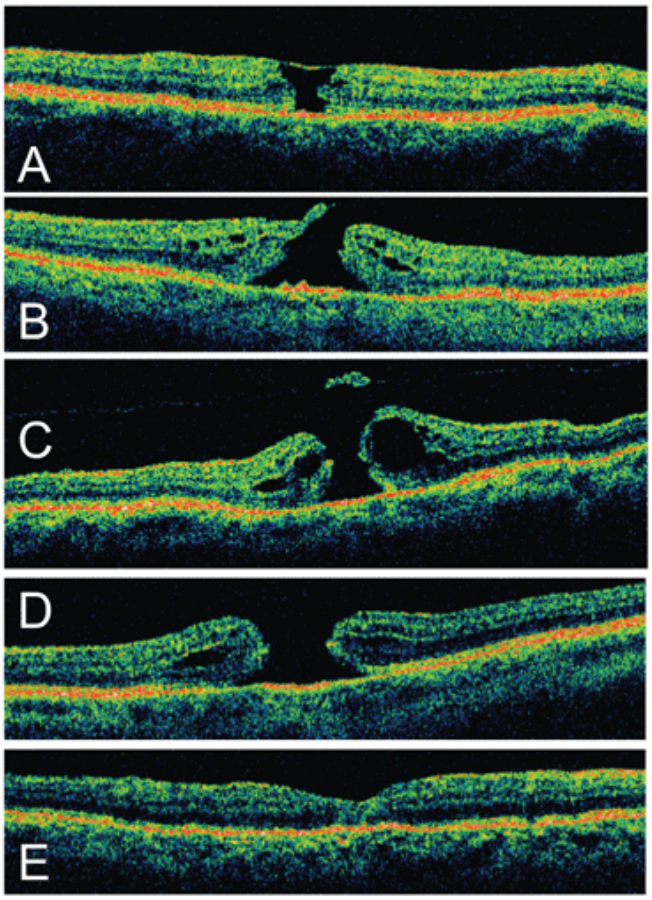

***Figure 9:** Macular hole progression*

A) Stage 1B with an occult hole – vision is about 6/12
B) Pseudo-operculum lifts and the hole goes to Stage 2. On examination the VA is approximately 6/24
C) Pseudo-operculum is now separated from retina - Stage 3 macular hole. The VA is about 6/48

D) The macular hole is Stage 4 when the posterior vitreous detaches. The VA is reduced to 6/60
E) Two months after surgery with vitrectomy, fluid-gas exchange and face-down positioning the hole is closed and the VA has returned to 6/9

