The Eye in Systemic Diseases

Objectives:
By the end of this course the student should be able to:

- Be aware that many systemic diseases have ocular signs and symptoms. Some of these diseases are destructive to vision while being frequently asymptomatic and therefore must be referred to the ophthalmologist.
- Be able to spot the characteristic signs of systemic disease which are known to have ocular manifestations.
- Understand how an ophthalmologist may sometimes be able to incidentally discover an underlying systemic disease.
- Learn and practise direct ophthalmoscopy as a simple method to examine the fundus

Contents:
1) In this chapter we will discuss some selected disease states, which are considered important being very commonly seen in Egypt and worldwide.

2) We will then point to some characteristic ocular signs, which are very specific or pathognomonic of certain systemic disorders.

1) Common systemic diseases affecting the eye:

Diabetes Mellitus :

Diabetic retinopathy is the most important ocular manifestation of diabetes mellitus. This was discussed in chapter 8. Other ocular disturbances due to diabetes include:

1) Refractive changes: hyperglycemia induces index myopia. This turns into hypermetropia with control of blood sugar. Therefore, stable blood
sugar level must be present before prescribing eyeglasses for the diabetic patient.

2) Higher incidence of cataract which may start at an earlier age (presenile cataract)

3) Diabetic eyes are more prone to infections and inflammations (styes, corneal ulcers, iritis and postoperative infections including endophthalmitis)

4) Diabetes may affect the ocular nerves:
   - neuropathy of the pupil resulting in poor pupillary dilatation in response to mydriatics
   - exataocular muscle palsies due to involvement of the 3rd, 4th, or 6th cranial nerves
   - diabetic papillopathy or ischemic optic neuropathy

5) Glaucoma may be seen due to:
   - Known association between diabetes and primary open angle glaucoma (POAG).
   - Neovascular glaucoma secondary to iris and angle neovascularization

**Hypertension and Arteriosclerosis:**
See chapter 8

**Thyroid Eye Disease:**
See chapter 7

**Inflammatory and Autoimmune disorders:**

**a - Behcet’s disease**
A common cause of immune uveitis in the Mediterranean region and Middle East commonly affecting young and middle aged males. Diagnostic hallmarks are: panuveitis, vitritis and retinal vasculitis associated with oro-genital ulcerations. HLA-B5 is more much more common in patients with Behcet’s disease.
b- Vogt Koyanagi Harada Syndrome (VKH): (uveoencephalitis)

This is a bilateral granulomatous panuveitis (with exudative RD and disc edema), often accompanied with meningeal irritation, skin pigmentary changes and auditory disturbance. It is possibly an autoimmune process against melanocytes. It is commonly found in Asia but also in the Middle East.

**Ocular symptoms** include decreased vision, photophobia, and ocular pain. **Systemic symptoms** include headache, stiff neck, deafness and tinnitus. **Skin manifestations** include alopecia, vitiligo and poliosis.

Diagnosis may be helped by the presence of CSF pleocytosis.

The disease responds well to topical and systemic steroids. These should be continued for a prolonged period (6 months) to minimize the chances of recurrence. Prognosis for vision is generally good.
c- Arthritis and the eye:

**Juvenile idiopathic arthritis (JIA)** is an important childhood autoimmune condition which can cause iritis characterized by being asymptomatic. Severe ocular complications (such as cataract, glaucoma and band keratopathy) may arise if the iritis is not recognized and treated. Therefore, patients who have JIA, especially the pauciarticular form (involves four or fewer joints), require visits to the ophthalmologist every 3 months.
Iritis is also a common complication of **ankylosing spondylitis** patients.

**Ankylosing spondylitis (AS)** is a disease of middle age, commonly males, that is characterized by inflammation, calcification and finally ossifications of ligaments and capsules of joints resulting in bony ankylosis of the axial skeleton. It usually presents with insidious onset of pain and stiffness in the lower back.

Fig 6: Sclerosis of the sacroiliac joints in AS (a)  
Fixed flexion deformity in AS (b)

**Rheumatoid arthritis** It is another joint involving autoimmune disease more prevalent in adult females. It mainly involves the small joints (hands, wrists, and feet). It is a well-known cause of keratoconjunctivitis sicca. It may also cause scleritis, episcleritis or marginal corneal ulcers.

Fig 7: Joints deformities in RA (a)  
 marginal corneal ulcer in collagen diseases.(b)
**d- Sarcoidosis**

Sarcoidosis is a multisystem granulomatous disease that often presents first in the eye and frequently causes uveitis.

The sarcoid granuloma can affect the uvea, conjunctiva (appears as follicles) or the lacrimal gland (common cause of bilateral enlargement of lacrimal glands).

The disease is common in the chest where it causes bilateral hilar lymphadenopathy and pulmonary infiltrates (fig 8).

