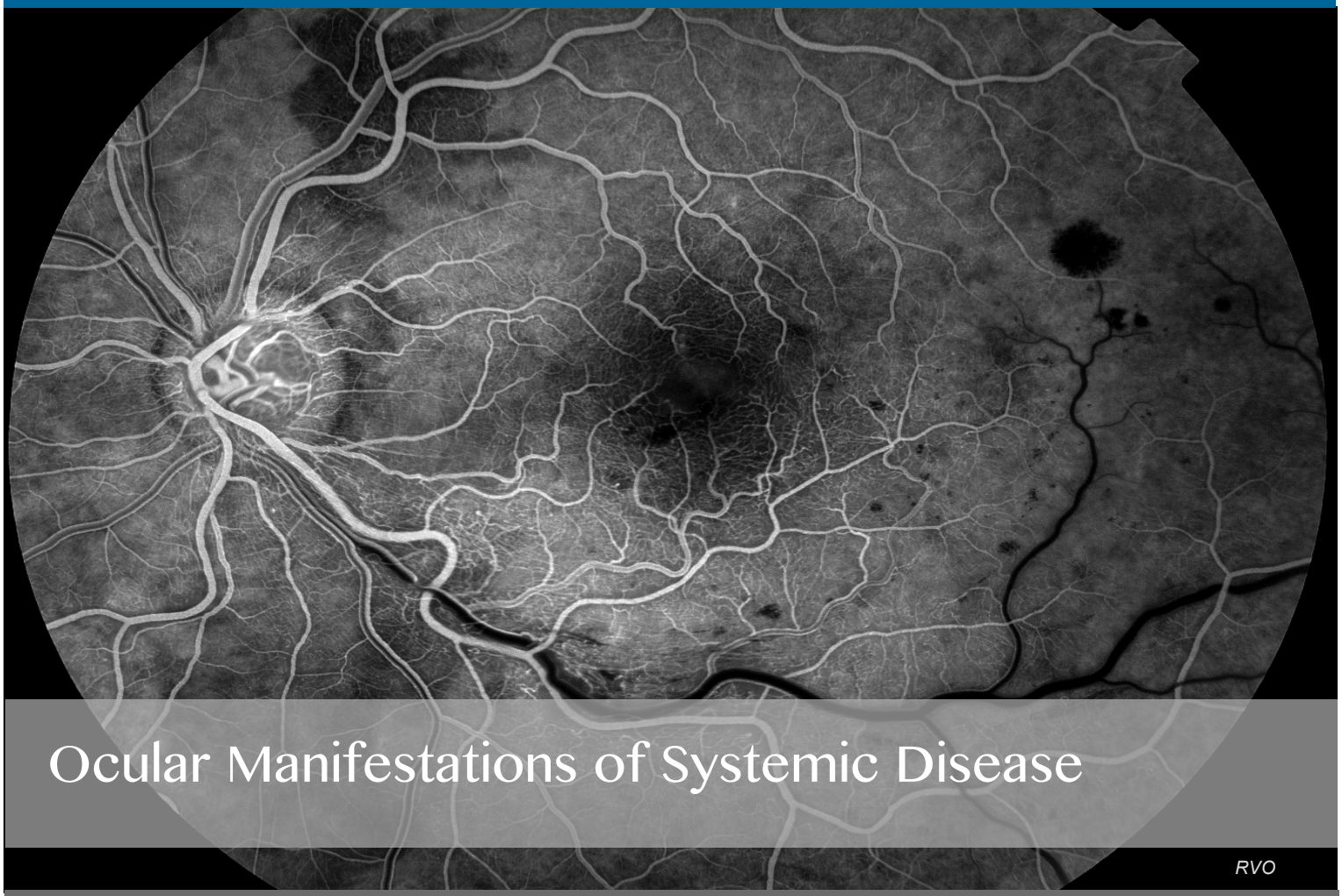

# Ocular Manifestations of Systemic Disease

*RVO*

## 429 Ophthalmology Team (F)

Sources: the team notes were prepared using Prof. Abu Al-Asrar's slideshow, 429 Ophtha. Team Notes, Toronto Notes 2011, and Vaughan & Asbury's General Ophthalmology 17ed.

