

OCULAR MANIFESTATIONS OF SYSTEMIC DISEASES

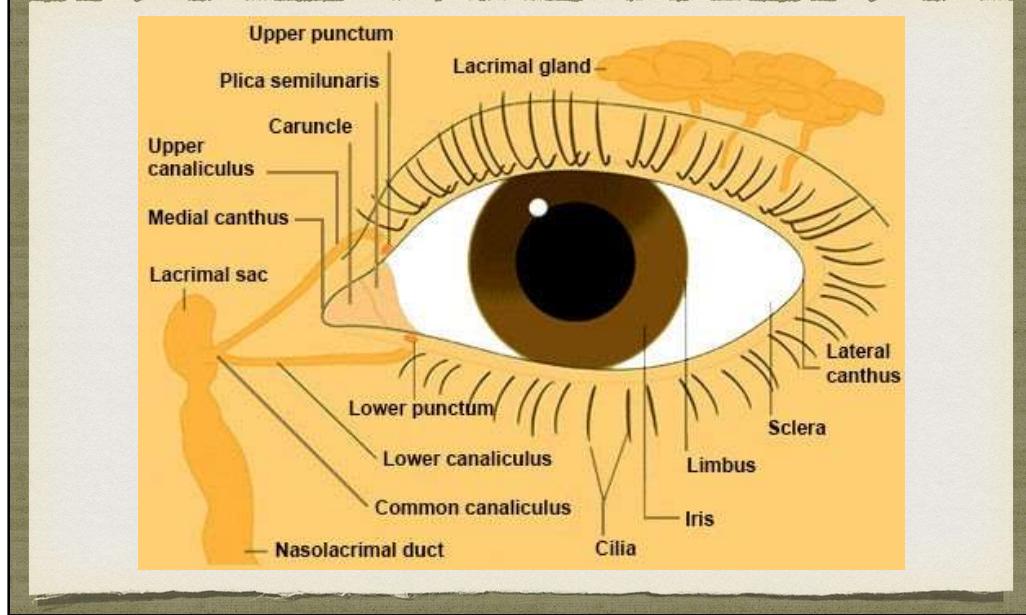
Lili Phung MD

(with thanks to Gail Feinberg, DO and Nina Ni, MD)

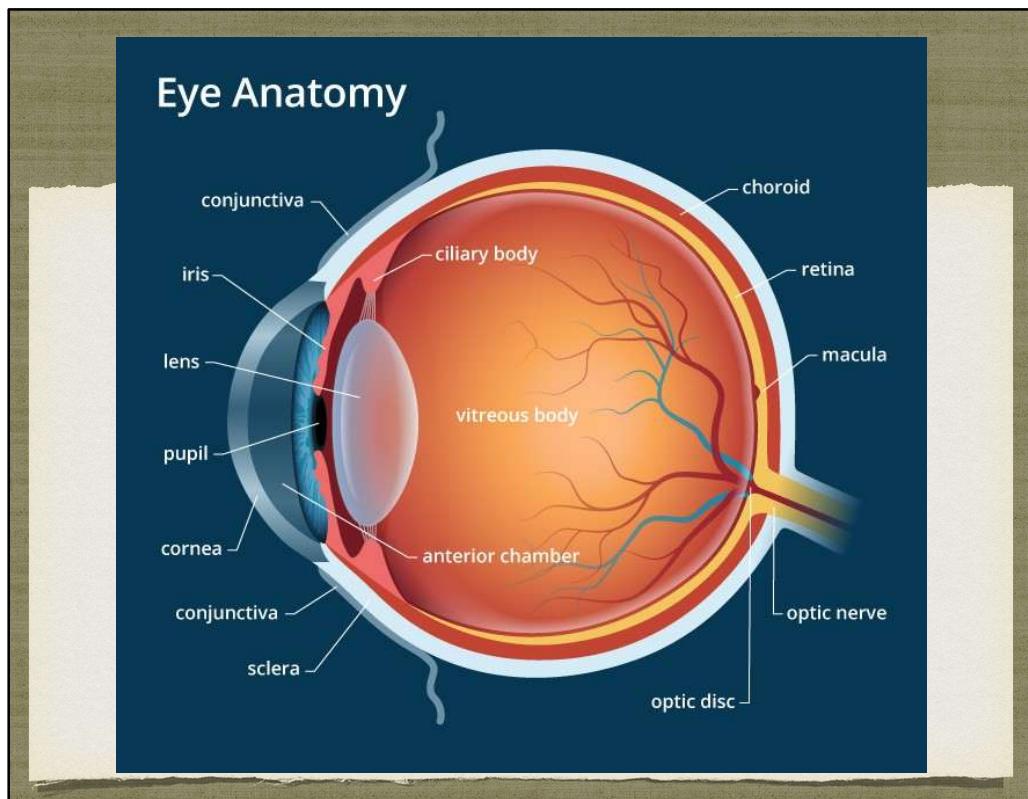
OBJECTIVES

- Recognize systemic diseases that may result in ocular pathology
- Identify ocular signs and symptoms associated with systemic conditions
- ★ • Know how to treat and when to refer

EYE ANATOMY

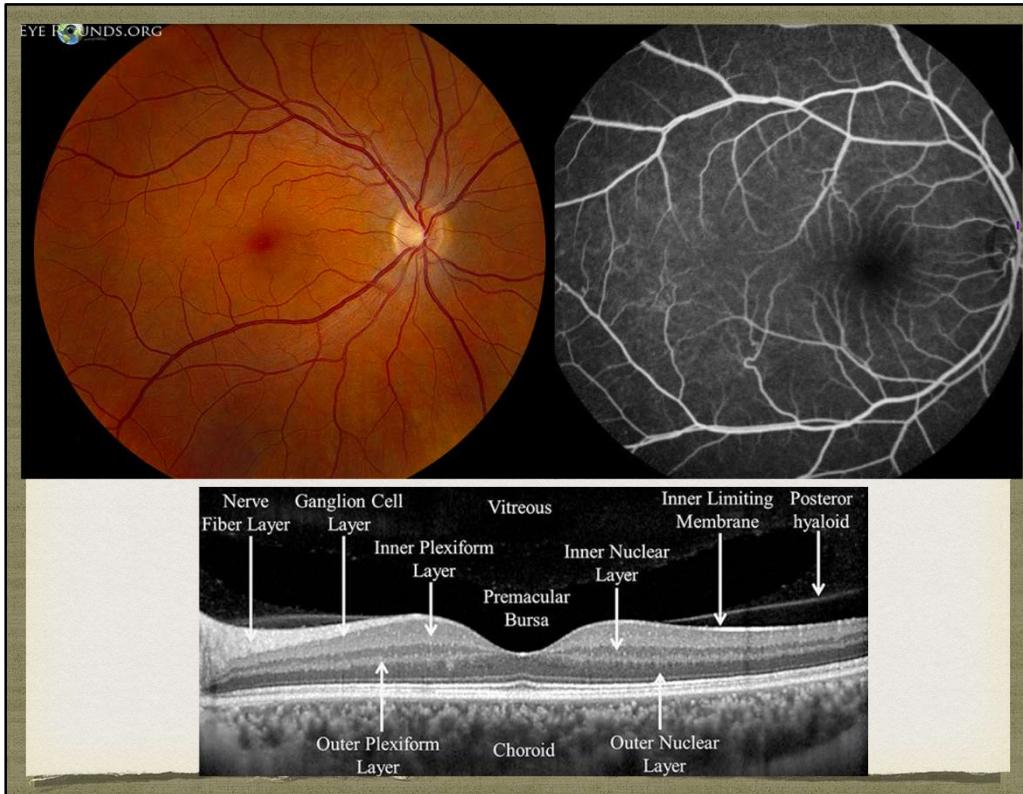


go through anatomy on own



norma fundus

normal FA



normal OCT

Dr. Phung won't test on retinal layers but Massa will

CATEGORIES OF SYSTEMIC DISEASE

- Congenital
- Vascular
- Endocrine
- Autoimmune/Inflammatory
- Infectious
- Drugs and Toxins
- Miscellaneous

CONGENITAL DISORDERS

- Down Syndrome Prevalence 1 in 640
- Marfan Syndrome Incidence 1 in 5,000
- Osteogenesis Imperfecta Incidence 1 in 16-20,000
- Neurofibromatosis Incidence 1 in 2,600 -3,000
- Wilson's Disease Prevalence 1 in 30,000

New stat on down syndrome prevalence in US Per CDC website May 2024. change in marfan prevalence per 2019 genetics study quoted on CDC website May 2024. change in OI incidence per 2021 NIH paper stating 1 in 16,000-20,000 live births recognizable at birth, similar stats for milder recognized later. Neurofibromatosis type 1 1:2600-3000 (uptodate 2024) but type 2 rare at 1:50,000. Wilsons worldwide 1:30,000 but as high as 1:7000 gene defect in UK

other ones more rare but really popular for boards

DOWN SYNDROME: OCULAR MANIFESTATIONS

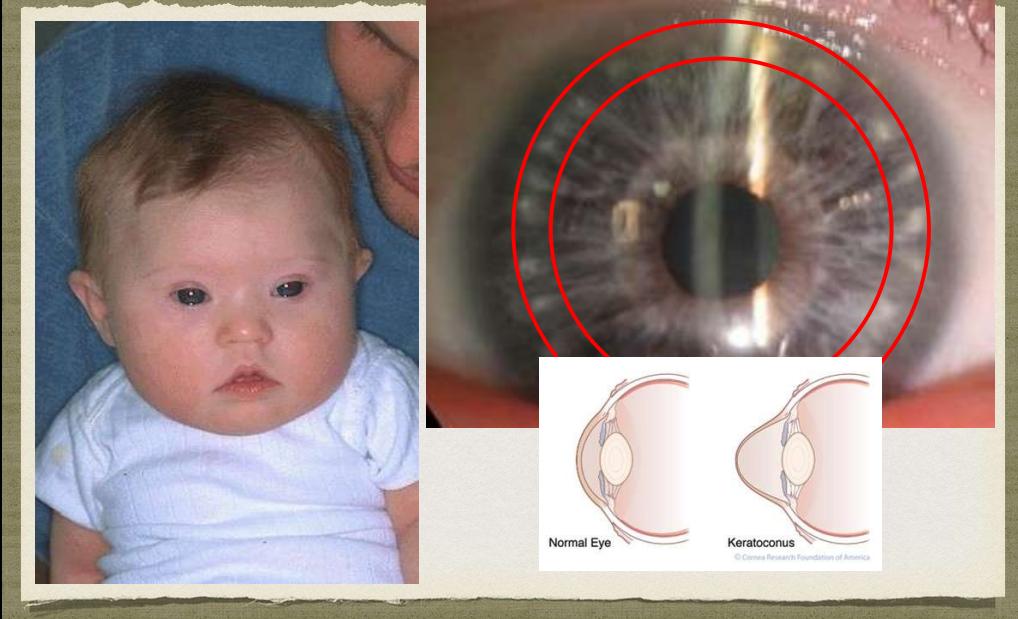


- Autosomal disorder related to maternal age
 - Ocular features:
 - Oblique palpebral fissures
 - Epicanthic folds
 - Brushfield spots on iris
 - Strabismus
 - Refractive error
 - **Keratoconus** dramatic finding
 - Cataract
- all things that can cause visual system to not develop



Brushfield spots are white/grey/brown spots in a ring on the peripheral iris. They are not pathognomonic. When seen in patients without trisomy 21 they can be called Kunkmann-Wolffian bodies/nodules. Appear in up to 78% infants with trisomy 21, especially obvious in light irides.

OCULAR FEATURES OF DOWN SYNDROME



can cause high astigmatism
keratoconus
responds well to corneal transplant

Brushfield spots are white/grey/brown spots in a ring on the peripheral iris. They are not pathognomonic. When seen in patients without trisomy 21 they can be called Kunkmann-Wolffian bodies/nodules. Appear in up to 78% infants with trisomy 21, especially obvious in light irides

like to ask question about the brushfield spots bc not only in down

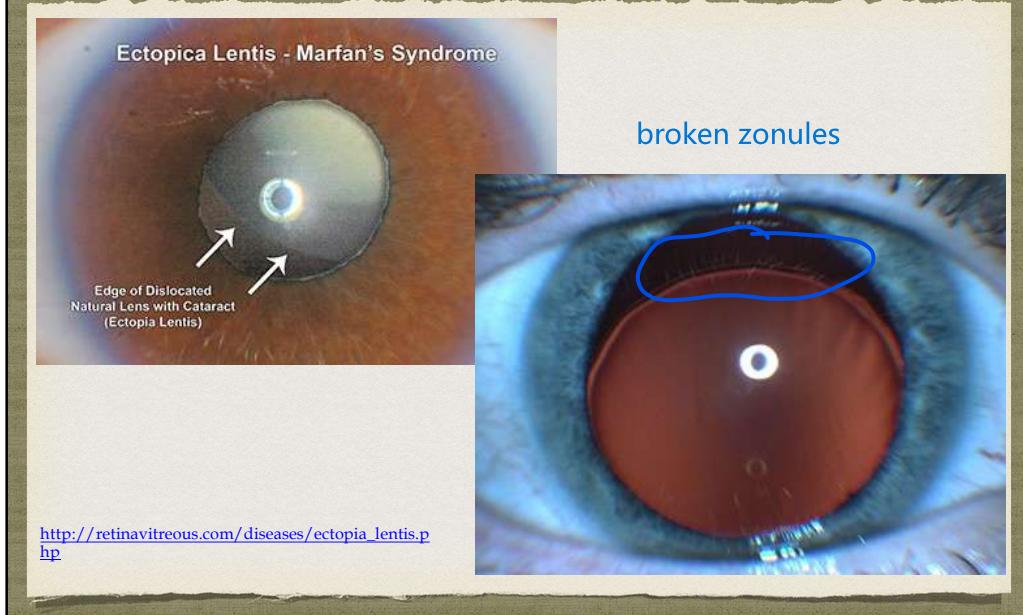
MARFAN SYNDROME

- Autosomal dominant disorder of collagen that has skeletal, cardiovascular and ocular findings
- At risk for ectopic lentis, usually upward and temporally
- Also at risk for myopia, retinal detachment, early cataract

people love
this question
bc very
dramatic
looking



DISLOCATION (SUBLUXATION) OF THE LENS (ECTOPIA LENTIS)



zonules of zyn are weakend and whole capsule is decente
cataract with intact capsule

OSTEOGENESIS IMPERFECTA “BRITTLE BONE DISEASE”

- A rare inherited disorder of connective tissue with skeletal, ear and eye manifestations **very brittle bones**
- Usually autosomal dominant mutation affecting Type I collagen
- Several subtypes I to IX classified by degree of involvement (mild to severe, Type II is lethal)
- Major ocular sign is thinned **blue sclera** 
- At risk for corneal thinning and congenital glaucoma

make sure to look under the lids

BLUE SCLERA IN OSTEOGENESIS IMPERFECTA

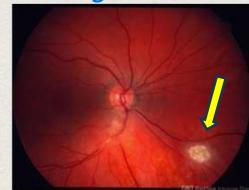


does not have to be all blue

NEUROFIBROMATOSIS TYPE 1 (VON RECKLINGHAUSEN'S DISEASE)

