Chapter 8 The Retina: Functions and Diseases

Objectives:
By the end of this course the student should be able to:
• Understand the general retinal morphology and its intricate fine structure
• Be familiar with the basic pathological changes which can involve this tissue
• Recognize how the retinal examination can help in diagnosing and assessing some systemic disorders
• Understand some intrinsic retinal pathological situations and the principles of their corresponding methods of prevention and management

The Retina and The Fundus
The retina is the light sensitive layer of the eye. It can only be seen when we look into the inside of the eye (the fundus).
Fundus of the eye is the clinical term used to describe the retina together with its intimately related structures such as the optic disc, choroid and vitreous. These structures are conventionally examined by a method called ophthalmoscopy.
Methods of Fundus Examination:

1) Direct ophthalmoscope

2) Indirect ophthalmoscope
3) The Slit lamp biomicroscopy

Appearance of the normal fundus:

The retina is a transparent tissue. The red color of the fundus is attributed to the color of the blood in the underlying choroid. In some eyes (especially the highly myopic eyes) the color is less reddish and more or less mottled (tigroid fundus). Both of the above photos are from perfectly normal fundi.
Retinal Anatomical and Clinical Landmarks:

Clinically, we classify the retina into two distinct parts based on different anatomical and functional characteristics:

1. **Central retina;** the retina between the upper and lower vascular arcades, it includes the yellowish macula lutea (diameter 5mm) with the fovea (a small depression) at its center (fovea centralis)
   Central retina is rich in cones and is responsible for form vision (visual acuity), color vision and central field (30°)
2. **Peripheral retina;** the retina outside the arcades responsible for field and light and motion detection
Figure: Central retina landmarks

**Note** 1) The diameter of the fovea is comparable to that of the optic disc. (1.5 mm or 1500 micron). The distance between them is about 2 disc diameters.
2) The fovea is much thinner than the rest of the retina.
Photoreceptors

The light detectors (receptors) in the retina are 2 types; cones and rods.

<table>
<thead>
<tr>
<th></th>
<th>Rod cells</th>
<th>Cone cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in retina</td>
<td>Found outside of fovea</td>
<td>Found in fovea</td>
</tr>
<tr>
<td>Optimal light conditions</td>
<td>Dim light ('night' vision)</td>
<td>Bright light ('day' vision)</td>
</tr>
<tr>
<td>Visual acuity (resolution)</td>
<td>Low (many rod cells add up)</td>
<td>High (one cone cell per signal)</td>
</tr>
<tr>
<td>Connection to nerve fibre</td>
<td>Several rods attach to single bipolar cell</td>
<td>One cone cell per bipolar cell</td>
</tr>
<tr>
<td>Colour sensitivity</td>
<td>All wavelengths</td>
<td>Certain wavelengths (red, green, blue)</td>
</tr>
<tr>
<td>Type of vision</td>
<td>Achromatic (black and white)</td>
<td>Colour</td>
</tr>
<tr>
<td>Number of types</td>
<td>One (all have rhodopsin pigment)</td>
<td>Three (each with different pigment)</td>
</tr>
<tr>
<td>Relative abundance</td>
<td>High</td>
<td>Low</td>
</tr>
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The retinal layers:

Above is a histological section of the retina showing its intricate complex structure. Below is a diagram simplifying the retinal structure.

As can be seen from this diagram:

The photoreceptors (rods and cones) are the deepest layer of the retina, they relay their signals to bipolar cells present in the middle retina which in turn relay to ganglion cells in the superficial retina.
The axons of the ganglion cells form the retinal nerve fiber layer. These fibers enter the optic canal in a specific arrangement (see details in chapter 6) to form the optic nerve, which passes the signal to the brain.
Blood supply of the retina

1. The inner half of the retina (half towards the vitreous) is supplied by the central retinal artery (CRA). The CRA is an end artery (no anastomosis) and a branch of the Ophthalmic artery coming from the ICA.

2. The outer half of the retina including the important photoreceptor layer is non-vascular and receives oxygen and nutrition by diffusion from the choroid.