* It is absolutely essential to study this lecture in conjunction with the picture slides

Gray boxes: mostly contain professor's slides

Page 10 contains a summary table

Page 11 contains an extra table

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# 1 DIABETES MELLITUS

- The risk of blindness is 25% greater in diabetics
- Diabetic retinopathy (DR) is the commonest cause of legal blindness in individuals between the ages of 20 and 65 years
- Most important factor in development of DR is: duration of the disease (non modifiable risk factor)
- Other important modifiable risk factors: 1) glycemic control (2) blood pressure control (3) hyperlipidemia & obesity (magnify macular edema) (4) smoking (5) pregnancy (accelerates progression)
- Consider diabetes in the case of unexplained retinopathy, cataract, extra-ocular muscle palsy, optic neuropathy or sudden change in refractive error

## 1.1 THE RETINA

- The most important structure affected by DM

**Pathophysiology**: changes that occur in the retina (Prof. notes):

1st is: continuous neuro-degeneration of the ganglion cells; can take place before any vascular changes
  - Induced by hyperglycemia

2nd is: breakdown of the blood-retina barrier (loss of peri-cytes, altered vascular permeability, and thickening of capillary basement membrane) → fluid leakage → macular edema → visual loss
  - Can happen long before detachment
  - Due to loss of peri-cytes, microaneurysms develop
  - Hemorrhages can occur (flame-shaped)

3rd is: progressive vascular occlusion → retinal ischemia → angiogenesis → bleeding → vitreous hemorrhage → fibrous tissue formation → traction → detachment

- **Classification:**
  - **Non-proliferative**: increased vascular permeability and retinal ischemia
    - Dot and blot hemorrhages
    - Microaneurysms (≥1 = mild)
    - Hard exudates (lipid deposits)
  - **Advanced non-proliferative**; non-proliferative findings plus:
    - Venous beading (diameters of veins are not uniform) or looping “omega sign” (in ≥2 of 4 retinal quadrants) ☞ most reliable signs
    - Retinal hemorrhages (in 4 quadrants)
    - Intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, tortuous, leaky vessels within the retina
    - Cotton wool spots (nerve fiber layer infarcts)
  - **Maculopathy:**
    - Due to fluid leakage from breakdown of blood-retina barrier
    - Can also be due to ischemia
    - Signs: microaneurysms and hard exudates (circinate rings)
    - More common in type II DM
  - **Proliferative:**
    - 5% of patients with diabetes will reach this stage
    - Progressive retinal ischemia causes release of vascular endothelial growth factor (VEGF); newly formed vessels (from veins) are fragile and prone to bleeding
    - Neo-vascularization of iris, disc, retina to vitreous
      - Recurrent vitreous hemorrhage → tractional retinal detachment

## 1.2 THE IRIS

- Neo-vascularization of iris (rubeosis iridis) → leads to neo-vascular glaucoma
- Sign of severe retinopathy

## 1.3 THE LENS

- Earlier onset of senile sclerosis and cortical cataract
- May get hyperglycemic cataract due to sorbitol accumulation (rare)
- Poor glycemic control can suddenly cause refractive changes by 3-4 diopters

## 1.4 THE EXTRA-OCULAR MUSCLES & OPTIC NERVE

- Usually CN III infarct
- Pupils usually spared in diabetic CN III palsy but get ptosis (Why? Parasympathetic fibers run around the nerve not in it)
- May involve CN IV and VI
- Usually recover within few months
- Visual acuity loss due to infarction of optic disc/nerve