17 letters in
neurofibromato
sis =
chromosome 17

- Autosomal dominant mutation in neurofibromin with 1:1 familial/de novo. **Chromosome 17**
- 1:2,600-3,000
- NIH criteria based upon clinical findings
- Ocular manifestations:
 - Lid/orbital neurofibroma (can cause strabismus, glaucoma)
 - **Lisch nodules: iris hamartomas** rarely before age 3 but obvious before
 - Optic nerve glioma
 - Retinal astrocytic hamartoma (not pathognomonic)



posterior to globe
can cause proptosis

Need two of 7 clinical criteria for NF1, 2 of which are ocular

Mnemonic: Chase Bank LOANS (Café au lait spots, Bony abnormalities, Lisch nodules, Optic glioma, Axillary freckling, >1Neurofibroma/1plexiform neurofibroma, Sister (1st degree relative with NF1)

Optic nerve glioma: presents as painless vision loss, usually unilateral to start. Proptosis, strabismus. Usually a tumor of childhood in NF1, 20% bilateral.

astrocytic hamartoma is benign proliferation of glial cells, most commonly associated with tuberous sclerosis but also seen in neurofibromatosis among other systemic diseases

NEUROFIBROMATOSIS TYPE 1 (VON RECKLINGHAUSEN'S DISEASE)



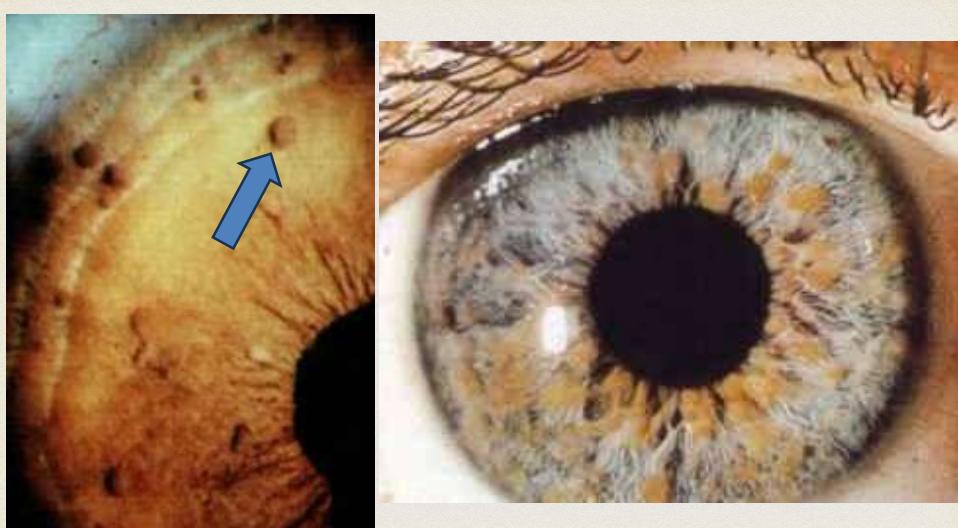
Top photo: characteristic s-shaped plexiform eyelid neurofibroma, right upper eyelid

Bottom left: right eye proptosis and strabismus [risk of tumors](#)

Bottom right: bilateral optic nerve glioma [often bilateral but may be asymmetric](#)

[risk for amblyopia b/s
of obstruction of
pupil](#)

LISCH NODULES IN NEUROFIBROMATOSIS



blue eyes but turning brown - normal to be blue at birth but will turn within the year

Lisch nodules are hamartomas (dendritic melanocytes of the iris) not present at birth and rarely present prior to 3 years old. More common as patient ages, Present in 55% of 6-year-olds and 90-100% of adults over age 20 with neurofibromatosis type 1. Often appear prior to neurofibromas.

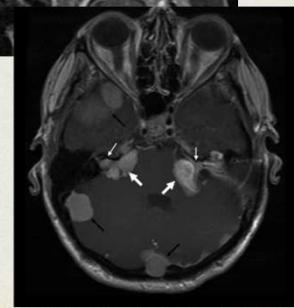
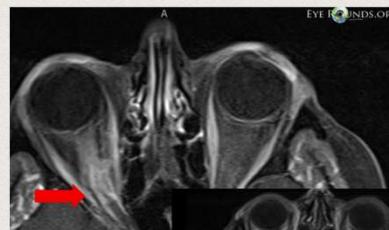
Type 2 =
chromosome 22
(tumor
suppression
gene)

NEUROFIBROMATOSIS TYPE 2

- Autosomal dominant mutation with 1:1 familial:de novo
- 1:40,000-50,000 (rare)
- ⇒ • Bilateral vestibular schwannomas
- Ocular manifestations:
 - Cataracts (especially PSC)
 - Optic nerve sheath meningioma
 - Combined hamartoma of the retina and the retinal pigmented epithelium

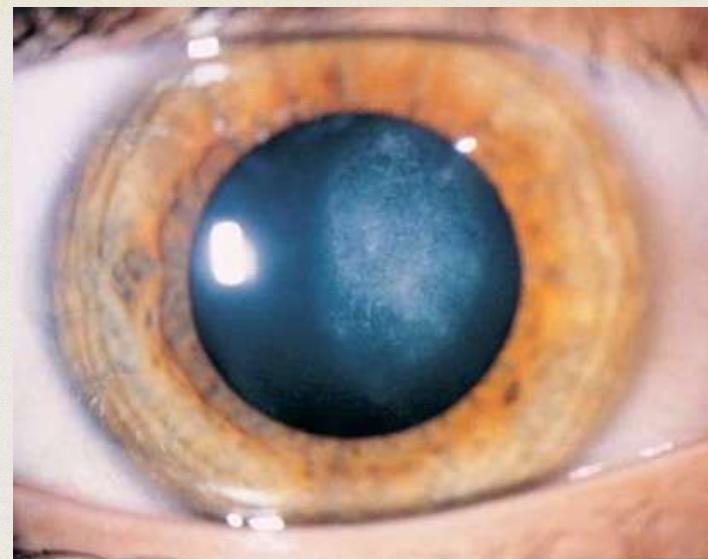
NF2 is caused by a mutation of the Merlin gene, a tumor suppressor gene, on chromosome 22

lots of tumors



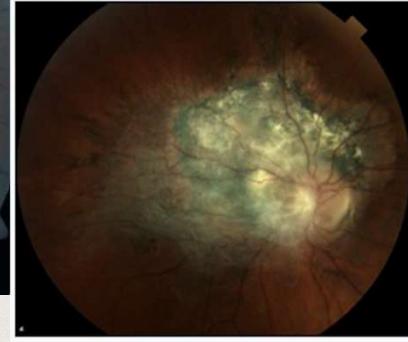
Red arrow shows optic sheath meningioma. Lower MRI (photo from neurology.org) shows bilateral gadolinium enhancing masses in cerebellopontine angles (large white arrows) with extension into the internal auditory canals (small white arrows), e.g. acoustic (vestibular) schwannomas. The black arrows show extra-axial masses consistent with meningiomas.

Posterior Subcapsular (PSC) CATARACT



PSC also often seen in diabetes, systemic steroid use. NOT pathognomonic for neurofibromatosis!

COMBINED HAMARTOMA OF RETINA AND RPE



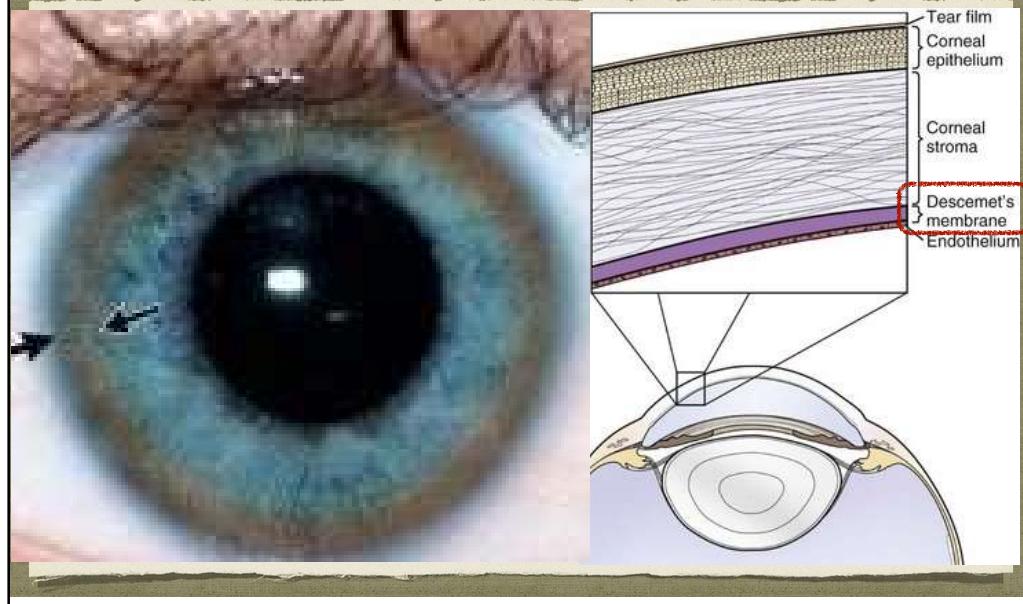
Combined Hamartoma of the Retina and the Retinal Pigment Epithelium in a 24-year-old Female.
Courtesy of Stephen Schwartz, M.D.

very dramatic

WILSON'S DISEASE

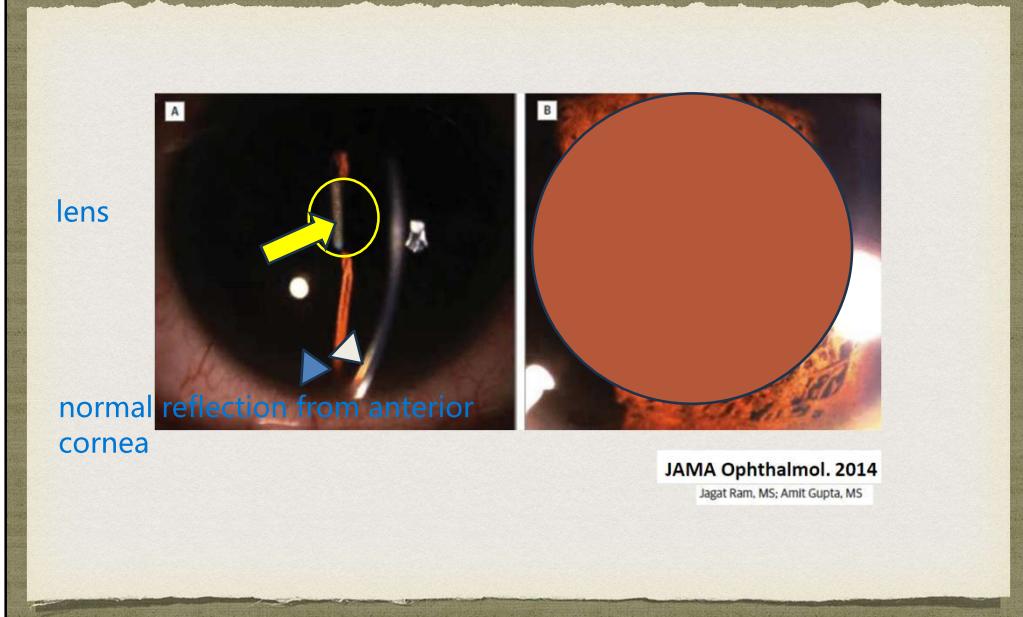
- Rare autosomal recessive disease that results in defective copper transport in liver
 - Toxic copper buildup in liver, brain, kidney, eyes
- Asymptomatic **Kayser-Fleischer Rings**
- Classic **Sunflower Cataract** in children
- Treatment: lifetime penicillamine chelation

KAYSER-FLEISCHER RING IN WILSON'S DISEASE



Contrast this to arcus senilis, lipid deposits at descemet's membrane in 60% of people by age 60
gray ring - depositions at same level but is cholesterol

Sunflower cataract in Wilson's Disease



Typically seen in late childhood/early adolescence. Reversible copper deposition under the anterior capsule, not a true cataract

VASCULAR DISORDERS

Hypertension

Emboli

Sickle Cell Syndrome

HYPERTENSIVE RETINOPATHY



- Mild: arteriolar narrowing, sclerosis, thickening of vessel walls
 - “Copper wire,” “silver wire” appearance
 - **Arteriovenous nicking** can lead to **vein occlusion**
- Moderate: Exudative stage with breakdown of blood-retina barrier, necrosis of vessel walls, exudation of blood and lipids, retinal ischemia
 - Microaneurysms, hemorrhages, hard exudates, **cotton-wool spots** (infarcts of nerve fiber layer)
- Severe: may result in bilateral **optic nerve edema** and exudative retinal detachment
 - BP of 180/120 mmHg or higher — hypertensive emergency with end organ damage