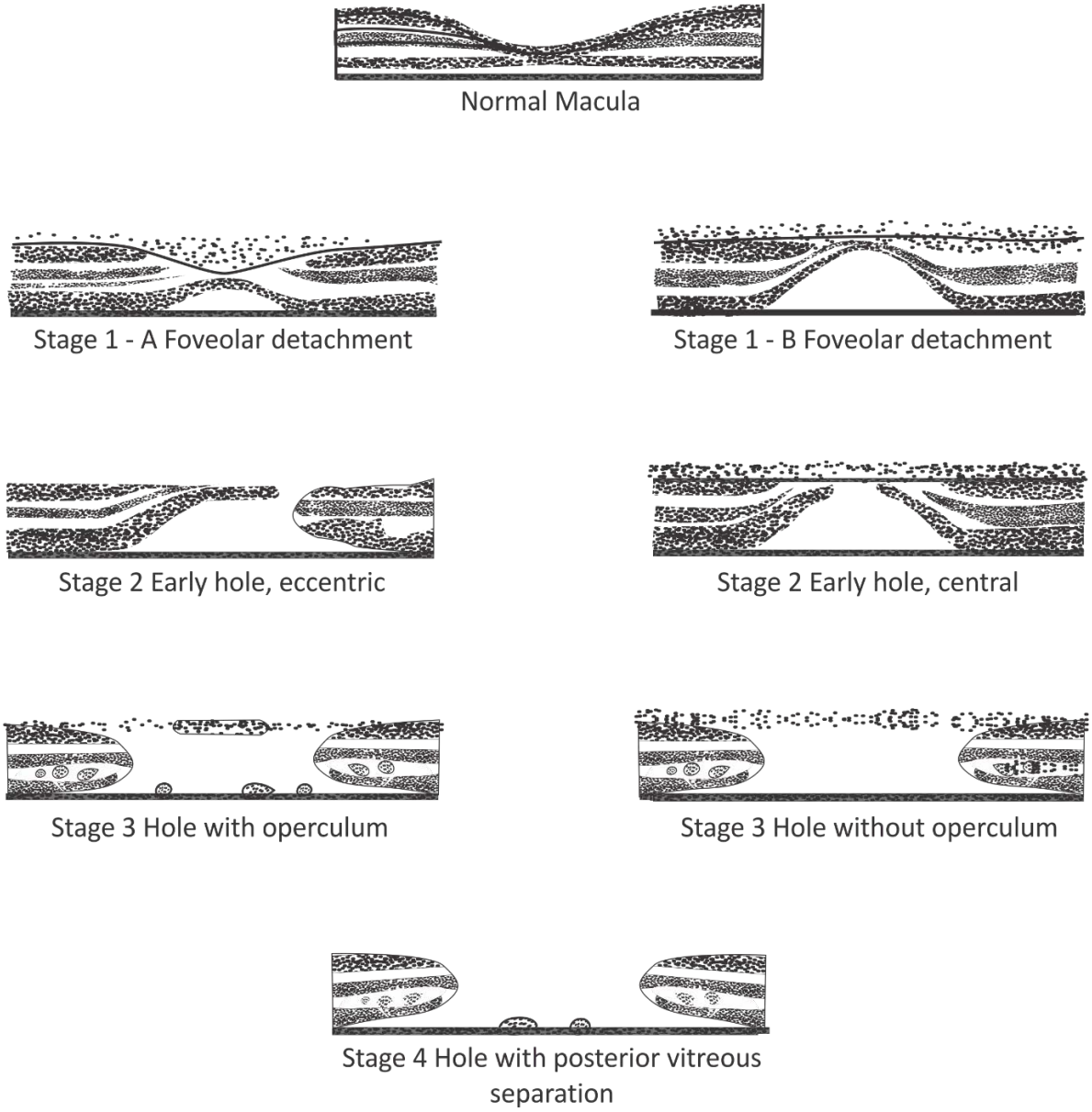

Figure 10: *Macular hole formation (After Gass, 1995)*

An operculum can also be described as a lid, flap or cover. An operculated retinal hole therefore represents a round, red full-thickness retinal defect with an associated avulsed piece of retinal tissue free floating in the vitreous cortex.

Gass described the following classification of a macular hole:

- Stage 1A – impending macular hole
  - Early contraction of outer part of vitreous cortex with foveolar detachment. Further vitreous contraction and condensation of the pre-foveolar vitreous cortex with foveal detachment
- Stage 1B – occult hole
  - In this stage note the yellow spot or ring centered on foveola (xanthophyll migration)
- Stage 2
  - Hole with early separation of condensed pre-foveolar vitreous cortex, formation of pseudo-operculum that is larger than hole
- Stage 2 (variation)
  - Hole with tear in vitreous cortex at junction of pre-foveolar vitreous cortex and edge of macular hole
- Stage 3
  - Hole with pseudo-operculum
- Stage 4

- Hole after posterior vitreous separation

(Gass JD. Reappraisal of biomicroscopic classification of stages of development of a macular hole. Am J Ophthalmol 1995; 119:752)

MACULAR HOLE MANAGEMENT

The American Academy of Optometry guidelines recommend that Stage 2 macular holes be managed with either surgery or monitoring at 4 to 8 month intervals, while surgery is recommended for Stage 3 and Stage 4 holes.

MACULAR HOLE SURGERY

1. Indications: full-thickness macular hole, VA < 6/18, duration < 1 year
2. Technique – vitrectomy and fluid-gas exchange
3. Results – closure occurs in about 60% of cases and approximately 40% of people regain two or more lines of VA.