## 1.5 SCREENING & PREVENTION

- How do we prevent blindness in diabetics?
    - The only way is to establish regular screening programs where a picture of the fundus (digital fundal photography) is taken on a regular basis, using non mydriatic fundus cameras, then the photo would be sent to a reading center which will provide certain instructions
- Why do we need screening programs?
    - Because the patient may be asymptomatic. The only case where the patient will have a complaint is if they develop vitreous hemorrhage, which is very late.
    - The goal is to treat DR while the pt has 20/20 vision.
- Who to screen?
    - Type 1 diabetic should be screened between 3-5 years after diagnosis, because it is unlikely to develop DR before. Screening is not indicated before onset of puberty.
    - Type 2 diabetic should be screened once the diagnosis is made
    - Female diabetics who are planning to get pregnant
    - Pregnant diabetics during the first trimester of pregnancy, and every 3 months after
- Findings will determine the intervention:

| Findings | Intervention |
|---|---|
| **Good fundus, no sign of Dr** | 1 year follow-up |
| **Mild non-proliferative disease** | 8 month follow-up |
| **Moderate non-proliferative disease** | 6 month follow-up |
| **Severe non-proliferative disease** | **Start focal laser** |
| **Clinically significant macular edema** | **Start focal laser** |
| **Proliferative DR** | Pan-retinal photocoagulation |

- Pan retinal photocoagulation:
    - Several thousand regularly spaced burns are applied throughout the retina to reduce the angiogenic stimulus from ischemic areas. The central region bordered by the disc and major temporal vascular arcades is spared.
- Intra-vitreal anti-VEGF has been proven to be effective (usually as an adjunct to laser); faster onset of action, but short duration.

# 2 GRAVE'S DISEASE

- Grave's disease is hyperthyroidism due to an autoimmune process.
- Not all Grave's disease patients develop "Grave's ophthalmopathy" or thyroid eye disease.
- Other characteristic manifestations: pretibial myxedema

**Ocular features:**

1) Eyelid retraction
2) Infiltrative ophthalmopathy
3) Proptosis
4) Dysthyroid optic neuropathy
5) Restrictive thyroid myopathy

## 2.1 LID RETRACTION

- Almost pathognomonic
- Unilateral or bilateral; upper or lower lids
- Due to hyperstimulation of the sympathetic nervous system and direct inflammatory infiltration of the levator muscle

## 2.2 EXOPHTHALMOS

- Usually asymmetric; may be unilateral
- Due to and increase in the bulk of the ocular muscles and the orbital fat
    - The increase is due to infiltration by inflammatory cells
- Dx: MRI/CT

## 2.3 OPHTHALMOPLEGIA

- Restrictive myopathy is due to fibrosis of extra-ocular
- Limitation of elevation is the most common finding – due to tethering of the inferior rectus
- There's usually limitation of movement in all positions of gaze

## 2.4 RETINAL AND OPTIC NERVE CHANGES

- Compression of the globe may lead to elevation of intra-ocular pressure
- Optic neuropathy occurs either as a result of compression or due to ischemia

## 2.5 CORNEAL CHANGES

- Normally, the upper lid covers 1-2 mm of the cornea
- Lagophthalmos is the inability to close eyelids completely
- Keratitis lagopthalmos: is inflammation of the cornea due to dryness from excessive exposure

# 3 GRANULOMATOUS DISEASE

## 3.1 TUBERCULOSIS

**Ocular features:**

1) Phlyctenular keratoconjuctivitis
2) Interstitial keratitis
3) Uveitis
4) Retinal vasculitis (Eale's disease)

- TB is very common and increasing worldwide

- **It is the most common cause of uveitis admissions**
- Ocular TB results from endogenous spread from systemic foci
  - But: Remember that you can have TB uveitis **without pulmonary TB** or any other
- TB affects the eye in 2 ways:
  - Direct infection: **choroidal granuloma** (appears as pinkish nodules)
  - Type 4 hypersensitivity immune reaction to tuberculin protein causes **retinal vasculitis** (appearance: whitish vessels; "sheathing")
- TB can mimic any eye inflammation so high index of suspicion is required in order not to miss it
- ***Suspect TB in a patient with eye inflammation who has been receiving steroids for long time without benefit***
- Rx: TB responds only to anti-tuberculosis drugs and needs a long course of treatment (6-9 months) ± a short course of steroids

**Extra note: Eale's Disease:**

Recurrent vitreous hemorrhage from areas of neo-vascularization
It is a diagnosis of exclusion.
The same clinical features occur in: TB, sarcoidosis, SLE, sickle cell disease and diabetes.