reality a lot of people have both htn and DM

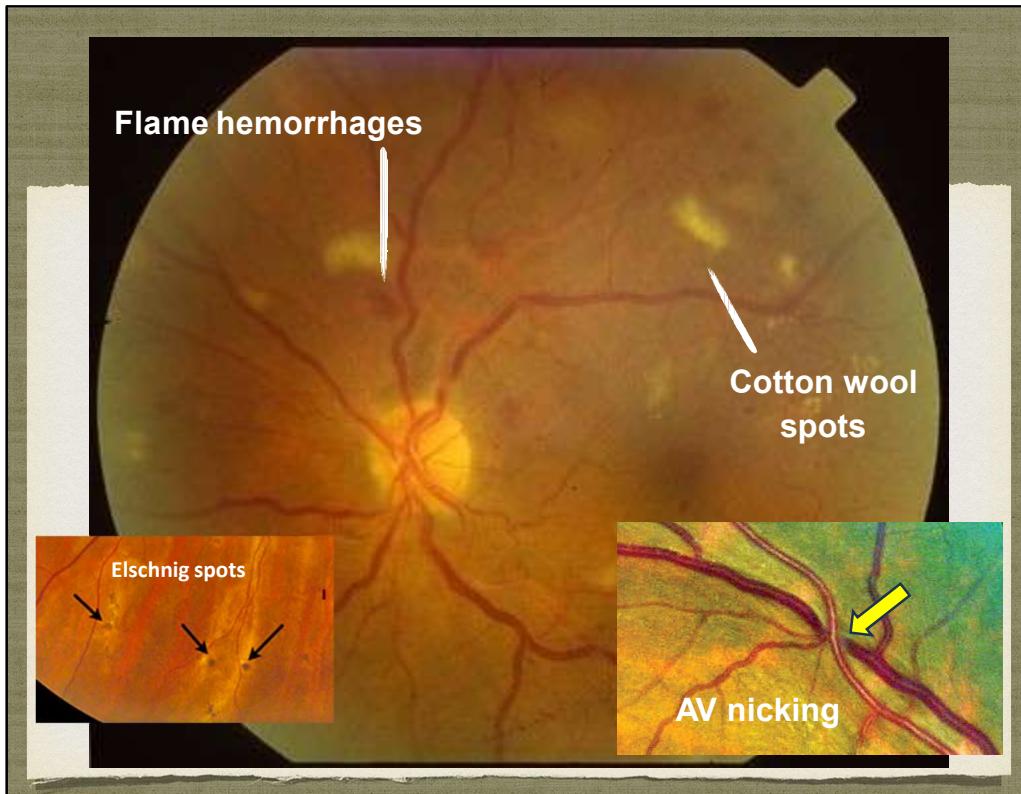
microaneurysms kind of like in diabetes

eye is an end organ - if getting damage there can have damage elsewhere

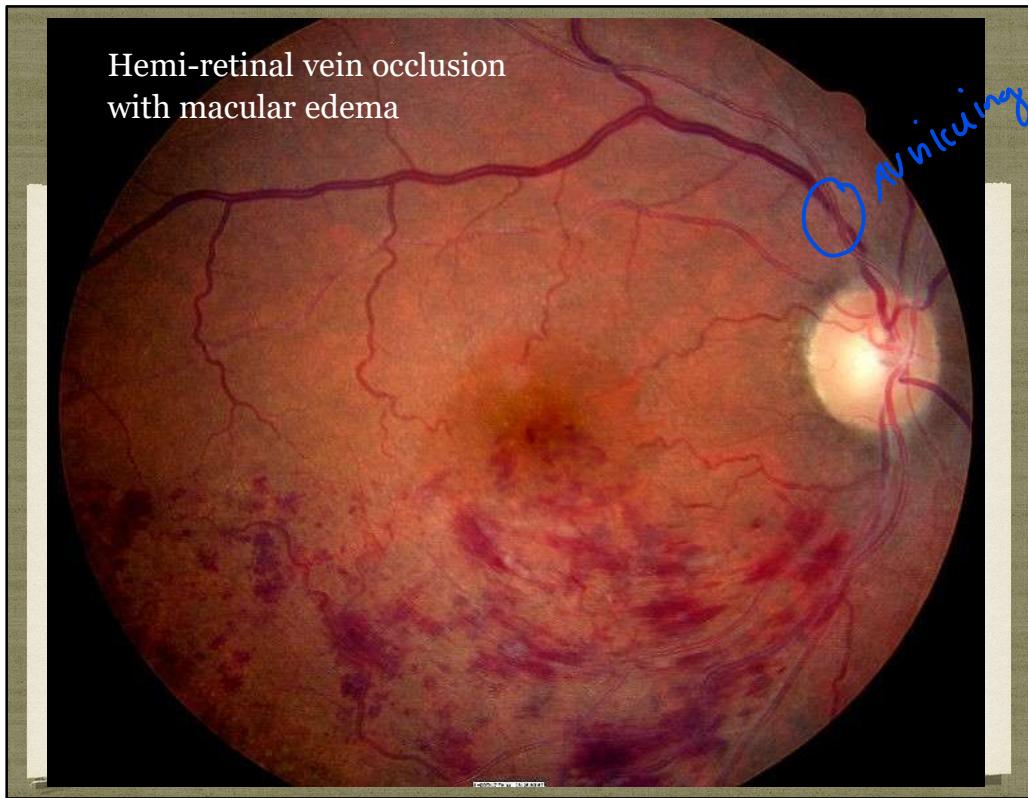
look more
feathery
when deeper

different than
laser spots

maybe also
copper wiring

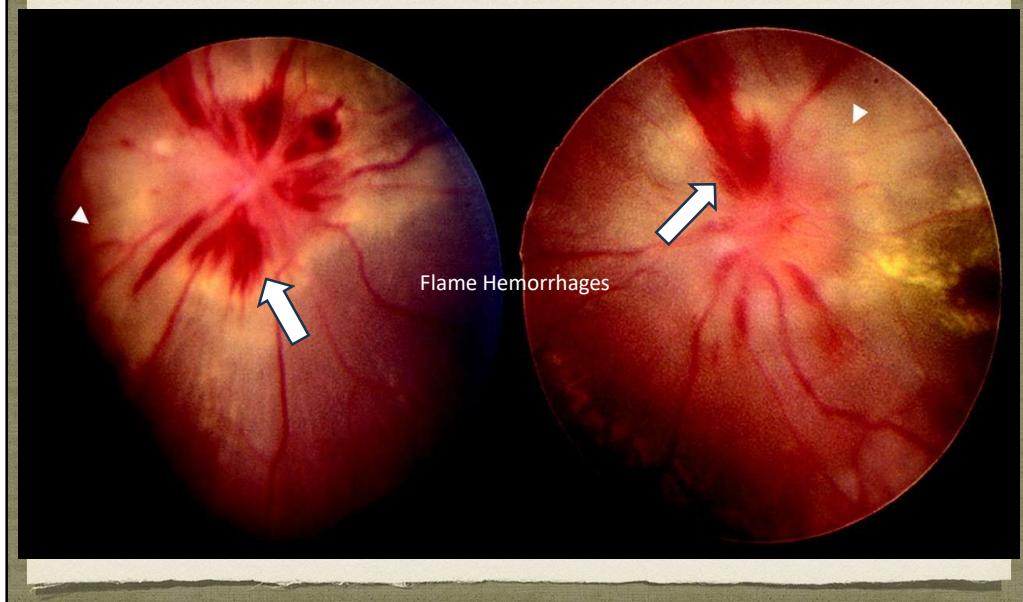


Vascular tortuosity. Black arrows show Elschnig spots (RPE infarcts, shows up as peripheral white spots with central hyperpigmentation deeper in retina than cotton wool spots) found in advanced hypertensive chorioretinopathy

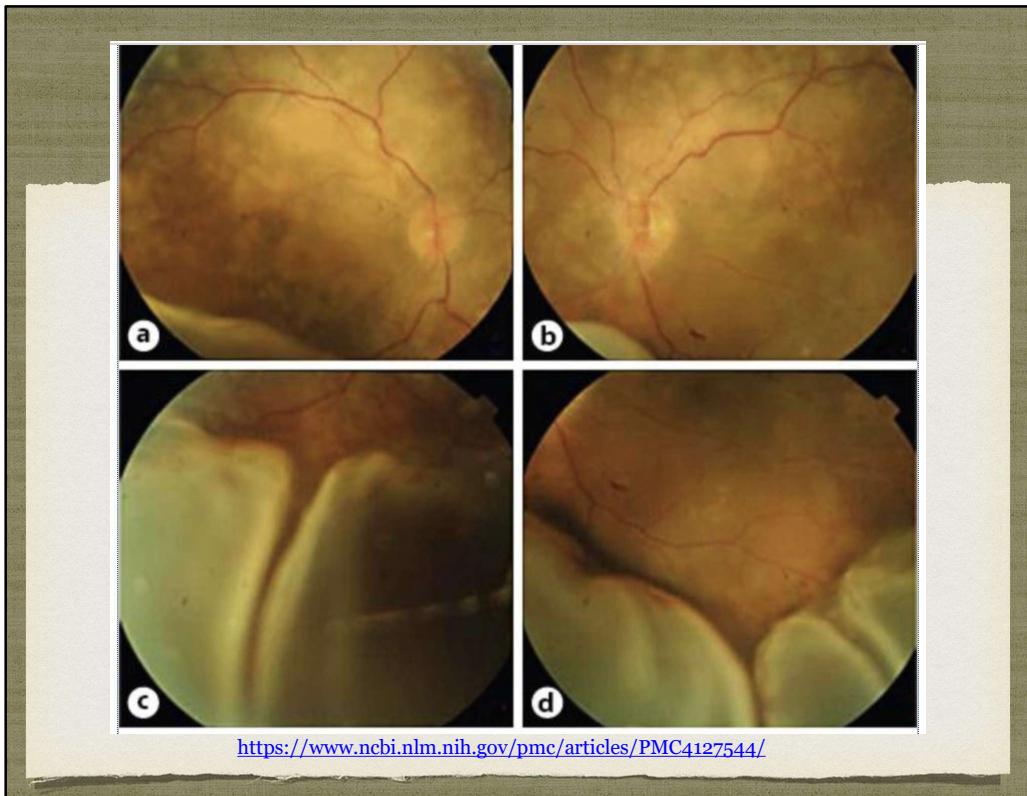


loss of normal foveal reflex
see av nicking
copper wiring look - not fully filling

BILATERAL OPTIC NERVE SWELLING



Flame hemorrhages can be found in other entities, too, like leukemia and acute bacterial endocarditis



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4127544/>

exudative retinal detachment

Serous retinal detachment with macular involvement due to hypertensive chorioretinopathy
get BP down

EMBOLI

- Manifests as acute painless loss of monocular vision
- Usually due to atherosclerotic/cholesterol plaques from ipsilateral carotid artery
- Can also be due to cardiac valvular disease, a-fib, coagulopathies, trauma, etc.
anything that can cause emboli to form

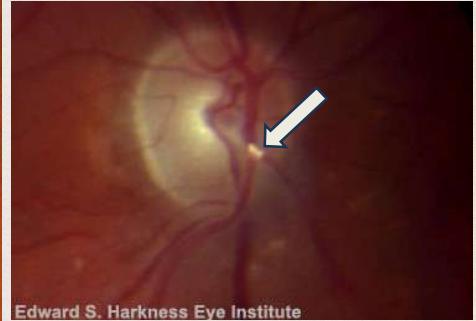
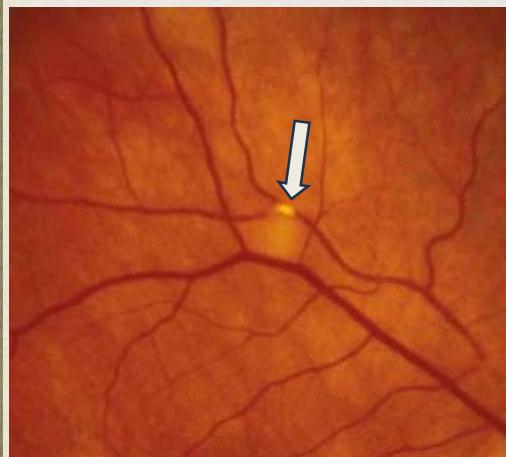
very rare that it's bilateral at the same time

SUSPECTED RETINAL ARTERY OCCLUSION



- **STROKE EQUIVALENT**, refer to ophthalmology to Confirm. If ophth not available, emergent stroke work-up
- Rule out giant cell arteritis which can rapidly blind the contralateral eye
- No proven treatment except lower IOP
- Poor prognosis
- Prevent sequelae such as macular edema and neovascularization

FIND THE HOLLENHORST PLAQUE



Edward S. Harkness Eye Institute

obvious finding but don't stay still but still have problems from temporary blood flow loss

Central Retinal Artery Occlusion



Table 2. Risk Factors Associated with CRAO and BRAO

- Age older than 70
- Atherosclerosis
- Diabetes Mellitus
- Endarteritis
- Glaucoma
- High Cholesterol levels
- Hypertension

Table 3. Differential Diagnosis in CRAO and BRAO

No cherry – red Spot

- Ophthalmic Artery Occlusion
- Commotio Retinae after trauma

Cherry- red Spot (Sphingolipidosis)

- Tay- Sachs
- Niemann – Pick type A

losing normal supports

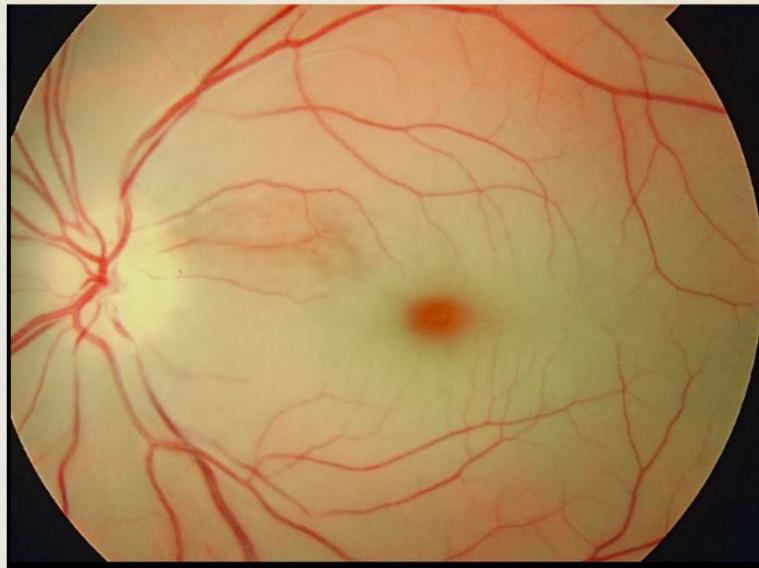
The sphingolipidosis diseases cause cherry red spots in very young patients due to accumulation of lipids in the ganglion cells of the macula.

ophthalmic artery fills the choroidal blood flow - cherry red spot
but if no choroidal flow no cherry red spot but still have embolus

CRAO with cherry red spot

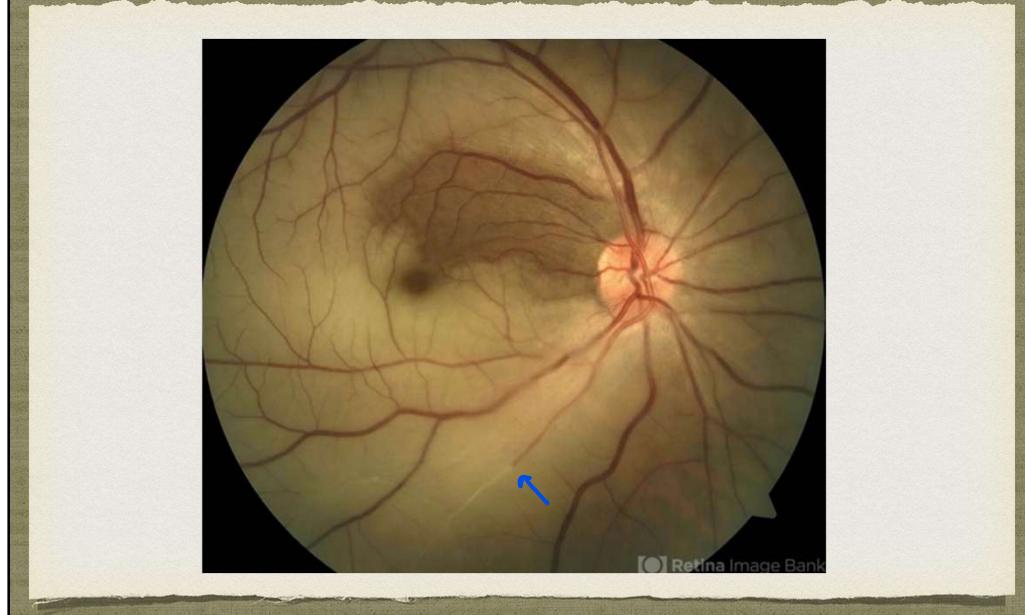


know what a
cherry red
spot looks like



Cherry Red spot due to relative transparency of the foveal retina, thus seeing normal circulation of the underlying choroid. There is no cherry red spot in ophthalmic artery occlusions because in those cases the choroidal circulation in addition to the retinal circulation is impaired.