The sarcoid granulomas secrete angiotensin converting enzyme (ACE) which is the lab test commonly used to diagnose the disease beside chest X-ray.

![Fig 8: bilateral hilar lymphadenopathy and lacrimal gland enlargement in Sarcoidosis](image)

**Malignancy and the Eye:**

Secondary involvement of the eye by cancer is much more common than primary ocular malignancy. **Metastases** usually infiltrate the choroid, but on rare occasions the optic nerve as well as the extraocular muscles may be affected.
Systemic lymphoma affects the eye in about 30% of patients by infiltrating the conjunctiva or the orbit and causing proptosis or limitation of extraocular movement. Lymphoma can "masquerade" in the elderly patient as a chronic uveitis or vitritis.

Masquerade syndrome include a group of diseases which mimic anterior or posterior uveitis in their clinical presentation, but having entirely different aetiologies and pathogenesis, being usually neoplastic or occasionally ischaemic.

In children, leukemic infiltration of ocular tissues can occur.

Cancer may have remote effects on the eye such as 1) autonomic dysfunction of the pupils and 2) rarely paraneoplastic retinal degeneration (eg, cancer-associated, retinopathy and melanoma associated retinopathy).

Radiation of tumors near the eye may lead to the development of cataract or retinal vasculopathy (similar to diabetic retinopathy) and optic neuropathy. In addition, radiation can contribute to dry eye.

Some cancer chemotherapeutic agents have secondary ocular effects.
AIDS and Cytomegalovirus:

Acquired immune deficiency syndrome (AIDS) is a viral infection transmitted sexually or through blood resulting in marked depression in the count of T-helper lymphocytes and severe immunodeficiency.

AIDS commonly presents in the eye as a retinopathy (fig 11) characterized by multiple large cotton wool spots.

Other ocular features are; lid and conjunctival Kaposi sarcoma, multiple lid lesions, and severe herpes zoster ophthalmicus (fig:12)
Cytomegalovirus (CMV) retinitis, an opportunistic retinal infection (affects immune compromised host), is the leading cause of visual loss in patients with AIDS. The distinctive ophthalmoscopic appearance of CMV retinitis is characterized by sectoral hemorrhagic necrosis of the retina, typically along a retinal vessel. The disease progresses over weeks to months and results in total atrophy of the affected retina.

Cytomegalovirus retinitis (fig 13) is treated by intravitreal injection of ganciclovir as well as systemic antiviral drugs.

Multiple Sclerosis:

Multiple sclerosis is one of the more common neurologic diseases that features immune breakdown of myelin sheaths in the CNS. Multiple patches of myelin breakdown scattered in the
brain characterize the disease and the manifestations depend on the sites of these “plaques”.

A very common site for these demyelination plaques is the orbital part of the optic nerve resulting in “retrobulbar” neuritis with acute drop of vision and retrobulbar pain (see chapter 9 for the treatment of this condition).

Another common manifestation is internuclear ophthalmoplegia resulting from a demyelination plaque in the medial longitudinal bundle that connects the cranial nerve nuclei 3 and 6 (fig 14).

**Fig 14: Internuclear ophthalmoplegia**

Internuclear ophthalmoplegia is a common ocular manifestation in MS due to affection of the medial longitudinal bundle (MLB).

It is characterized by:

a. Defective adduction of the ipsilateral eye.

b. Nystagmus of the contralateral (abducting eye)

c. Normal convergence
Myasthenia Gravis:

a. It is a disease characterized by autoantibodies against the acetylcholine receptors in the neuromuscular junction. As a result there is rapid fatigue of neuromuscular transmission through the day (manifestations increase as the day passes and are least in the morning). The levator muscle and extraocular muscles are particularly sensitive to the disease which frequently presents with variable ptosis and intermittent diplopia (fig 15)

Diagnosis depends on demonstrating the specific antibodies and by electromyography (EMG)

There are some clinical tests that help in the diagnosis as:

i. Increased ptosis with prolonged upgaze

ii. Improved ptosis with icepacks applied to the lids

iii. Tensilon (edrophonium) test: injection of the drug causes rapid improvement of ptosis

Fig 15: increased ptosis with sustained upgaze
Neurofibromatosis:

An autosomal dominant phakomatosis. Skin shows multiple neurofibromata and café-au-lait patches (fig 16)

The diseases can be diagnosed by finding Lisch spots in the iris (fig 16) present in 100% of cases. Other common manifestations are plexiform neuroma of lid (fig 16) and secondary glaucoma.

Fig 16: Neurofibromatosis

Phakomatoses are a group of neurocutaneous disorders characterized by involvement of structures that arise from the embryonic ectoderm (the CNS, skin and eyes)

Pregnancy:

a) Physiological changes:

Pregnancy is not a disease, but it can cause some changes in the eye that are not considered pathologic.