## 3.2 SARCOIDOSIS

**Ocular features:**

1) Lid margin and conjuctival granuloma
2) Acute iridocyclitis
3) Chronic granulomatous iridocyclitis
4) Peripheral retinal periphlebitis
5) Choroidal granulomas
6) Retinal granulomas
7) Optic nerve granulomas

- Sarcoidosis is a multisystem disease characterized by non-caseating granulomatous infiltration of affected tissues
- Patients may present with pulmonary, ocular, joint or reticuloendothelial system manifestations
- The most common cause of uveitis in Japan & Blacks (not common here)
- Causes granulomatous uveitis.
  - Mutton fat keratic precipitate (diagnostic)
  - Posterior synechiae (adhesions)
  - Choroidal granulomas
  - Granuloma of optic nerve head
  - Vasculitis
- Dx:
  - CT chest
  - Trans-bronchial lavage (biopsy)
  - Angiotensin converting enzyme
  - Serum lysozyme
  - LFT
- Rx: Unlike TB, granulomatous uveitis due to sarcoidosis responds well to steroids

**Extra note from the professor: Multiple Sclerosis**

a) Intermediate uveitis and retinal periphlebitis are rare manifestations of MS
   - Intermediate uveitis: inflammation involving the vitreous, peripheral retina and pars plana ciliaris
b) Patients with intermediate uveitis associated with MS develop a granulomatous anterior uveitis with mutton-fat keratic precipitates that mimic sarcoidosis
c) Rx: immunosuppression (Cellcept: Mycophenolate Mofetil; interferon etc)

## 3.3 SYPHILIS

**Ocular features:**

a) **Congenital** *(due to infection during 3rd trimester; if infection occurs in 1st trimester → abortion)*
   1) Interstitial keratitis
   2) Chorioretinitis
b) **Acquired**
   1) Ocular chancre
   2) Iridocyclitis
   3) Interstitial keratitis
   4) Chorioretinitis
   5) Neuro-ophthalmic

- Not common here
- More prevalent in Western countries due to higher prevalence of HIV infection

## 3.4 TOXOPLASMOSIS

**Toxoplasmosis:**

1) Etiology: Toxoplasma gondii, obligate intracellular protozoan parasite
2) **Congenital**
   i) **C**onvulsions
   ii) **C**horioretinitis
   iii) Intra**c**ranial **c**alcifications
3) **Acquired**
   i) Reactivation of old lesion; retinitis
4) Rx: clindamycin, sulfonamides, pyrimethamine (Daraprim), steroids

- Most common cause of infectious posterior uveitis
- Typically causes necrotizing retinitis

# 4 VIRAL: RUBELLA

- Maternal rubella during the 1st trimester causes serious congenital anomalies
- Features:
  - Eyes: small (microphthalmos), cataracts (most common), glaucoma, retinopathy
  - Ears: deafness
  - Heart: congenital anomalies

# 5 MULTISYSTEM AUTOIMMUNE

## 5.1 SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

- Features: butterfly rash, pericarditis, Raynaud's, renal disease, arthritis, anemia, and CNS signs
- Ocular features: most important is **retinopathy** that occurs only during active disease, "flare-ups"
  - Findings: cotton wool spots and large areas of infarction (signs of arteriolar occlusion)

- Dx: elevated ESR, antibodies: anti-nuclear antibodies (ANA), anti-double-stranded DNA antibodies, anti-phospholipid antibodies, etc
- **Anti-Phospholipid Antibody Syndrome**: recurrent thromboembolism, recurrent abortions, +ve anti-phospholipid antibodies → produces any kind of retinal vascular occlusive disease

## 5.2 RHEUMATOID ARTHRITIS (RA)

Sero**positive**
**Ocular features:**
1) Keratoconjuctivitis sicca
2) Scleritis
3) Keratitis

- Dryness and keratoconjuctivitis sicca are diagnosed by Rose Bengal staining (shows dead and devitalized tissue as well as tissue that is inadequately protected by mucin)
- The scleritis may lead to **scleromalacia perforans**: thinning of the sclera. This can lead to uveal tissue herniation and perforation of the globe.