CRAO with cilioretinal artery sparing



CRA in 20-40% normal population, from short posterior ciliary arteries rather than central retinal artery. If occluded in isolation need to consider GCA. Isolated CRA occlusion can be seen in conjunction with CRVO

SICKLE CELL RETINOPATHY

- May present as a proliferative or non-proliferative retinopathy
- More common with hemoglobin SC or S-Thal (less common in hemoglobin SS)
- Symptoms can be progressive vision loss or sudden visual loss, scotomas

Proliferative retinopathy in 33% SC patients and 14% S-Thal patients, but only 3% of SS despite the SS patients having the most severe systemic problems from their disease. Retinopathy due to occlusive disease caused by sickled erythrocytes.

less significant systemic usually have more eye findings

NON-PROLIFERATIVE SICKLE CELL RETINOPATHY



Black sunbursts are thought to be RPE migration and proliferation, possibly after hemorrhage, and are characteristic but not pathognomonic of sickle cell. Salmon patch hemorrhages are likewise common in sickle cell but not pathognomonic.

more peripheral than in posterior pole

SICKLE CELL RETINOPATHY

- Proliferative Retinopathy
 - Stage 1: Peripheral arteriolar occlusions
 - Stage 2: Peripheral arterio-venular anastamoses
 - Stage 3: Neovascularization
 - Stage 4: Vitreous hemorrhage
 - Stage 5: Retinal detachment
- First treat underlying disease sickle cell
- Ocular treatment may include laser photocoagulation, injection of anti-VEGF agents

tends to happen in far periphery first as opposed to DR where it starts in posterior pole first

STAGE 1: ARTERIOLAR OCCLUSIONS

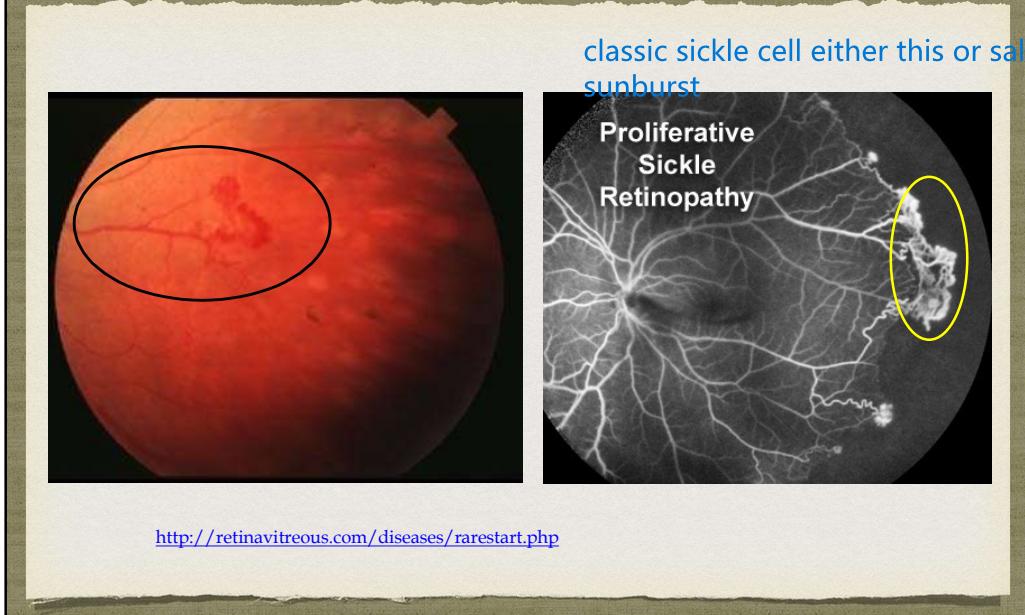


Fluorescein angiography. Note how the blood flow in the arteriole simply disappears peripheral to the occlusive site (red arrow)

STAGE 3: NEOVASCULARIZATION

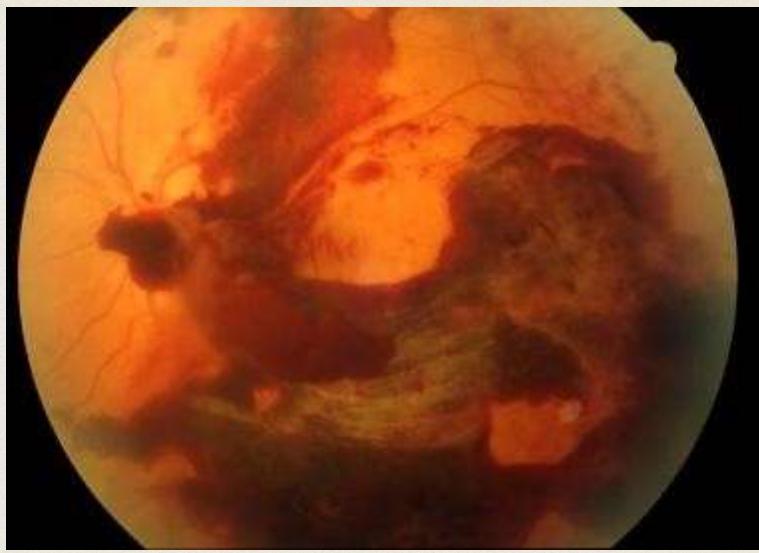
will send out VEGF

no blood vessels peripheral to that - like right at the end of the water where there's no more flow

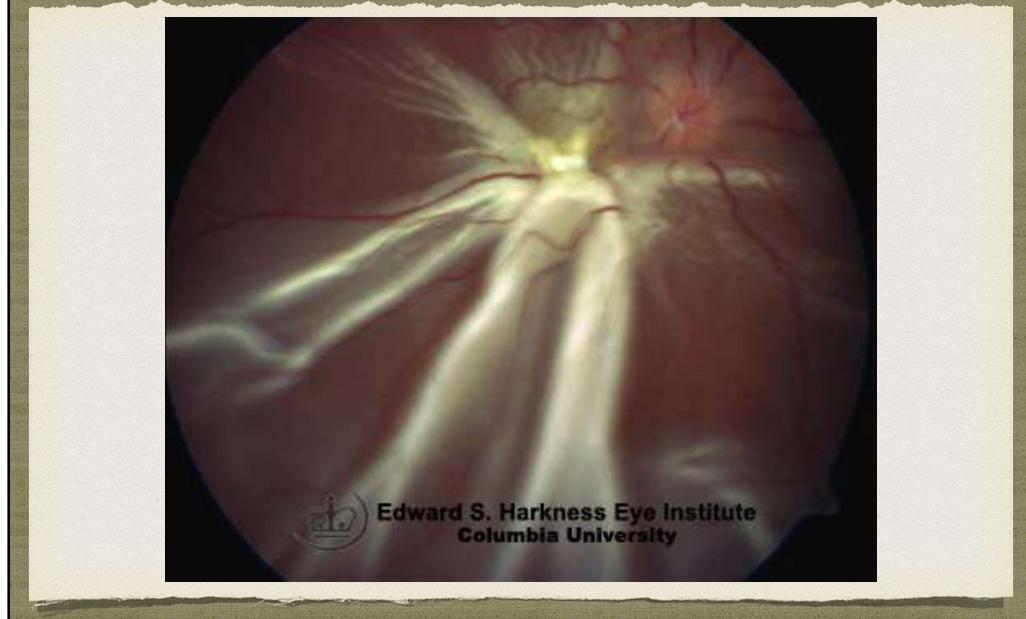


Sea Fan Retinopathy is classically associated with Sickle Cell, but can also sometimes be found in other diseases like thrombocytosis, sarcoidosis, and retinitis pigmentosa.

STAGE 4: VITREOUS
HEMORRHAGE



STAGE 5: RETINAL DETACHMENT



as neovascularization recedes can get tractional RD

ENDOCRINE DISORDERS

Diabetes Mellitus

Thyroid can cause a lot of problems so look at when considering things



DIABETIC RETINOPATHY

- The principle cause of vision loss in **patients ages 25 to 74**
- Affects 25% of all diabetics in the USA
- Standard of care: at least **annual** diabetic eye exam
- Visual loss occurs secondary to:
 - Macular edema **can happen even with well controlled diabetes**
- disturbing bc it's your central vision
 - Hemorrhage from new vessels
 - Retinal detachment
 - Neovascular glaucoma

type I - young even if really poor control do not tend to get DR

CDC : 40% of type 2 taking insulin have retinopathy at 5 years, 80% at 10 years. For all diabetics in US as of 2021 approximately 25% (9.6million)have retinopathy and of these 5%(1.8million) have vision threatening retinopathy. Retinopathy more common in age >65 (28% prevalence), least common age <25 (13% prevalence)

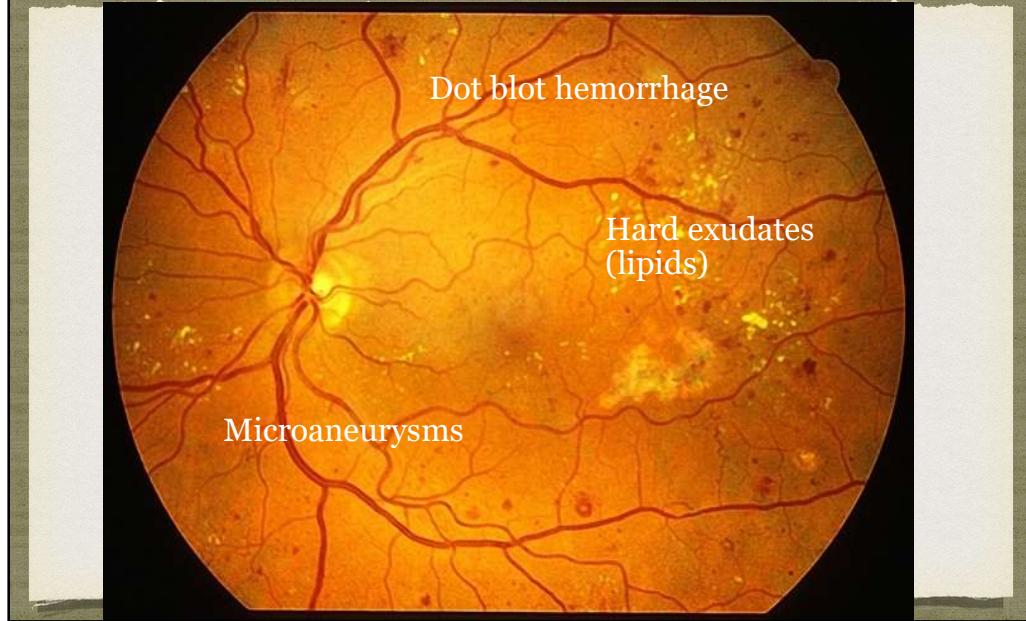
now getting better at controlling glucose so DR can go away too

PREVENTION OF LOSS OF VISION IN DIABETES BY FREQUENT EYE EXAMS

- First eye exam (ophthalmologist)
- 5 years after diagnosis for ages 0-30
- At the time of diagnosis for ages >30
realistically get eye exam early if possible
- Follow-up exams: Yearly
- Pre-existing DM and Pregnancy: first trimester and possibly every 3 months
accelerator for DR

There is accelerated progression of retinopathy during puberty and pregnancy

NONPROLIFERATIVE DIABETIC RETINOPATHY (NPDR)



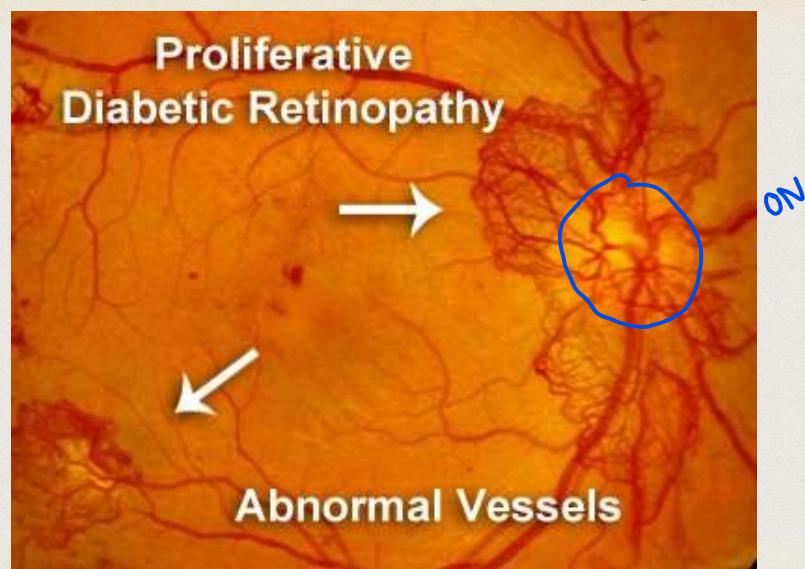
Microaneurysms are the earliest findings, tiny red dots that may or may not be surrounded by exudate. Dot blot hemorrhages are intraretinal.

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)



- Retinal ischemia triggers release of neoangiogenic factors (VEGF)
- **Neovascularization** leads to:
 - Vitreous hemorrhage
 - Tractional retinal detachment
- Symptoms range from normal vision, blurry vision, scotoma, to loss of vision