CYSTOID MACULAR OEDEMA

Cystoid macular oedema (CME) is a “final common pathway” or response of the central retina or macula to various insults.

Multiple cyst-like (cystoid) areas of fluid appear in the macula and cause retinal swelling or oedema. The fluid accumulation occurs in the outer plexiform layer (OPL) and the inner nuclear layer (INL) of the retina.

CME is associated with many conditions including:

- Vascular problems (e.g. diabetes and retinal vein obstruction)
- Inflammatory conditions (e.g. intermediate uveitis, pars planitis)
- Inherited diseases (e.g. RP or dominant CME)
- Tractional problems (e.g. vitreomacular traction syndrome)
- Use of medication (e.g. Latanoprost)
- Choroidal neovascularization (CNV)
- Posterior eye tumours (e.g. haemangiomas)
- Systemic diseases (e.g. leukaemia)
- Following ocular surgery (e.g. cataract surgery, YAG laser treatment for posterior capsule opacification, glaucoma filtration)

CME SIGNS AND SYMPTOMS

The classical signs and symptoms associated with CME include:

- Blurring and distortion of vision
  - Amsler chart is useful for detecting blur and distortion
- Decreased central VA
  - Presenting VA usually ranges between 6/9 and 6/24 but may be as poor as 6/120
- Metamorphopsia
- Micropsia
- Scotoma
- Ocular irritation
- Photophobia
- Loss of foveal depression
- Thickening of the retina
- Multiple cystoid areas
- Lamellar hole formation if the condition is longstanding
  - Best seen with OCT and slit-lamp fundoscopy
  - Fluorescein angiography (FA) can help

- Coalescence of leaking points
- Flower petal pattern in late stage of FA

TREATMENT OF CME

The type of treatment depends on the cause of the CME.

- No treatment required
  - Very mild case with good VA
  - Too early in the condition
    - Best to wait for a spontaneous improvement
  - Too late in the condition
    - e.g. poor VA (lamellar hole)
  - Treatment not beneficial
    - e.g. central retinal vein occlusion (CRVO)
- Laser photocoagulation
  - Diabetic retinopathy
  - Branch retinal vein occlusion (BRVO)
- Periocular steroids
  - Intermediate uveitis
  - Post cataract surgery
- Systemic carbonic anhydrase inhibitors
  - Intermediate uveitis
  - Post cataract surgery

EPIRETINAL MEMBRANE

This condition is also referred to as epimacular membrane, cellophane maculopathy and macular pucker.

The membrane may occur idiopathically or secondarily to other conditions. It appears as a sheet-like fibro-cellular structure on the retinal surface.

Proliferation and subsequent contraction of the membrane produces visual distortion due to retinal wrinkling. The condition may be associated with cystoid macular oedema.

- **Idiopathic cause**
  - Mostly glial cells
  - No readily apparent cause (mild cases)
- **Secondary cause**
  - Mostly following retinal surgery for detachment, retinal tears/breaks, etc.
  - Post-laser use
  - Cryotherapy
  - May involve the RPE and other cells – a more severe form
- **Signs**
  - VA is variable
  - Blurry vision
  - Metamorphopsia

ANGIOID STREAKS

Angioid streaks are usually bilateral, crack-like dehiscences in thickened, calcified and ‘abnormal’ areas of Bruch’s membrane.

They are often secondary to atrophy or changes in the RPE and choriocapillaris.

SIGNS

Mottled pigmentation of the posterior pole is an early sign ("peau d'orange"). Mottling of the RPE, particularly temporally, follows.