The retinal pigment epithelium (RPE)

One retinal layer; the retinal pigment epithelium (RPE) is not light sensitive. It separates the other layers (the neurosensory retina) from the choroid and plays an important role in:
   a. Regulating diffusion
   b. Keeping the retina dry from fluids in the choroid and tightly attached to the choroid by the active RPE pump
   c. Storing vitamin A which is very important in visual pigment formation (rhodopsin)

Specific clinical investigations:

a. Fundus fluorescein angiography (FFA)
FFA is achieved by intravenous injection of 5% sodium fluorescein dye with the use of special filters mounted on a computer connected camera. Rapidly successive photographs are taken. Thus a dynamic study of the retinal vasculature is provided.

b. Optical coherence tomography (OCT)
OCT is a relatively new and very useful diagnostic modality where computer composed optical sections of the retina are obtained without the use of a dye. It provides different information than those provided by FFA.

C – Ultrasonography

This is using ultrasound waves to assess the retinal position and the vitreoretinal relationship in eyes with opaque media.
Diseases of the retina

In this chapter these diseases will be discussed:

1) Diabetic retinopathy
2) Hypertensive and arteriosclerotic Retinopathy
3) Vascular occlusions
   a) Venous occlusions
   b) Arterial occlusions
4) Choroidal neovascular membrane and age related macular degeneration
5) Retinal detachment
6) Some heridofamilial retinopathies

Note: Retinal disorders related to systemic conditions such as pre-ecalmpsia, HIV virus, Toxoplasma retinitis etc, will be discussed in Chapter 11. Retinopathy of prematurity (ROP) will be discussed in chapter 10.

Diabetic Retinopathy (DR)

We will start with diabetic retinopathy because:
1) It is by far the most commonly seen retinal pathological situation.
2) The basic understanding of its pathological changes is believed to pave the way for understanding other vascular retinopathies as well as few other retinal disease states

Relationship between diabetes mellitus (DM) and diabetic retinopathy (DR):

- The duration:
  - In insulin dependent diabetes mellitus (IDDM, type 1), more than 20% have retinopathy after 5
years of onset of their DM and 80% have retinopathy after 15 years of onset.

- Non insulin dependent diabetes mellitus (NIDDM, type 2) may already have significant retinopathy at the time of diagnosis of diabetes. This is due to the possible delay in diagnosing diabetes in this group. The retinopathy prevalence and severity, however, tend to be less severe than that in type 1.

- **The glycemic control**: studies have clearly demonstrated that good glycemic control, (as reflected on the level of glycosylated hemoglobin A1C and not only on blood sugar level), can delay the onset of retinopathy and reduce the progression to the severe forms of the disease.

- **Systemic hypertension**: the association between DM and hypertension is known to predispose for blinding complications such as vitreous hemorrhage and macular ischemia

### Pathology:
DM is described as “microangiopathy” since it affects the small retinal vessels especially the capillaries.

![Pathogenesis of diabetic retinopathy](image)

All findings in DR can be attributed to: 1) microvascular leakage and 2) microvascular occlusion.
Clinical Picture:
(varies according to the stage of the DR)

1) Background or nonproliferative (BDR, NPDR)
   - Microaneurysms (red dots differentiated from red hemorrhages by FFA)
   - Dot hemorrhages, my be blot hemorrhages
   - Hard exudates
   - Possible macular edema
   
   - Soft exudates (previously described as cotton wool spots).
     These are nerve fiber layer infarcts due to ischemia and not true exudates.
   - Intra retinal microvascular abnormalities (IRMA).
   - Segmental dilatation of retinal veins (venous beading and sausaging)

   *The last 3 points denote ischemia*
2) **Severe non proliferative** (formerly called preproliferative):  
- This includes increased signs of retinal ischemia namely increased hemorrhages, venous beading and IRMA  
- 15% to 50% of these eyes progress to proliferative diabetic retinopathy (PDR) in 1 year

3) **Proliferative diabetic retinopathy (PDR)**

   \[ PDR = NPDR + NEOVASCULARIZATION \]

   - This is due to the fact that the ischemic retinal tissue releases a “vascular endothelial growth factor” (VEGF) which causes the development of new fragile vessels.  
   - Two types are differentiated: NVD and NVE (i.e. neovascularization at the disc and neovascularization elsewhere). NVD are more risky to result in massive vitreous hemorrhage and subsequent loss of vision.
4) **Advanced diabetic eye disease**: Includes the complications that result in severe vision loss such as
- Massive vitreous hemorrhage
- Traction retinal detachment
- Neovascular glaucoma (see chapter 6)

**Diabetic Macular Edema and Ischemic Maculopathy**
Macular edema is the most common cause of drop of vision due to diabetic retinopathy. It can occur in any stage of DR. The macula becomes thickened as detected clinically by biomicroscopy and the thickness measured by OCT. The fine perifoveal vessels can be affected by occlusion resulting in ischemic maculopathy detectable by FFA. Macular edema is amenable to treatment by focal laser and/or anti VEGF intravitreal injection (see later), whereas there is no available treatment for macular ischemia.