PDR: NVD AND NVE



PDR WITH VITREOUS HEMORRHAGE



PDR WITH VH AND TRACTIONAL RD

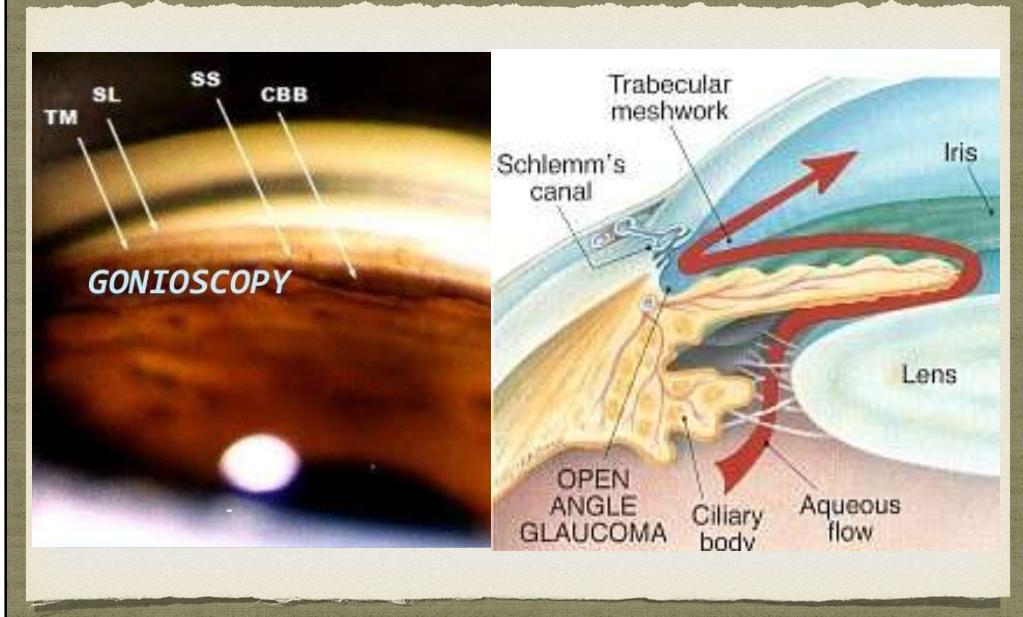


PDR WITH IRIS NEOVASCULARIZATION

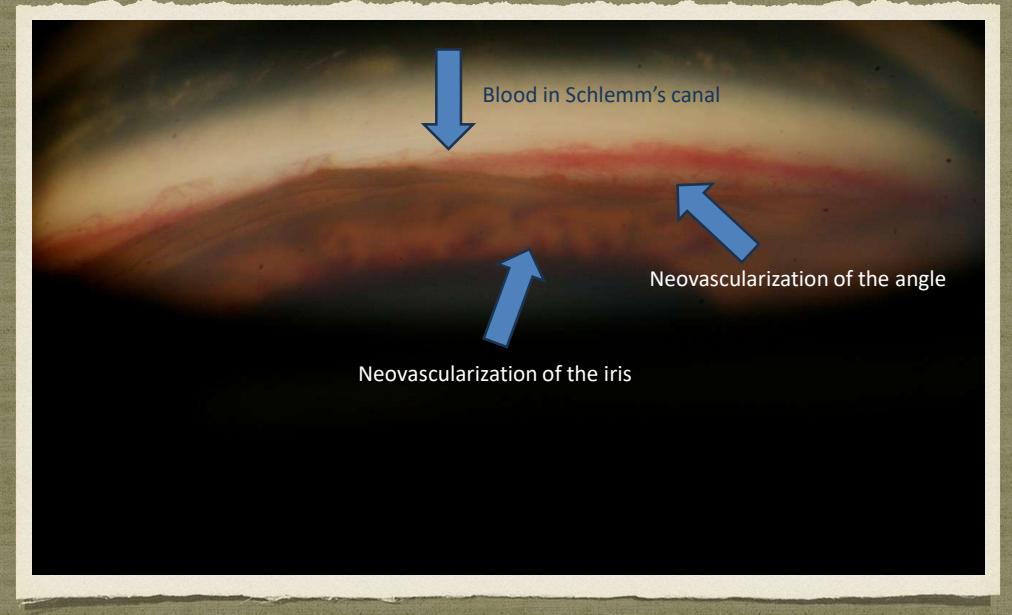
EyeRounds.org



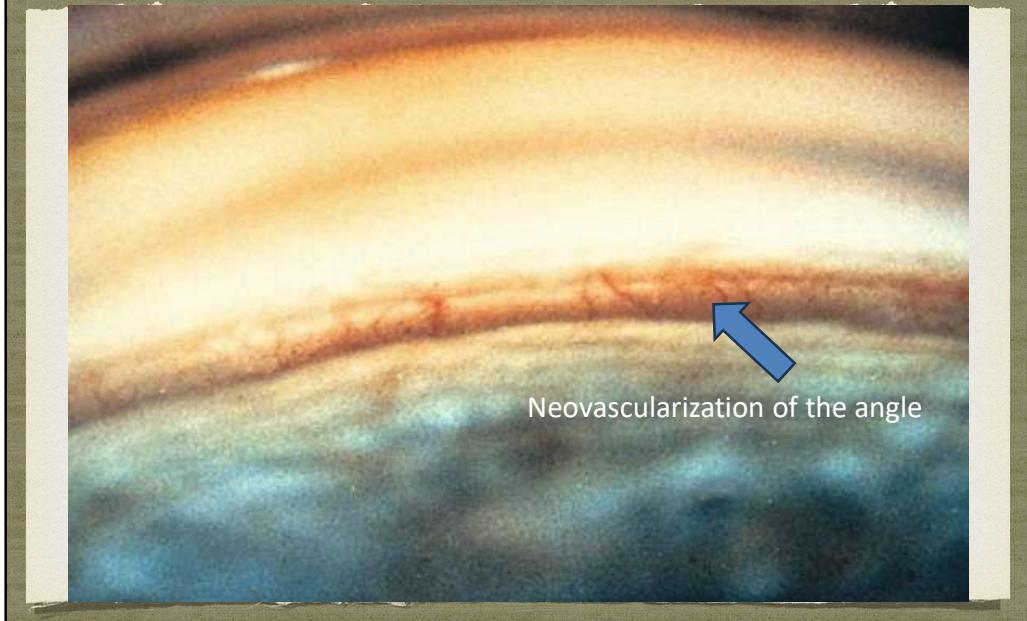
NEOVASCULARIZATION OF THE ANGLE LEADS TO GLAUCOMA



NEOVASCULARIZATION OF THE ANGLE LEADS TO GLAUCOMA



NEOVASCULARIZATION OF THE ANGLE LEADS TO GLAUCOMA



Neovascularization of the angle

VISION WITH PDR



Normal vision



Vision with
diabetic retinopathy

can't see peripherally but can see centrally = retinitis pigmento

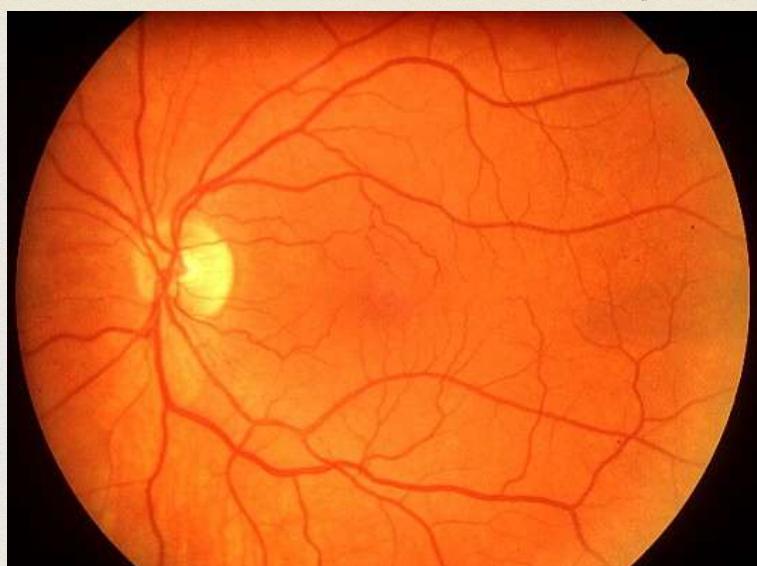
can't see center = macular

splotchy = other issues like DR

DIABETIC MACULAR EDEMA

- Loss of vision
- In eyes with NPDR or PDR
- Macular edema from fluid leakage, can lead to ischemia
- Diagnose with fundus exam, fluorescein angiography, and OCT

NORMAL RETINA

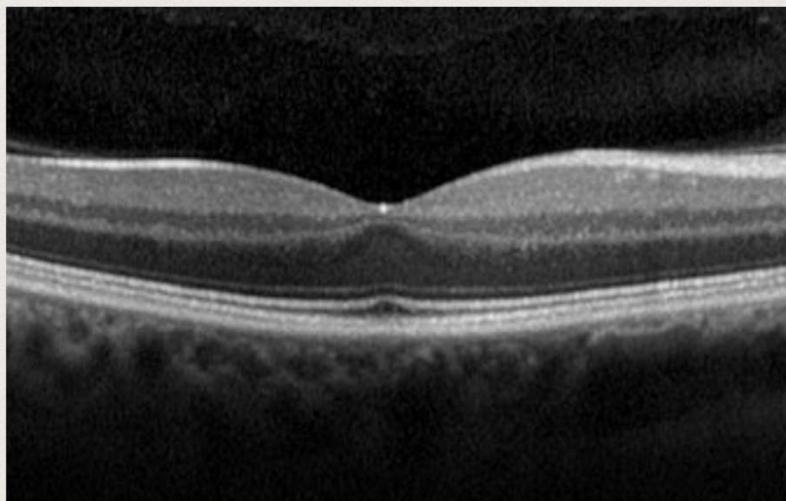


DIABETIC MACULAR EDEMA

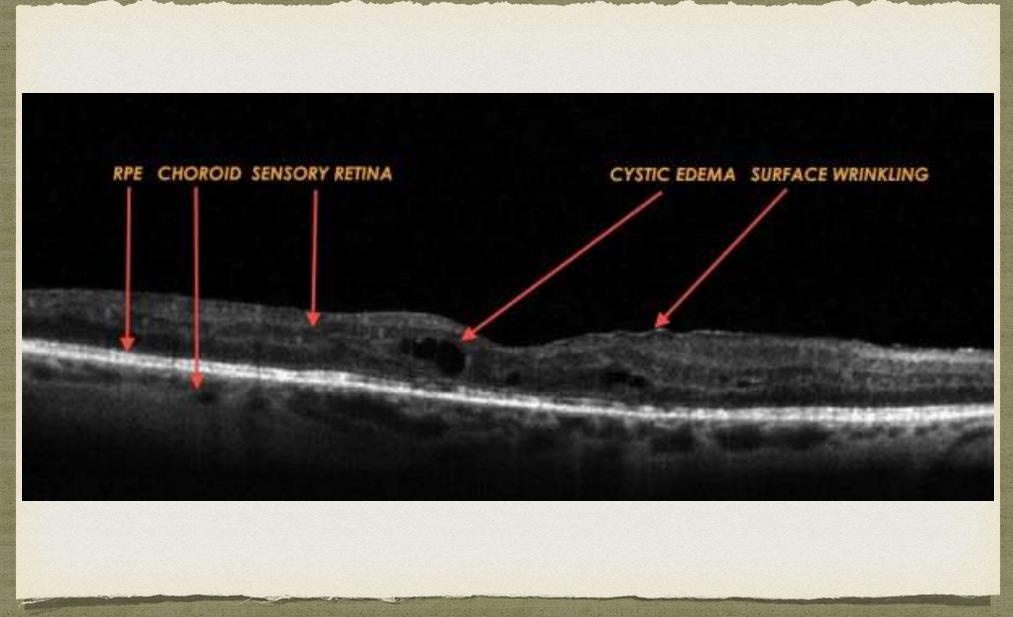


Mild macular edema on left, more severe macular edema and exudates on the right (note the laser scars). Bottom image shows OCT with macular edema and exudates.

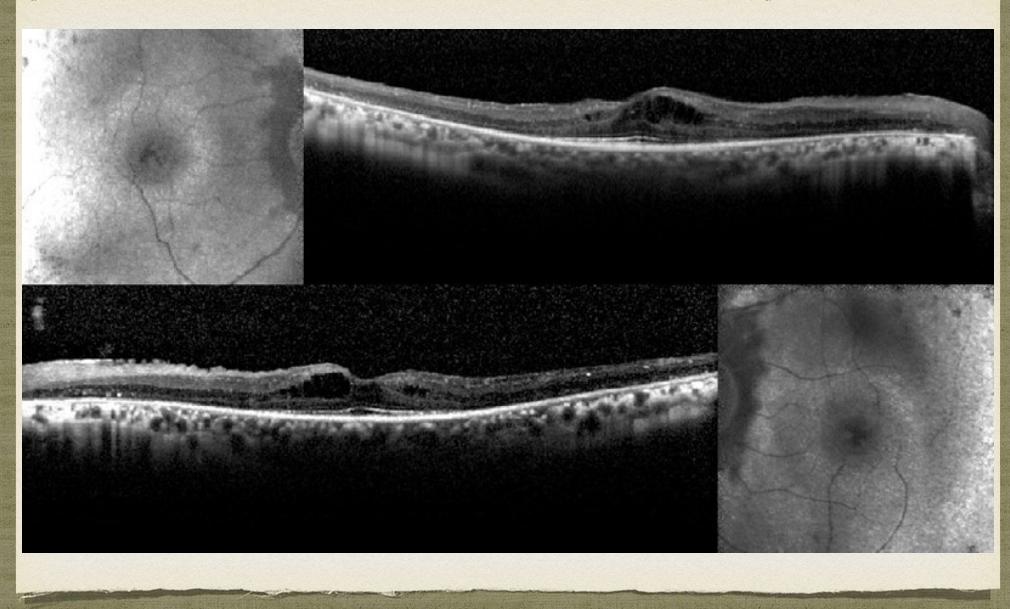
Normal OCT of the Macula



DIABETIC MACULAR EDEMA



DIABETIC MACULAR EDEMA



lose normal contour

FLUORESCEIN ANGIOGRAPHY OF MACULAR EDEMA



see where fluid leaks out

TREATMENT OF PDR AND DME

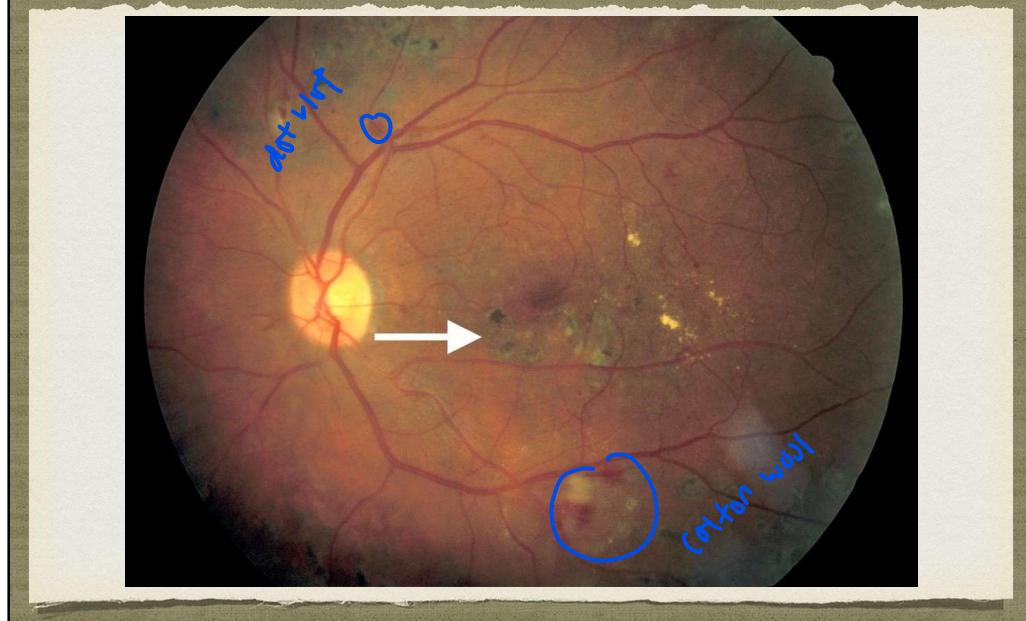
- **Maximize blood glucose control**
- Intraocular injection of VEGF inhibitors for macular edema
- Focal laser of leaking macular vessels for macular edema
- Panretinal laser photocoagulation if high risk (HRPDR) to prevent further neovascularization light laser to not kill the cells
- Vitrectomy for non-clearing vitreous hemorrhage

ANTI-VEGF INJECTIONS FOR PDR AND MACULAR EDEMA



tetracaine drop
not going into avascular zone to not cause retinal detachment
25 gauge or smaller to be self sealing