The usual signs of angioid streaks include:

- Linear lesions with irregular serrated edges seen beneath normal vasculature
  - Angioid streaks present as irregular and jagged lines that radiate from a concentric peripapillary ring toward the equator of the eye
  - Seen with an ophthalmoscope
  - Longstanding streaks develop secondarily to RPE atrophy or even hyperplasia
- Optic nerve drusen occur more often in eyes with angioid streaks

SYSTEMIC ASSOCIATIONS

- Most commonly seen in patients with:
  - Pseudoxanthoma elasticum (about 85%)
    - ABCC6 gene involved
  - Other connective tissue related diseases e.g. Paget's disease, Ehlers-Danlos syndrome
  - Haemoglobinopathies, etc.
- Pseudoxanthoma elasticum
  - Skin has characteristic changes due to defective elastin
  - Often lax and redundant with localized plaques of hyperkeratotic papules giving the typical 'plucked chicken' appearance
- Some differentials for angioid streaks include:
  - Lacquer cracks
  - Pathological myopia
  - Choroidal rupture
  - Toxoplasmosis
  - Wet AMD
    - Haemorrhage in the macula
  - CSRC
    - Macular oedema

COMPLICATIONS

Complications associated with angioid streaks include:

- Choroidal neovascularization
  - Prognosis after new vessel formation is variable
- Visual impairment occurs in greater than 70% of patients

CHOROIDAL FOLDS

The aetiology of choroidal folds may be related to an anatomical attachment of Bruch's membrane to the underlying choriocapillaris.

They are seen as dark and light streaks on ophthalmoscopy but are more apparent and differentiated from retinal folds by fluorescein angiography. Numerous patterns and orientations of choroidal folds are possible.

The folds are idiopathic in the majority of cases and can be associated with conditions such as hyperopia, optic disc drusen, central serous retinopathy, choroidal naevi, tumours and papilloedema. They may occur following surgical procedures such as cataract surgery, laser therapy and from post-operative choroidal oedema or inflammation.

MAIN CAUSES

- Idiopathic (often hypermetropic refractive error)
- Chronic papilledema

- Orbital disease e.g. tumours, thyroid
- Ocular disease e.g. choroidal tumours, posterior scleritis, ocular hypotony (very low IOP)

PRESENTATION

- VA may not be affected
- Symptoms related to underlying cause

SIGNS

- Parallel lines at the posterior pole
  - Horizontal striae or grooves in choroid, Bruch's membrane, RPE and sometimes the outer retina at the posterior pole
- Compression and stretching of the RPE
  - Differentiate from retinal folds
- Fluorescein angiography
  - Alternating hyperfluorescent and hypofluorescent streaks related to the RPE thickness

AUTOIMMUNE RETINOPATHIES

Paraneoplastic and autoimmune retinopathies are uncommon eye disorders where autoantibodies are directed at various retinal components leading to progressive vision loss.

The onset of visual symptoms and detection of antibodies may precede the diagnosis of malignancy by months to years.

In some cases, patients with an underlying malignancy have a high titer of anti-retinal antibodies but no evidence of visual loss.

Specific forms of paraneoplastic and autoimmune retinopathies identified include:

- Cancer-associated retinopathy (CAR)
- Melanoma-associated retinopathy (MAR)
- Cancer-associated cone dysfunction
- May also get paraneoplastic syndromes involving the optic nerves – these are less common than those involving the retina

Electrophysiology tests are very useful in these conditions.

CHLOROQUINE RETINOPATHY

PRESENTATION

Symptoms: Decreased visual acuity, abnormal colour vision, poor dark adaptation.

Signs:

- Bull's-eye macula (a ring of depigmentation surrounded by a ring of increased pigmentation), no foveal reflex.
- Pigmentation in the macula
- Blood vessel changes (narrowing, sheathing)
- Decreased colour vision
- Visual field changes

DOSAGE USUALLY REQUIRED TO PRODUCE TOXICITY

Chloroquine: More than 300 g total cumulative dose.

Hydroxychloroquine: Toxicity much rarer than with chloroquine. Usually more than 400 mg/day taken over months to years, with a cumulative dose of 1,000 g, though depends on person's weight.

NOTE: Once ocular toxicity develops, it usually does not regress even if the drug is withdrawn.

RECOMMENDED TESTS

Baseline evaluation should be performed within the 1st year of starting the medication. Annual screening should begin after 5 years of medication use.

- Best corrected visual acuity.
- Retinal examination, including dilated fundus exam paying attention to any pigmentary changes around the macula
- Consider fundus photographs
- Visual field
- Consider referral to ophthalmology

MANAGEMENT

Discontinue the medication if retinal changes develop.