**Note**: Most complications of diabetic retinopathy are preventable. The diabetic patient may have severe retinopathy with very serious neovessels while being completely asymptomatic. Hence, it is extremely important to direct the patient to have regular fundus examination in order to discover symptomless pathology and avoid the blinding complications of the disease.
Treatment of DR:
In addition to control of blood sugar and other systemic diseases especially hypertension, the three main lines of management of DR are:

1) Laser:
Thermal laser is the traditionally used type (See chapter 14 for the physical principle of different types of laser). In focal laser, the beam is directed to the leaking microaneurysms aiming at their occlusion with subsequent drying up of the edematous retina. Scatter or panretinal photocoagulation (PRP), aims at destroying large parts of the peripheral retina in order to minimize the release of VEGF. This helps prevent or regress neovascularization with its drastic complications.
2) **Intravitreal injections:**

   a) Anti-VEGF: have recently shown effectiveness both in treating macular edema and in managing neovascularization. The advantage is that they result in less tissue destruction than laser but the disadvantage is the high cost and that they need to be repeated several times.

   b) Triamcinolone: a long-acting corticosteroid which showed effectiveness in macular edema in selected cases. It is inexpensive but it must be used with caution since it might cause glaucoma in predisposed eyes.

3) **Pars plana vitrectomy (PPV):**

   This is a very useful technique to treat advanced complications of DR such as dense non-resolving vitreous hemorrhage or tractional retinal detachment.
Hypertensive retinopathy and arteriosclerotic retinopathy:

In its early stages, and in young individuals, systemic hypertension is not associated with arteriosclerotic changes. An example of this situation is seen in renal disease in a young patient. This is called “hypertensive retinopathy”.

With prolonged hypertension and in older patients, arteriosclerotic changes set in. These changes result in a picture called “arteriosclerotic retinopathy”.

Changes in the retinal blood vessels due to hypertension and arteriosclerosis are similar to those taking place in the brain. Hence the statement: “the eye is the window to the brain”.

Hypertensive Retinopathy

![Images of retinal images A, B, C, D]
Arteriosclerotic changes in retinal vessels:

Two ophthalmoscopic observations are noteworthy:

a) The arterial wall becomes gradually opaque. It starts to reflect some of the incident light of the ophthalmoscope. Hence a **copper wire** arteriole and then a **silver wire** arteriole are described.

b) Arteriovenous crossing changes (see figures)
   - concealment of a part of the vein

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**Hypertensive Retinopathy - Grade 4**

![Image of retinal changes](image)

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Grade I: Slight or modest narrowing of the retinal arterioles, with an arterial:venous ratio of $\geq 1:2$.

Grade II: Modest to severe narrowing of retinal arterioles with an arterial:venous ratio $<1:2$ or arteriovenous nicking.

Grade III: Soft exudates and flame-shaped hemorrhages.

Grade IV: Grade III changes and bilateral optic nerve edema.
- apparent tapering of the vein under the artery
- lateral or vertical deflection of the vein
- dilatation of the distal part of the vein due to pressure of the artery (banking)
Vascular Occlusions

1) Retinal venous occlusions

This is more common than arterial occlusions.

Causes:

i. The most common cause is hypertension/atherosclerosis which causes the artery to compress the vein at the lamina cribrosa of the optic disc (central vein occlusion), or at an arterio-venous crossing (branch vein occlusion).

ii. Less common causes are increased blood coagulation (leukemia, polycythemia, dysproteinemia).

iii. Ocular hypertension and open angle glaucoma are risk factors for venous occlusion (pressure from outside)
Clinical types:

Retinal vein occlusion may be classified into **ischemic** type and **non-ischemic** type.

a- Ischemic type commonly occurs in the elderly. The typical presentation is rapid onset of visual deficit (marked blurring in one eye), usually on waking up in the morning. Examination of the fundus shows dilated tortuous veins.
together with many retinal hemorrhages from venous stasis

b. Non ischemic type: similar picture may occur in the young with lesser degree of retinal hemorrhages and milder diminution of vision.