## 5.3 ANKYLOSING SPONDYLITIS (AS)

- Sero**negative**
- X-ray of sacro-iliac joints
- **Ocular features:**
  Acute recurrent non-granulomatous iridocyclitis

- History: **young man** with acute recurrent non-granulomatous anterior uveitis
  - Ask if he has **lower back pain** which is worse in the morning
- Dx: **HLA B27** detection and x-ray of sacroiliac joints

## 5.4 JUVENILE CHRONIC ARTHRITIS

1) Systemic onset "Still's disease" (***fever, rash & pericarditis***) → Uveitis is extremely **rare**
2) Polyarticular onset (*>5 joints*) → Uveitis is fairly **rare**
3) Pauciarticular onset (*1-5 joints; esp. ankle & wrist*) → **20%** develop uveitis

- Girls are more prone than boys (x3)
- If the child develops the disease **before the age of 4,** the risk of eye involvement is high
- Associated with **positive antinuclear antibodies (ANA)**; increases the risk of eye involvement
- Referral to a pediatric ophthalmologist is necessary as soon as the diagnosis is made, because uveitis may be asymptomatic and this can lead to blindness

## 5.5 BEHÇET'S DISEASE

- Recurrent oral ulceration
- Genital ulceration
- Skin lesions
- Uveitis

- **HLA B51** association. Common in areas of the "Silk Road" (East, South, Western Asia, the Mediterranean and Europe, as well as parts of North and East Africa). Most common in **Turkey**.
- Diagnosed clinically: recurrent **oral ulcers (painful)** and 2 of the following
  - Genital ulcers (recurrent)
  - Skin lesions
  - Uveitis (severe, occasionally with **hypopyon**, which is pus collection in ant. chamber)
  - Positive Behcet's test

- Behcet's uveitis is a blinding disease if not treated; it causes severe **retinal vasculitis**, venous occlusions & **hemorrhages**
- Rx: steroids (short course), cyclosporine, azathioprine (Imuran). If no response: infliximab (anti α-TNF)

## 5.6 SJÖGREN'S SYNDROME

- Autoimmune disease. Causes **DRYNESS**.
- Involvement of salivary glands
- Involvement of bronchial epithelium
- Involvement of vaginal epithelium
- **Ocular features:** keratoconjuctivitis sicca

## 5.7 VOGT-KOYANAGI-HARADA SYNDROME

- Pigmented individuals (rare in Caucasians)
- Cutaneous signs
- Neurological signs
- **Ocular features:**
    - Anterior and posterior uveitis

- Autoimmune disease with **HLA DR4** association
- 2nd most common cause of eye inflammation
- T-lymphocytes attack melanin containing structures:
    - Skin → vitiligo
    - Hair → alopecia
    - Lashes → poliosis
    - Meninges → severe headache, meningitis
    - Inner ear → tinnitus, deafness
    - Eye → uveitis
- When the choroiditis is exudative → (fluid under retina) → serous retinal detachment
- Irregular pupil due to posterior synechiae, keratic precipitates (due to anterior uveitis)
- Rx: large doses of systemic steroids for at least 1 year + mycophenolate mofetil (Cellcept), to prevent permanent visual loss
- Prognosis: visual recovery is not always complete → residual **depigmentation of the fundus**