FOCAL LASER OF LEAKING AREAS



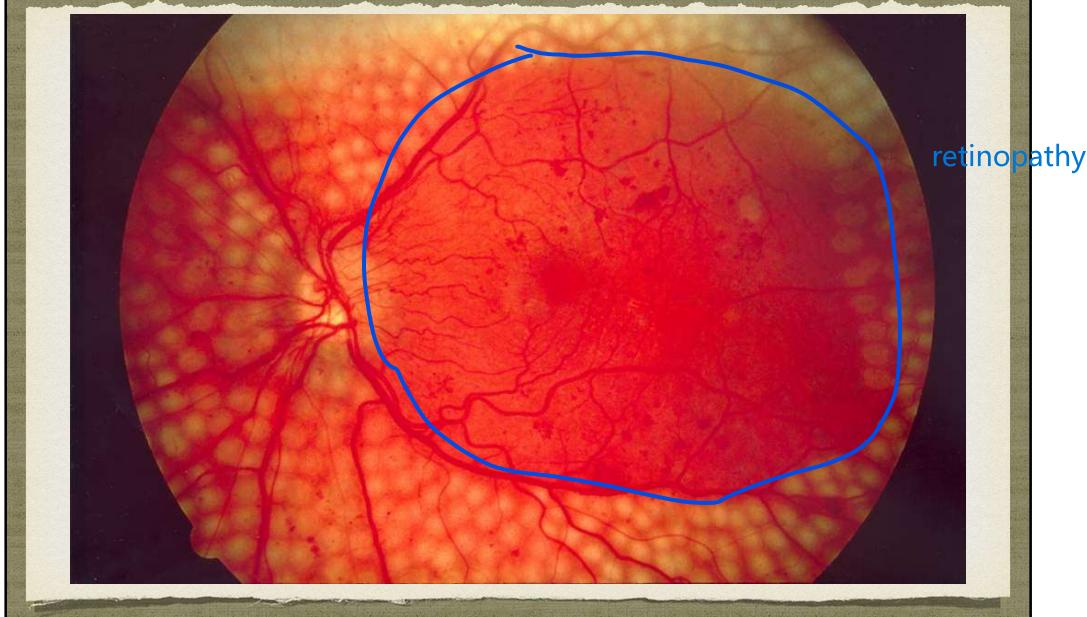
old scar - has pigmentations

PANRETINAL PHOTOCOAGULATION (PRP)

- Laser destroys a portion of the peripheral retina and thereby decreases release of vasoproliferative growth factors
- Also creates multiple choroid-to-retina adhesions that limit progression of retinal detachment
- Treatment reduces risk of blindness by 50% (independent of blood glucose management)

sacrificing peripheral retina to save central retina

PRP



new PRP looks like fawn spots - yellow-white spots
full PRP can be ~5000 spots usually spread out over a couple of treatments sometimes done with a retrobulbar block bc eye can be really sore

THYROID EYE DISEASE (TED)



can also be
seen in
hypothyroidism
bc is
autoimmune

- Most commonly in Grave's disease - an autoimmune disorder affecting both the thyroid gland (hyperthyroidism) & retro-orbital tissues
- Manifestations:
 - Proptosis/exophthalmos
 - Periorbital edema
 - Lid retraction
 - Exposure keratopathy / corneal drying
 - Compressive optic neuropathy with vision loss **eye is going forward**
 - Restrictive strabismus with diplopia

80% of TED in hyperthyroid (Grave's). 10% in hypothyroid (Hashimoto's). In 80% of patients TED signs appear within 18 months of systemic thyroid manifestations like (in graves) tachycardia, heat intolerance, weight loss. Active phase can last 2-3 years (longest in smokers), typically then there is a stable or regressive phase, but reactivation can occur.

EXOPHTHALMOS & LID RETRACTION



sense on strings and being pulled back = lid retraction

Bilateral exophthalmos and eyelid retraction with scleral show

mall diagnoses bc is obvious sign

EOM ENLARGEMENT



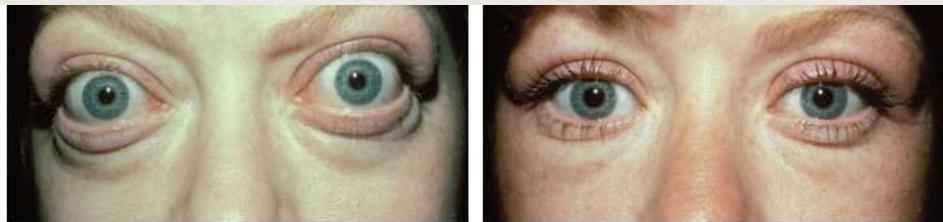
Fusiform enlargement due to tendon sparing,
most commonly IR then MR
but could be all

restrictive strabismus - can change day to day

save the corneal
first
artificial tears
maybe ointment

TREATMENT OF TED

- Lubrication for corneal exposure
- Smoking cessation
- Steroid, possibly radiation (controversial), or optic sheath decompression for optic nerve compression; teprotumumab-trbw for less vision threatening sx
- **Surgery must be done in correct order:** orbital decompression, strabismus correction, lid repair



Teprotumumab-trbw is marketed under the brand name Tepezza. The monoclonal antibody that inhibits the insulin-like growth factor -1 receptor is administered as a series of 8 IV infusions over 24 weeks and the full treatment costs approximately \$386,500. There are several side effects, many are infusion effects, but currently there are over 100 cases of reported severe hearing loss which may be permanent. These cases are being further investigated but the FDA has put out a warning regarding this potential side effect.

ppl still need surgery bc getting treated early and thyroid eye disease takes ~2 years to burn c support patient as go through natural course of disease

want to tx in the right order: 3 wall decompressions to create space for swelling to go -
makes strabismus worse
then strabismus surgery
then eyelid repair bc of sheared sheaths of the muscles

radioactive iodine will help with hyperthyroidism but doesn't do anything about thyroid eye di autoimmune and still attacking orbit

AUTOIMMUNE DISORDERS: NEUROLOGIC

- Myasthenia gravis
- Multiple sclerosis

MYASTHENIA GRAVIS (MG)

- Antibodies against acetylcholine receptor at the neuromuscular junction
- Proximal limb weakness, difficulty swallowing, chewing, ptosis, diplopia
- Note normal pupils — different from CNIII palsy



Myasthenic crisis: difficulty speaking without stopping to catch breath, choking on saliva (constant cough, drool), inability to hold head up, difficulty breathing. ER!

ice pack test - see if cold makes it better = myasthenia

MYASTHENIA GRAVIS

- REFER EMERGENTLY for new onset diplopia along with lid abnormalities, orbital signs, or pupil sign
Ddx include thyroid eye disease, cranial neuropathy, intracranial bleed / fistula / mass
- MG diagnosed primarily on exam, confirm with blood test, possibly single fiber EMG
- Thyroid studies and a chest CT to check for thymoma
- Treatment:
 - Anticholinesterase inhibitors: pyridostigmine (Mestinon)
 - Symptomatic management of ptosis & diplopia

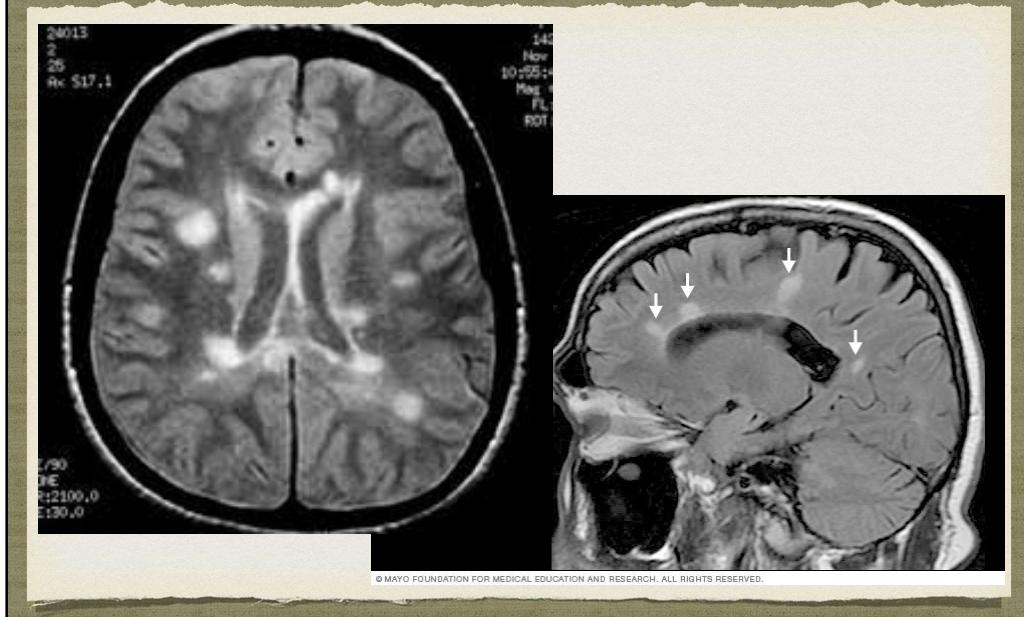
can't do surgery bc it changes everyday
most pts not in amblyopic age range are adults so
already
developed

MULTIPLE SCLEROSIS

- Optic neuritis
 - Unilateral vision loss over hours or days and **pain with eye movement**
 - 30% of patients have disk edema at presentation
- Diplopia due to internuclear ophthalmoplegia (INO)
 - INO results from a demyelinating lesion in the medial longitudinal fasciculus (MLF) pathway

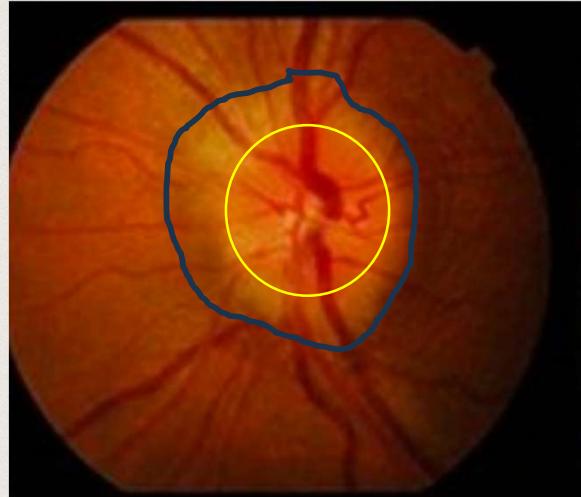
often will have APD may be mild
swinging flashlight test - pupil slightly dilating when shine light = optic neuritis

MRI WARRANTED FOR PREDICTION OF DISEASE PROGRESSION



Demyelinating lesions seen as hyperintense on T2 and FLAIR. Triangle lesion perpendicular to ventricle seen on parasagittal image = Dawson's fingers. The Optic Neuritis Treatment trial (1988-1991) followed 454 patients and then had extended follow up for 15 years. About 50% of the optic neuritis patients developed clinically evident MS but it differed based on initial MRI presentation. Only 25% of patients with optic neuritis and no lesions on initial brain MRI developed MS vs. 72% of optic neuritis patients with 1 or more demyelinating lesions on initial MRI.

Optic Disc Edema

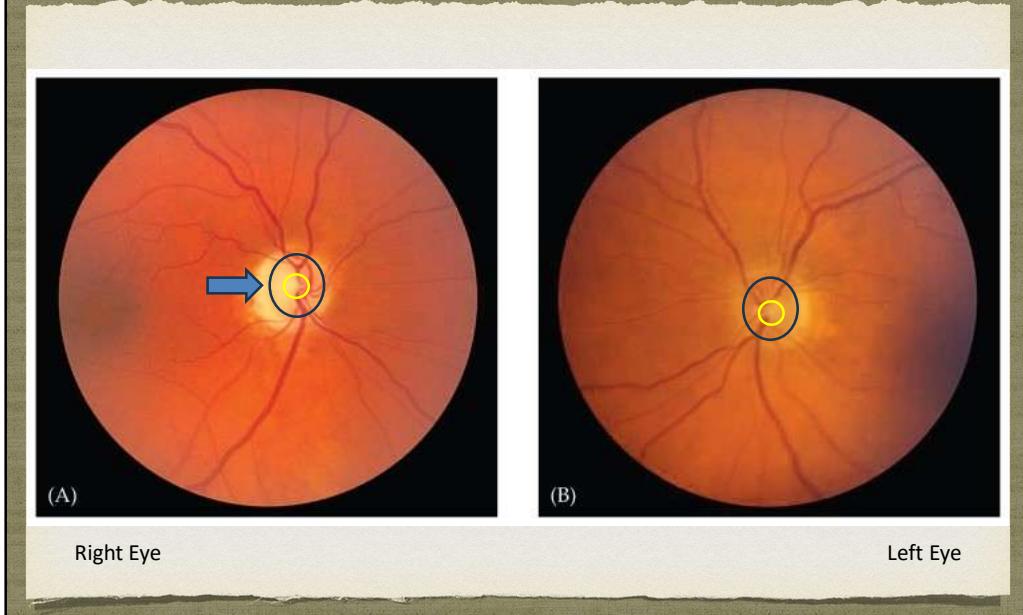


Differential on unilateral optic disc edema? Vascular (NAION, AION), compressive (TED, tumor), infiltrative/inflammatory (tumor, optic neuritis, syphilis, lyme, intracranial hypertension with its own differential, diabetic papillitis). Note that TED, infectious, ICH, diabetic papillitis can also be bilateral but often asymmetrical. HISTORY!

slit lamp can see 3d view and see it lifting
syphilis, Lyme disease, intracranial HTN

OLD RIGHT OPTIC NEURITIS

macula always temporal if using direct
when using slit lamp everything is upside down and backward



old - will get pallor = longer term systemic disease

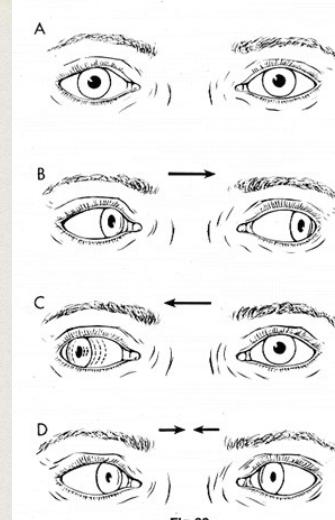
When looking at bilateral fundus photos, it is as if the patient is sitting in front of you; therefore, the image on the examiner's left is actually the patient's **RIGHT** eye, and the image on the examiner's right is the patient's **LEFT** eye. Note the pallor of the right eye disc (photo on the left). Compare to normal looking left eye disc (photo on the right). Takes from 3-6 weeks after ischemia of axons for pallor to set in

LEFT INO FROM MLF LESION

Normal eye movements on left gaze

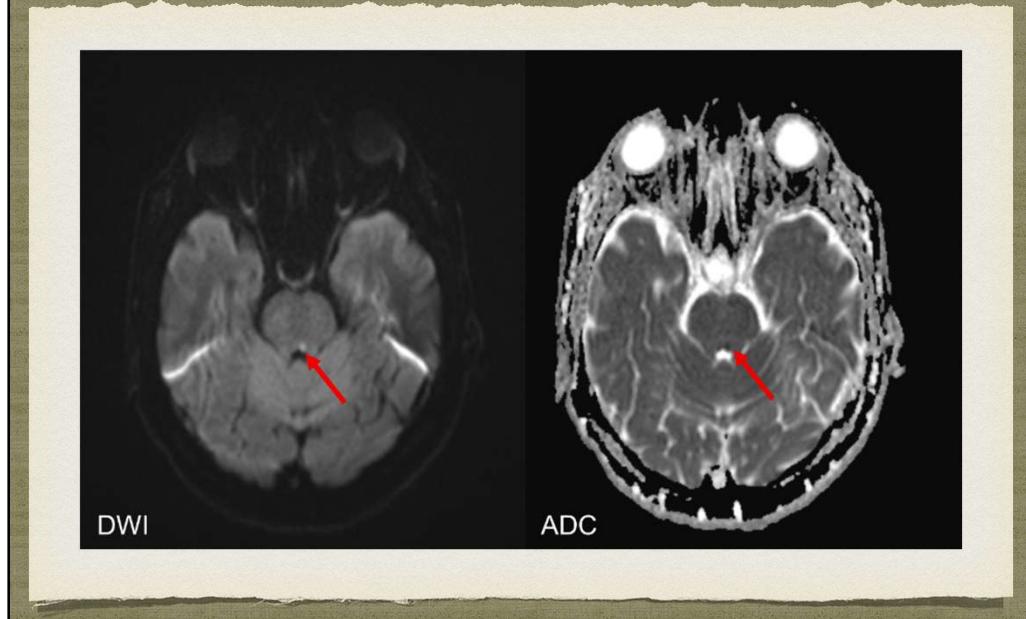
Failure of left eye to adduct on right gaze
with nystagmus of abducting eye

Preserved convergence (indicating
normal muscle function)



INO: 38% due to infarct (87% unilateral), 34% due to MS (73% bilateral), rest due to unusual causes like tumor, infection, trauma, vasculitis, hemorrhage, tentorial herniation. Take home point is that if bilateral INO and young person, think MS. If unilateral INO and older patient, think stroke. Lesion in MLF affects yoked horizontal eye movement but usually the fibers of the convergence pathway (CN3) are spared.