FFA is done to evaluate the degree of retinal ischemia (figure).

c. **Complications:**

The most important complications are
i. Macular edema diagnosed clinically and by FFA and OCT
ii. Neovascularization at the retina, neovascularization of the iris (NVI) and neovascular glaucoma.
iii. Vitreous hemorrhage.
d. Treatment:
   i. In the acute stage we do monthly injections of anti-VEGF into the vitreous up to 6 months for the macular edema.
   ii. If NVI (previously called rubeosis iridis) develops we do pan-retinal laser photocoagulation to prevent neovascular glaucoma

2) Retinal arterial occlusions

Central retinal artery occlusion (CRAO) and Branch retinal artery occlusion (BRAO)

Causes
   iii. In the elderly the most common is thrombosis
   iv. In the young embolization is more common
Clinical presentation at the onset
The most typical presentation is sudden painless complete loss of vision, the fundus shows attenuated arteries.

Signs
a) If the occlusion is temporary (usually by small platelet thrombi) there will be loss of vision for few minutes (amaurosis fugax).
b) Later on, if the occlusion persists, in few to several hours the central retina becomes milky white due to coagulative necrosis and, in contrast, the thin fovea looks cherry-red in color.
c) Loss of upper or lower half of vision in branch artery occlusion.
**Treatment:**
If the patient hurries to the emergency, he must be treated within few minutes to hours before the retinal damage is permanent, there is NO time to waste. The emergency treatment is marked lowering of intraocular pressure (by massage, mannitol or paracentesis) to induce vascular dilatation and other ways for vasodilatation by drugs or breathing 5% carbon dioxide.

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**Choroidal neovascular membrane (CNVM)**

The central retina especially the fovea may be involved by the abnormal growth of neovessels from the choroid into the subretinal space. This often causes disturbing metamorphopsia and eventually
leads to the formation of a macular scar with deterioration of central vision and loss of reading ability.

The commonest causes of CNVM are: 1) age related (in patients above 50 years) 2) Idiopathic (below 50 years) 3) degenerative myopia 4) trauma and 5) rarely iatrogenic secondary to intense laser burn.

Neovessels, having abnormal structure and located in abnormal site, can bleed or leak lipids under the retina and, if untreated, end by a scar involving the neurosensory retina.

Symptoms:
- Distortion of the images especially during reading or near work (metamorphopsia)
- Later: loss of reading ability and diminution of distant vision. Peripheral field is usually maintained

Signs:
- Loss of the normal foveal reflex and greyish or yellowish appearance of the fovea
- Distorted or missing squares on Amsler grid (see figure)
Diagnosis:
- Confirmed by FFA and OCT

Treatment:
- Repeated intravitreal injections of anti VEGF
- Special magnifiers for reading (low vision aids) if central vision is lost.

Age related macular degeneration

The central foveal cones with their underlying RPE are probably the most metabolically active cells in the whole body. Ageing affecting this spot is the leading cause of legal blindness in the above 50 age group.

Age related macular degeneration is of two main types:
1) The dry type:
   a) Drusen (yellowish white dot like thickening of the basement membrane of the RPE)
   b) Central choroidal atrophy (without CNVM)

Note:
1) Dry AMD is much more common than wet AMD.
2) There is no presently available treatment for dry AMD apart from low vision aids
2) **The wet type** (due to CNVM, see above)

## Retinal Detachment (RD)

### Definitions and Classifications:

RD is the separation of the sensory retina (inner retinal layer) from the retinal pigment epithelium (RPE, outer retinal layer) by subretinal fluid (SRF).

There are three main types:

1) **Primary or rhegmatogenous RD.**
   
   This is caused by a retinal break, which permits fluid, derived from the liquefied vitreous (subretinal fluid or SRF) to gain access to the subretinal space.

2) **Tractional RD:**

   In which the sensory retina is pulled away from the RPE by contracting fibrous tissue in the vitreous (vitreoretinal traction). The most common cause is proliferative diabetic retinopathy (PDR). Other causes include penetrating trauma and retinopathy of prematurity (ROP).