## 5.8 GIANT-CELL ARTERITIS

- Autoimmune vasculitis of large and medium sized arteries
- More common in **elderly >60 years**
- Features: **Sudden monocular visual loss** due to ischemic optic neuropathy (infarction of optic nerve); disc will be pale and swollen, and other features:
    - Pain over the temporal artery
    - Jaw claudication (pain with chewing)
    - Scalp tenderness (gangrene of the scalp may occur)
    - Polymyalgia rheumatica (muscular pain, esp. neck, shoulders and hips)
    - Constitutional symptoms
- Dx: temporal artery biopsy (**gold standard**), ESR, CRP
- Rx: large doses of systemic steroids to prevent visual loss in the other eye (the affected eye will be irreversibly damaged at the time of presentation)

## 6 HERITABLE CONNECTIVE TISSUE DISORDERS: MARFAN'S

**Ocular features:**

1) Lens sublaxation (important; usually superiorly and nasally)
2) Angle anomaly
3) Glaucoma
4) Hypoplasia of the dilator muscle
5) Axial myopia
6) Retinal detachment

- Rare syndrome due to fibrillin-1 gene mutation on chromosome 15; autosomal dominant
- Features: increased length of long bones, esp. fingers and toes (arachnodactyly) +
    - Scanty (little) subcutaneous fat
    - Relaxed ligaments
    - Congenital heart disease
    - Deformities of the spine and joints

**Extra note from the professor: Lens sublaxation DDx**

a) Trauma
b) Homocysteinemia
c) Hyperlysinemia

## 7 HEREDITARY METABOLIC DISORDERS: WILSON'S DISEASE

**Ocular features:**

1) Kayser-Fleischer ring
2) Green sunflower cataract

- Also called "hepatolenticular degeneration"
- Pediatric disease
- Deficiency of alpha-2 globulin ceruloplasmin (copper carrier) → abnormal copper metabolism
- So copper will deposit:
    - In the cornea at the level of descemet's membrane in the peripheral part (Kayser-Fleischer ring)
    - In the lens (green sunflower cataract)
    - In the liver → cirrhosis
    - In the basal nuclei

## 8 HEMATOLOGIC: SICKLE CELL DISEASE

- Sickled RBC's will occlude the peripheral retinal circulation → retinal ischemia → neovascularization - - → vitreous hemorrhage and tractional retinal detachment
- Rx: (as in diabetes) focal laser ± vetriectomy

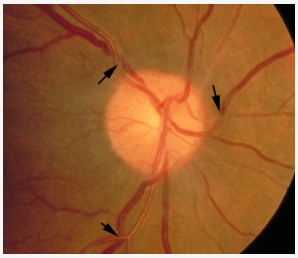
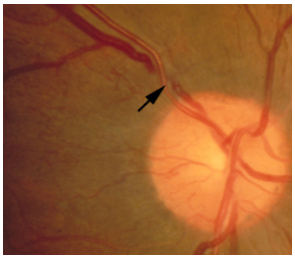
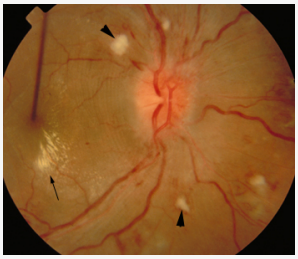
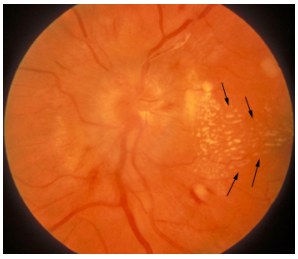
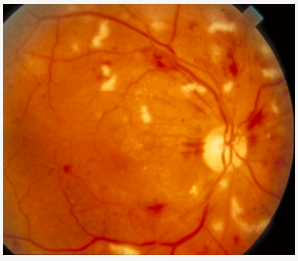
## 9 VASCULAR: HYPERTENSIVE RETINOPATHY

- Ocular features:
    - Attenuation of arteries (↓ diameter), sometimes referred to as "copper/silver wiring"
    - Nipping of the retinal veins where they are crossed by arterioles
    - Narrowing of arterioles → breakdown of blood-retina barrier: hard exudates & hemorrhages
    - If severe → signs of capillary occlusion: cotton wool spots
    - Optic disc edema (bilateral = papilledema) → blurring of vision and temporary visual loss