MRI WARRANTED



Hyperintense pontine lesion on diffusion weighted imaging (DWI) and hypointense on apparent diffusion coefficient (ADC) imaging in area of left MLF

AUTOIMMUNE/INFLAMMATORY DISORDERS

- Seronegative spondyloarthropathies
- Sjogren's syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sarcoidosis
- Inflammatory Bowel Disease

OCULAR INFLAMMATION

- Conjunctivitis
- Episcleritis
- Scleritis
- Keratitis
- Uveitis: anterior, intermediate, posterior
(retina and optic nerve)

EPISCLERITIS AND SCLERITIS

- Most episcleritis not associated with systemic disease
- Scleritis up to 50% associated with systemic disease, top culprits:
 - **Rheumatoid arthritis**
 - IBD
 - ANCA vasculitis
 - Relapsing polychondritis
 - TB
 - Syphillis
 - Herpes zoster ophthalmicus
 - Lyme



Top picture: diffuse episcleritis in polyangiitis. Bottom picture: nodular episcleritis in Crohn's disease. Episcleritis will blanch with instillation of phenylephrine, the deeper vessels affected in scleritis will not.

tx with topical and oral nsails

RHEUMATOID ARTHRITIS

- Chronic systemic inflammatory joint disease
- Ocular effects
 - Keratoconjunctivitis sicca: burning irritation, foreign body sensation, photophobia
 - Filamentary keratitis: epithelial debris & strands with adherent mucous painfully attached to the corneal surface
 - Sterile corneal melt **sterile peripheral ulcers**
 - Scleritis

fluorescein staining
make sure cornea stays hydrated

RHEUMATOID ARTHRITIS



Figure 1: Left eye showing peripheral corneal ulcer with thinning in the lower part.

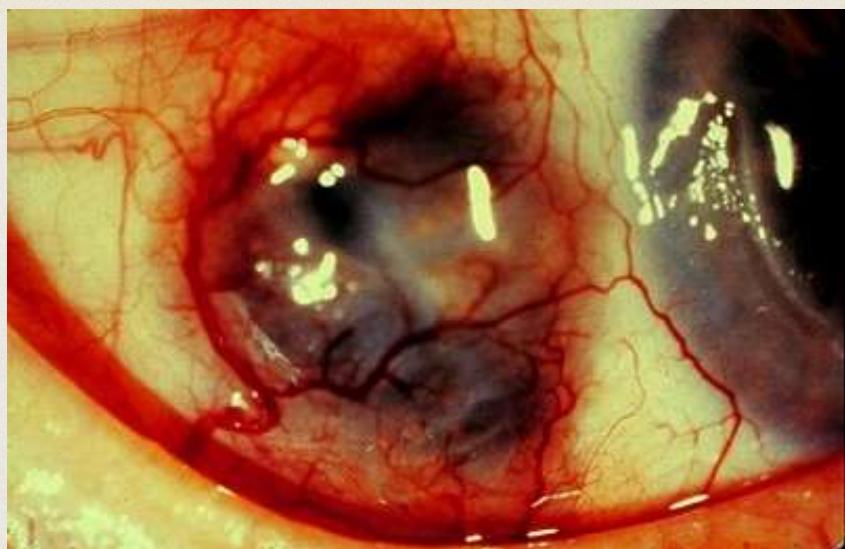
Image from Reddy, J Clin Exp Ophthalmol 2019, 10:3

NON-NECROTIZING SCLERITIS IN RA



purple bc seeing underlying uvea bc white sclera is so thin
necrotizing is red and angrier looking

NECROTIZING SCLERITIS IN RA



SJOGREN'S SYNDROME

- An autoimmune disorder causing chronic dysfunction of the exocrine (lacrimal and salivary) glands
- Occurs most often in middle-aged women
- May be primary (no associated systemic disease) or secondary (associated with rheumatoid arthritis, lupus and other disorders)
- Diagnosis 2/3:
 - Ocular dryness score
 - +anti-SSA (Ro), +anti-SSB (La) OR +ANA and RF
 - Labial salivary gland biopsy

Anti-SSA and anti-SSB can also be found in Lupus as well as in healthy patients. Don't depend only on a lab test for a diagnosis.

SJOGREN'S SYNDROME

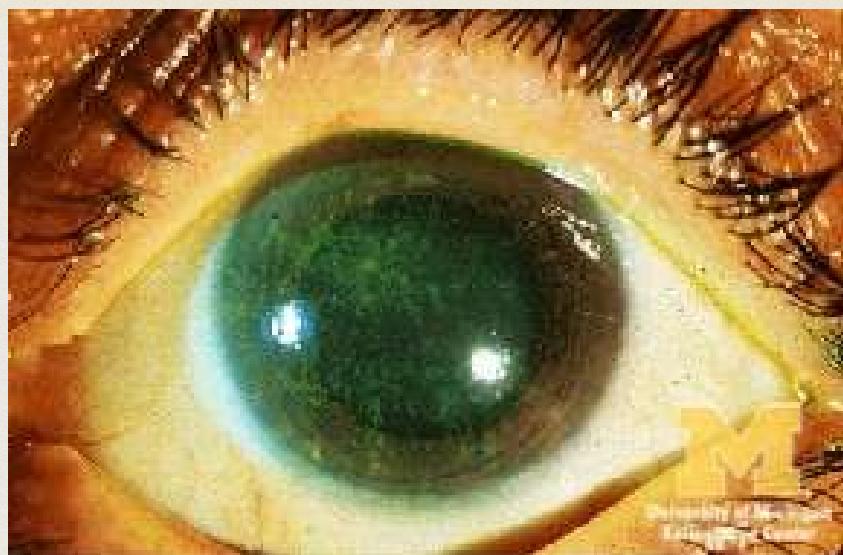
pieces of filter paper and put them in the eye can do with or without anesthesia and it measures different things (basal vs reactive)

- May use **Schirmer test**, which measures the quantity of tears secreted over 5 minutes but is not reliable
- Ocular Treatment:
 - All patients: Avoid medications which may cause dryness such as tricyclic antidepressants, antihistamines, diuretics, beta-blockers
 - Mild symptoms: Ocular lubrication w/o preservative
 - Moderate symptoms: Cyclosporine, punctal occlusion, serum tears



dry mouth = more cavities, gum disease, etc.
punctal occlusion - stopping the drain so eyes can be moisturized

KERATOCONJUNCTIVITIS SICCA (KCS) FLUORESCEIN STAIN



Diffuse epithelial drying in addition to non-existent tear lake

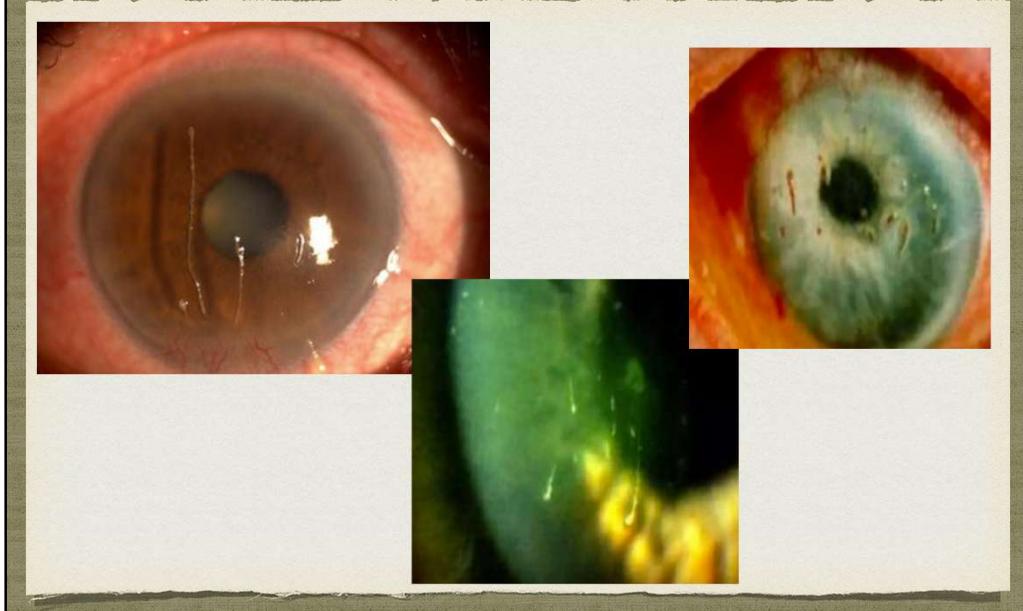
KCS ROSE BENGAL



Rose Bengal stains for devitalized cells or mucin deprived cells vs. fluorescein stains for areas of disrupted cell junctions; however rose Bengal is more irritating than fluorescein

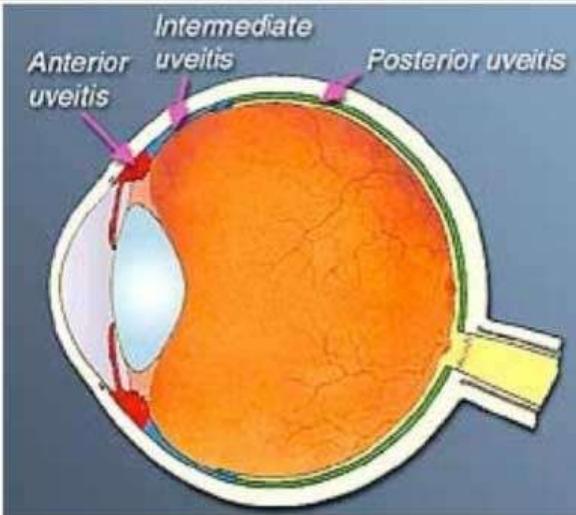
[rose bengal good alternative to fluorescein](#)

FILAMENTARY KERATITIS



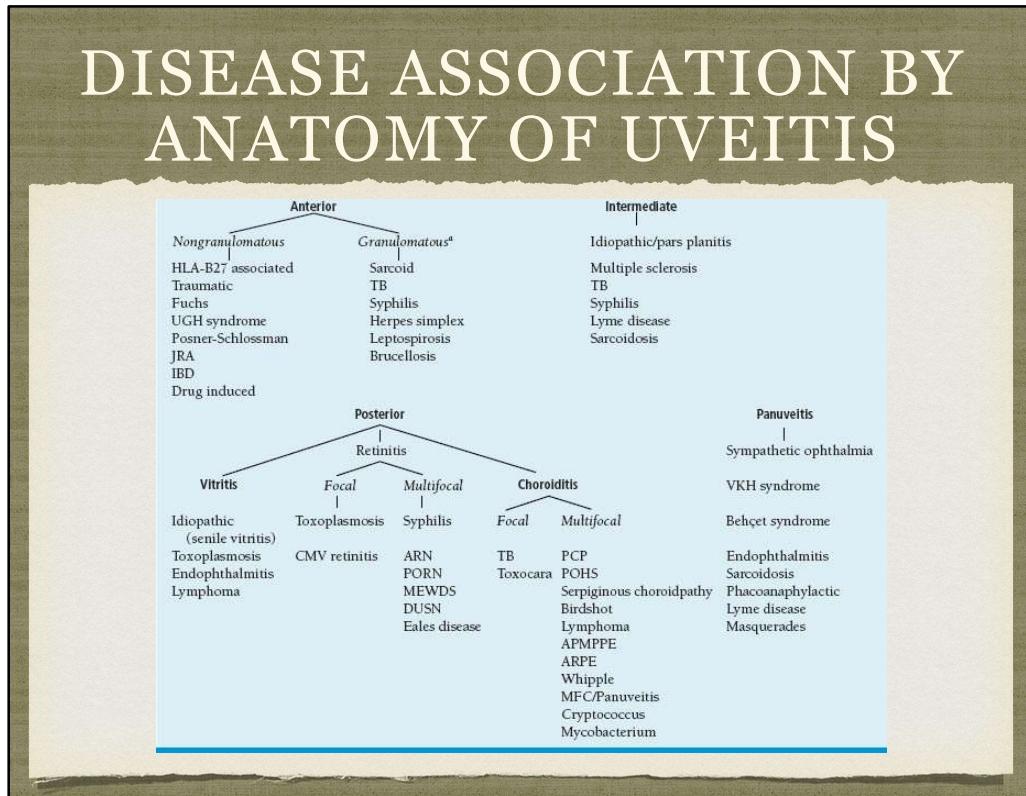
Filaments are mucin/cellular debris strands that connect at areas of devitalized epithelial cells.
Indicates an abnormal mucin to aqueous ratio,