3) **Exudative RD:**

   In which subretinal fluid, derived from the choroid, gains access to the subretinal space and elevates the retina. Examples include some cases of posterior uveitis such as Vogt Koyanagi Harada disease (VKH), toxemia of pregnancy and choroidal tumors such as hemangioma or melanoma.
PRIMARY (RHEGMA TOGENOUS) RD

This is retinal detachment due to **retinal break**. Its importance comes from two points:

1) It is **rather common** (incidence: 1 per 10000 of the population per year).
2) It is a cause of **surgically treatable** blindness. The surgery has witnessed considerable improvements and refinements in the past few decades.

**Risk Factors:**

1. High myopia.
2. Aphakia and pseudophakia
3. Trauma (blunt or perforating).
4. Family history of RD or history of RD in the fellow eye.

**Posterior vitreous detachment (PVD):**

The primary event leading to formation of retinal break and subsequent retinal detachment is **acute PVD**. In the greatest majority of cases PVD is an innocent phenomenon. It is merely a sign of ageing. However, like many other signs of ageing (grey hair for example) it has individual variations in the age of its occurrence. This **physiological PVD** is known to occur at an earlier age in myopic patients as well as in patients who had previous cataract surgery.

With acute PVD, the vitreous fibrillae become condensed together and form shadows in front of the retina which are perceived by the patient as floaters (Musca volitans) or cob webs. Because of its acute nature it is often a very alarming and annoying symptom. However, most PVDs are quite innocent with no serious consequences (physiological). In few situations, where there is some preexisting strong vitreoretinal adhesion, the acute PVD results in vitreoretinal traction and retinal tear formation (pathological PVD).
Patients complaining of acute symptoms of PVD (floaters, flashes and cob webs must have their retina examined by a specialist. In most cases, reassurance is the only needed management. But if retinal tears are detected they must be treated prophylactically with laser or cryopexy. (see later)

**The retinal breaks:**
A retinal break is a full thickness defect in the neurosensory retina. The most important types are the rounded **holes** and the horse-shoe shaped or U shaped **tears**.

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**Clinical Picture:**

**-Symptoms:**

1. Flashes of light (photopsia): due to mechanical stimulation of the photoreceptors due to traction by the vitreous
2. Floaters (musca volitantes): A sudden shower of minute red-colored or dark spots usually indicates vitreous hemorrhage secondary to tearing of a peripheral retinal blood vessel.
3. A black curtain of loss of vision coming from one side.
4. Loss of central vision: when the fovea becomes involved

**-Signs:**

There is a greyish reflex from the fundus instead of the normal red reflex

Fundus examination using binocular indirect ophthalmoscopy reveals:

- Retinal break(s) appear red in color
- Wavy convex configuration of the retina and retinal vessels
Management of Rhegmatogenous RD:

A- Prophylactic treatment:
  If a retinal tear is detected before the development of RD, it should be surrounded by laser burns or cryopexy. The principle is to induce a sterile inflammatory reaction and localized choroiditis with chorioretinal adhesions around the break. This prevents fluid from passing into the subretinal space and causing RD

B- Scleral Buckling (conventional retinal surgery):
  An inert material is used to indent the sclera and choroid to approximate them to the detached retina at the site of the retinal break. A chorioretinal scar is created by one of the above described techniques in order to seal the retinal break(s).
C- Pars Plana Vitrectomy:

This is the method used for fixing the RD from inside via 3 ports of minute incisions in the pars plana. This site is chosen for entering the eye in order to avoid retinal injury if entry is made more posteriorly and to avoid lens injury if entry is made more anterior.
Some Heredofamilial Retinal Disorders

1) Retinitis Pigmentosa and other pigmentary retinopathies: This is a group of genetically determined degenerative retinal conditions affecting the photoreceptors (rods and cones). They generally affect young individual and usually manifest in the second or third decade of life with diminished vision especially by night (night blindness). Often there are several pigmented spider like lesions in the retinal midperiphery. The retinal vessels become attenuated and the optic disc becomes atrophic with a pink but apparently non vivid appearance described as “waxy” in color. Electroretinogram (ERG) is diagnostic.

At present, there is no known treatment for these disorders. Ongoing genetic engineering research is hoped to provide treatment in the future.
2) Stargardts’s disease

Another heridofamilial disease which affects the macula. It also manifests in the second or third decade of life. It can be easily missed but FFA gives the clue to diagnosis since it shows the characteristically mottled fluorescence of the macular area. Also no treatment is available at the moment.