## 10 SUMMARY

| Structure | Disease | Manifestation |
|---|---|---|
| **Conjunctiva, Cornea, and Sclera** | | |
| | Grave's disease | Keratitis lagophthalmos |
| | Tuberculosis | Phlyctenular keratoconjuctivitis, interstitial keratitis |
| | Sarcoidosis | Lid margin & conjunctival granulomas<br>Mutton-fat keratic precipitates |
| | Syphilis (congenital & acquired) | Interstitial keratitis |
| | Rheumatoid arthritis | Keratoconjuctivitis sicca, scleritis & scleromalacia perforans |
| | Sjögren's syndrome | Keratoconjuctivitis sicca |
| | Vogt-Koyanagi-Harada syndrome | Keratic precipitates |
| | Wilson's disease | Kayser-Fleischer ring |
| **Lens** | | |
| | Diabetes mellitus | Earlier onset of senile cataract, hyperglycemic cataract<br>Sudden change in refractive error |
| | Rubella | Cataract |
| | Marfan's syndrome | Lens sublaxation (superiorly & nasally) |
| | Wilson's disease | Green sunflower cataract |
| **Uveal Tract & Retina** | | |
| | Diabetes mellitus | Rubeosis iridis |
| | Tuberculosis | Uveitis (most common cause), retinal vasculitis |
| | Sarcoidosis | Acute iridocyclitis, chronic granulomatous iridocyclitis<br>Retinal periphlebitis, choroidal & retinal granulomas |
| | Syphilis | Iridocyclitis, chorioretinitis |
| | Toxoplasmosis | Posterior uveitis (most common cause) |
| | Rubella | Glaucoma, retinopathy |
| | SLE | Retinal artery occlusive disease |
| | Ankylosing spondylitis | Anterior uveitis "iridocyclitis" (non-granulomatous) |
| | Juvenile chronic arthritis | Uveitis w/pauciarticular type |
| | Behçet's disease | Uveitis (w/hypopyon), retinal vasculitis, RVO |
| | Vogt-Koyanagi-Harada | Anterior and posterior uveitis, retinal detachment |
| | Marfan's syndrome | Glaucoma, retinal detachment |
| | Sickle Cell Disease | Retinal ischemia & neovascularization ± vitreous hemorrhage |
| **Optic Nerve** | | |
| | Diabetes mellitus | Optic neuropathy (ischemic) |
| | Grave's disease | Optic neuropathy |
| | Sarcoidosis | Optic nerve granulomas |
| | Giant cell arteritis | Ischemic optic neuropathy |

***Extra notes: hypertensive retinopathy findings:***

| Grade | Description | A:V Ratio | |
|---|---|---|---|
| **I** | • ***Normal A:V ratio is 2:3***<br>• **Minimal Narrowing of the retinal arteries**<br>• **Generalized arteriolar constriction seen as "silver wiring"**<br>• **Vascular tortuosities** | **50%** |  |
| **II** | Narrowing of the retinal arteries in conjunction with regions of focal narrowing and arteriovenous nipping (the vessel wall thickens due to arteriolosclerosis, the vein is displaced. If, as the artery crosses over the vein, the vein is compressed, it will appear "nicked") | **33%** |  |
| **III** | **Abnormalities seen in Grades I and II, as well as**<br>• **Retinal hemorrhages (intra-retinal)**<br>• **Hard exudation (exudation of fluid & lipids)**<br>• **Cotton-wool spots (contain cell organelles; are due to damage to nerve fibers)** | **25%** |  |
| **IV** | Abnormalities encountered in Grades I through III, as well as<br>• Swelling of the optic nerve head<br>• Macular star<br>(**Blurring of the borders of the optic disk with hemorrhages**) | **<20%** |  |
| | Flame-shaped hemorrhages (blood accumulates at the level of nerve fiber layer) | |  |