These include lowering of the intraocular pressure, decrease in corneal sensitivity, and transient loss of accommodation. Pregnant women frequently
suffer from dry eyes and can experience changes in their refractive error. Therefore, pregnant patients should be discouraged from changing their prescriptions for glasses or contact lenses until after delivery. In the early postpartum period and while breast feeding, the patient should not have corneal refractive surgery performed.

b) Pathological changes:

- Increased incidence of central serous chorioretinopathy (CSCR) in pregnant versus non pregnant women.

Fig 17 : central serous chorioretinopathy (CSCR)

**CSCR** is a primarily a disease of young adult males in which there is idiopathic elevation of the central retina by serous fluid. The condition usually resolves spontaneously with little effect on vision.

- Pregnancy-induced hypertension can cause visual disturbances
  Fundus examination may show focal or generalized retinal arteriolar narrowing.

- Visual changes may be a sign of severe pre-eclampsia and impending seizures of eclampsia. The fundus may show
hemorrhages, soft exudates, diffuse retinal edema, and papilledema.

- Serous exudative retinal detachments occur in 10% of patients with eclampsia. It is usually bilateral.

**Pre-eclampsia:** hypertension developing after 20 weeks of gestation in previously normotensive mothers accompanied with proteinuria. It usually resolves few weeks postpartum.

- **Pre-existing diabetic retinopathy** can worsen during pregnancy. Some of the changes were, however, reported to be reversible after delivery. All pregnant diabetic patients should have a baseline exam in the first trimester and each trimester thereafter. But women with gestational diabetes are not at risk for retinopathy.

2) **Some characteristic or pathognomonic ocular signs of certain systemic diseases:**

**The cornea:**

Examination of the cornea can give a clue to some systemic diseases such as:

- **Wilson's disease** (hepatolenticular degeneration; an inherited disease of copper metabolism). In this disease, the cornea shows a peripheral golden ring of copper deposition known as Kayser-Fleischer ring (fig 18).
- Epithelial deposits may be seen in metabolic diseases as Mucopolysaccharoidosis (MPS) and cystinosis.
- Corneal nerves may be enlarged in neurofibromatosis (fig 19).
The iris:

Iris examination can settle the diagnosis of:
- Neurofibromatosis by demonstrating Lisch nodules (fig 20 a)
- Down's syndrome by demonstrating Brushfield spots (fig 20 b).
- Iris neovascularization may be seen in aortic and carotid occlusive diseases (after exclusion of diabetes and vein occlusion)
The lens:

- Lens subluxation can diagnose Marfan’s syndrome or the metabolic disease homocystinuria.

Marfan’s syndrome:
An autosomal dominant syndrome characterized by tall stature, spider-like fingers, subluxated lenses (fig 21) and aortic dilatation.

Fig 21: Arachnodactyly and subluxated lens

   Lens subluxation is commonly a clue to the syndrome and should raise attention to the disease of the aorta.

   Retinal detachment is another common complication.

- A newborn with “oil-droplet” cataract (fig 22) can spot the diagnosis of neonatal Galactosemia.
Fig 22: Oil-droplet cataract in Galactosemia

- **Cushing syndrome** may present as bilateral posterior subcapsular cataract in a young patient.

**The fundus:**

- Fundus signs of diabetes and hypertension/arteriosclerosis are characteristic (see chapter 8).

- Certain blood diseases and coagulopathies such as anemia, thrombocytopenia and other coagulopathies can display preretinal, subhyaloid (saucer shaped) hemorrhages and intraretinal hemorrhages. Leukemia and pernicious anemia may show hemorrhages with pale or whitish centers (Roth spots) (Fig 23).

The presence of recurrent subconjunctival hemorrhages and spontaneous hyphema can point to thrombocytopenia or anemia.
Sickle cell retinopathy:

This is a herido-familial disease where the hemoglobin is abnormal and the red blood cells acquire a sickle shape. Intravascular sickling, hemolysis, hemostasis, and then thrombosis lead to arteriolar occlusion followed by capillary nonperfusion. As with diabetes, inadequate perfusion of the retina can stimulate retinal neovascularization, which is typically more peripheral and having a sea fan like appearance. (figure 24). This can lead to vitreous hemorrhage and tractional retinal detachment.

- The presence of sea fan type of neovascularization is pathognomonic of sickle cell retinopathy.
- The management depends on early detection of the peripheral retinal ischemia or neovascularization in order to apply scatter laser photocoagulation to ablate the ischemic retina.

**Optic nerve:**

The occurrence of retrobulbar neuritis can settle the diagnosis of MS in asymptomatic young female.