TYPES OF UVEITIS

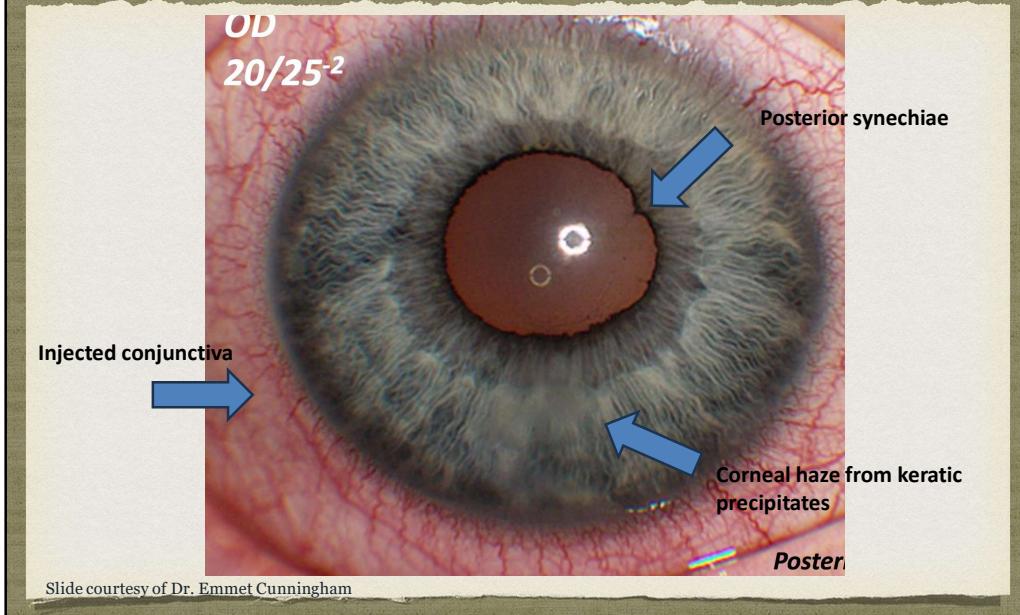


- Anterior:
 - Iris
 - Ciliary body
- Intermediate:
 - Pars plana
 - Vitreous
- Posterior:
 - Retina
 - Vessels
 - Choroid
 - Optic nerve
- Panuveitis

will not be tested but look how many things can cause problems in the eye
 syphilis, toxo, TB all show up in multiple places



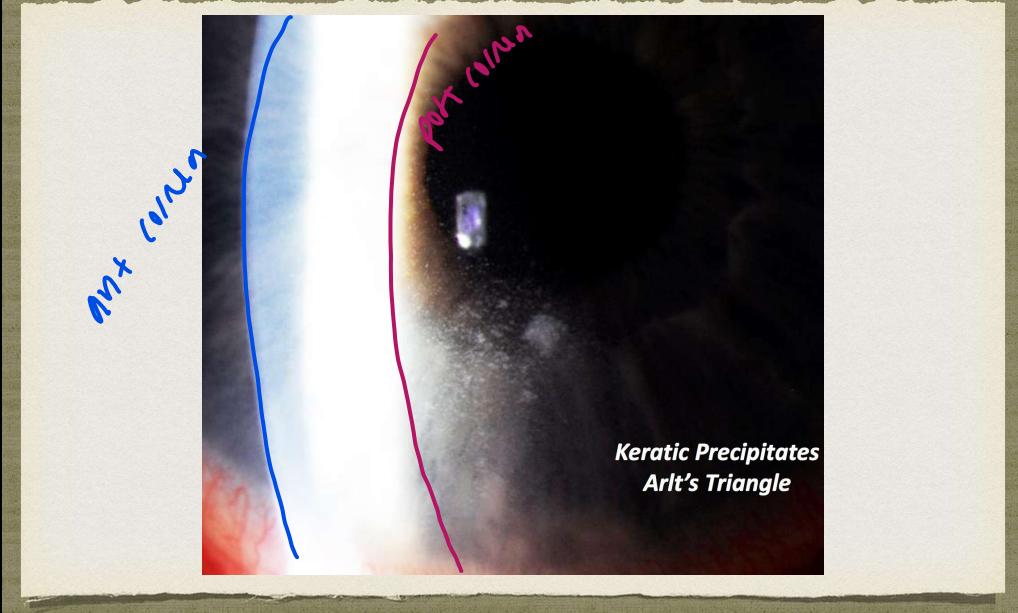
ANTERIOR UVEITIS (IRIDOCYCLITIS)



tissues are sticky

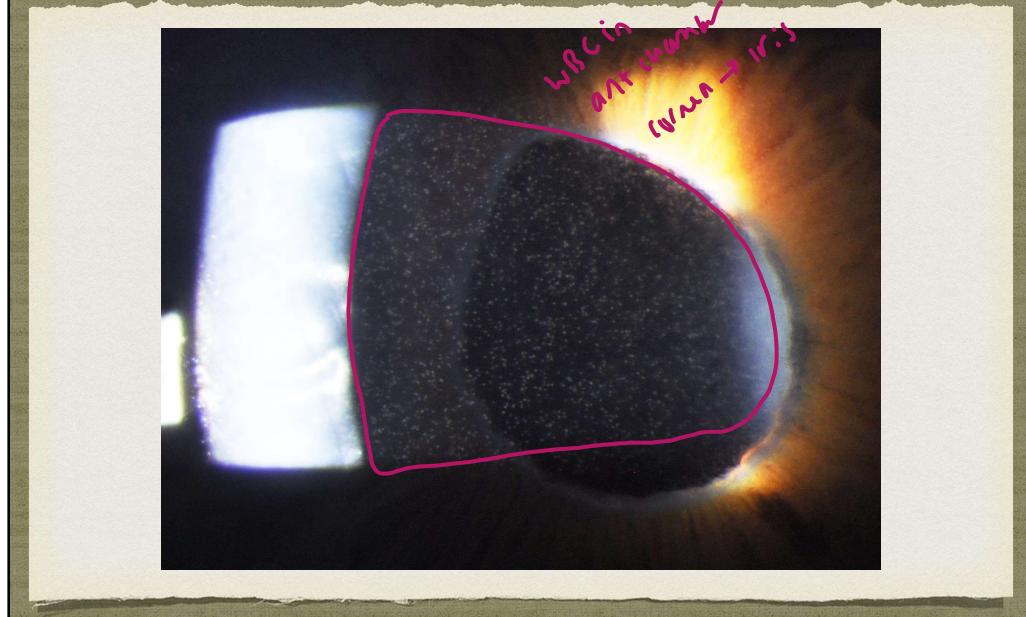
Conjunctival injection, sense of haze on inferior cornea may be keratic precipitates, subtle posterior synechiae keeping pupil from being round. Patient is likely very photophobic despite good vision.

ANTERIOR UVEITIS KERATIC PRECIPITATES



leaves a triangle of debris
see sometimes in pigment dispersion glaucoma

ANTERIOR UVEITIS ANTERIOR CHAMBER CELL

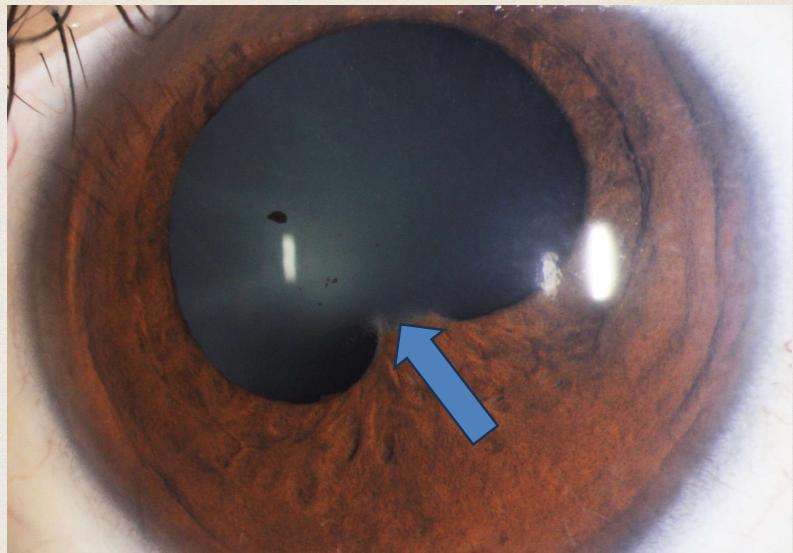


dust in window - not enough to ppt out and create a hypopyon like in an infection

POSTERIOR SYNECHIAE



some sort of
inflammation in the
eye
if get enough of
these will get a
pupillary block



Most common cause of posterior synechiae: anterior uveitis. Other causes: trauma, post surgical inflammation, pseudoexfoliation syndrome (risk for glaucoma in all cases)

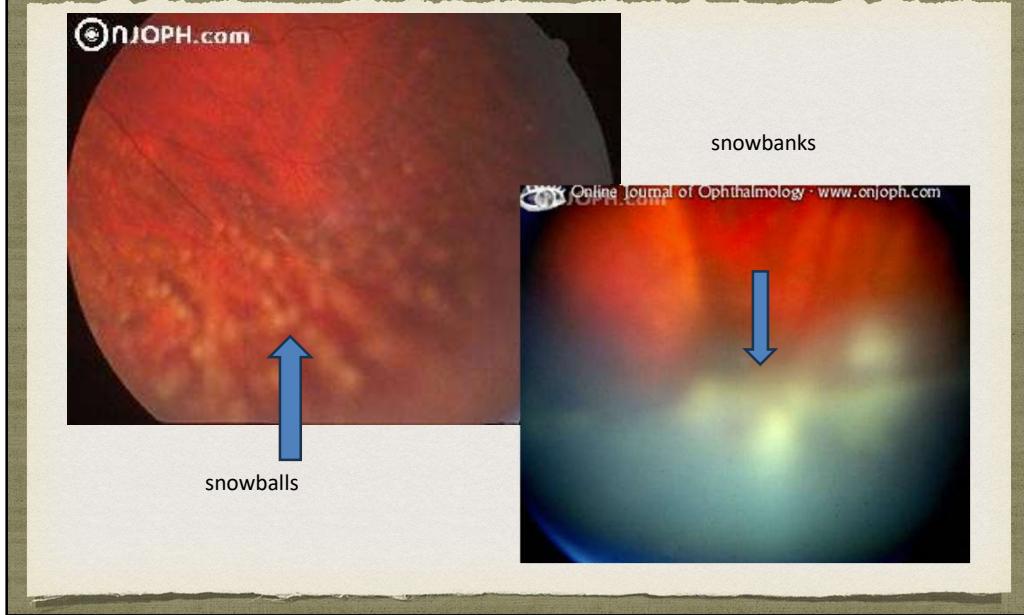
ANTERIOR UVEITIS AND HLA B27

- ◆ Inflammatory disorders associated with HLA-B27
 - ◆ Ankylosing spondylitis
 - ◆ Reactive arthritis (formerly Reiter's syndrome)
 - ◆ Psoriatic arthritis
- ◆ HLA-B27 disease: up to 50% of anterior uveitis
 - ◆ ~25-40% of patients will develop acute anterior uveitis
 - ◆ No association between activity/severity of eye disease and those of articular disease
 - ◆ Cataracts and glaucoma may also occur due to chronic inflammation

Differential dx of anterior uveitis other than inflammatory includes infectious (syphilis, TB, HSV, CMV, toxoplasmosis, rubella, zoster), malignancy (lymphoma, retinoblastoma), medication induced (rifabutin, cidofovir, sulfonamides, bisphosphonates), idiopathic.

INTERMEDIATE UVEITIS

maybe described
in a test question



Snowballs = fluffy clumps of cells in front of the retina. Snowbanking: white, fluffy exudate and vitreous cell seen best at inferior pars plana [way far in periphery](#)

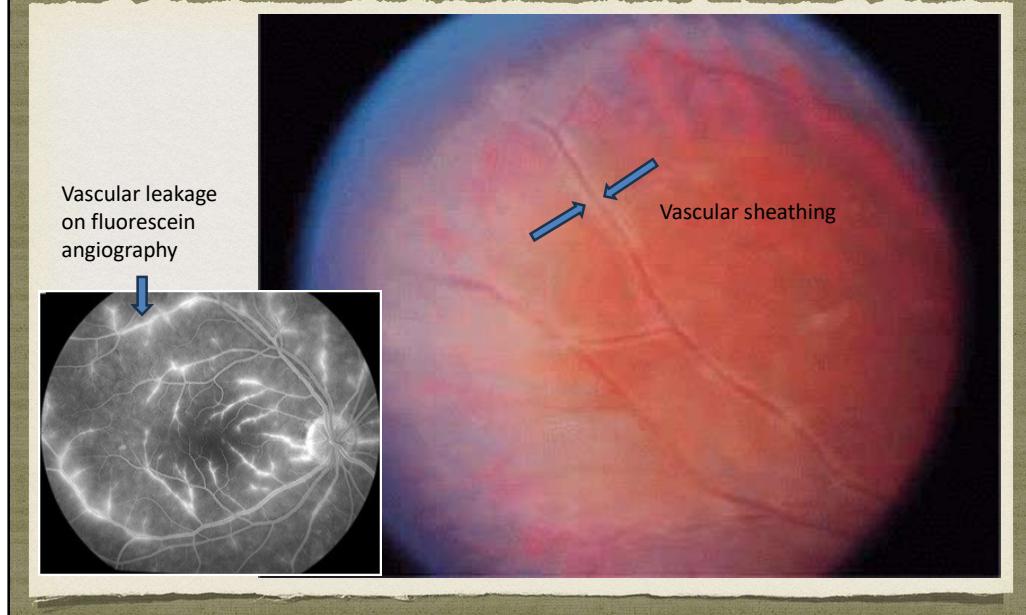
POSTERIOR UVEITIS RETINAL VASCULITIS AND NECROSIS

very sight threatening



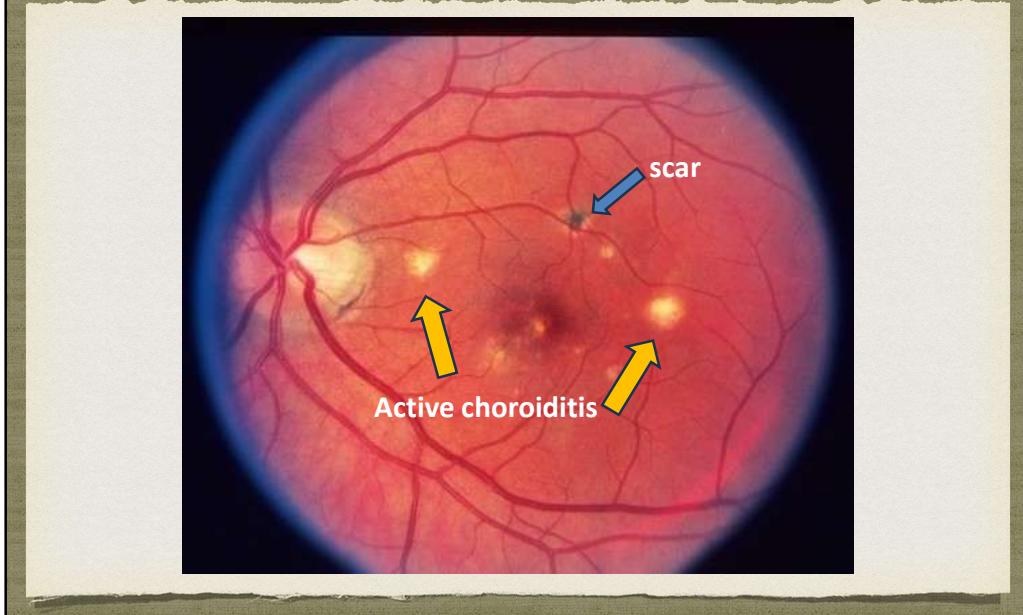
Acute Retinal Necrosis in posterior uveitis. Classically associated with Varicella Zoster or Herpes Simplex viral infection, less commonly with cytomegalovirus.

POSTERIOR UVEITIS VASCULITIS



Vascular sheathing (collection of inflammatory cells around the vessels) seen on the color fundus photo, Vascular diffuse leakage on fluorescein angiogram

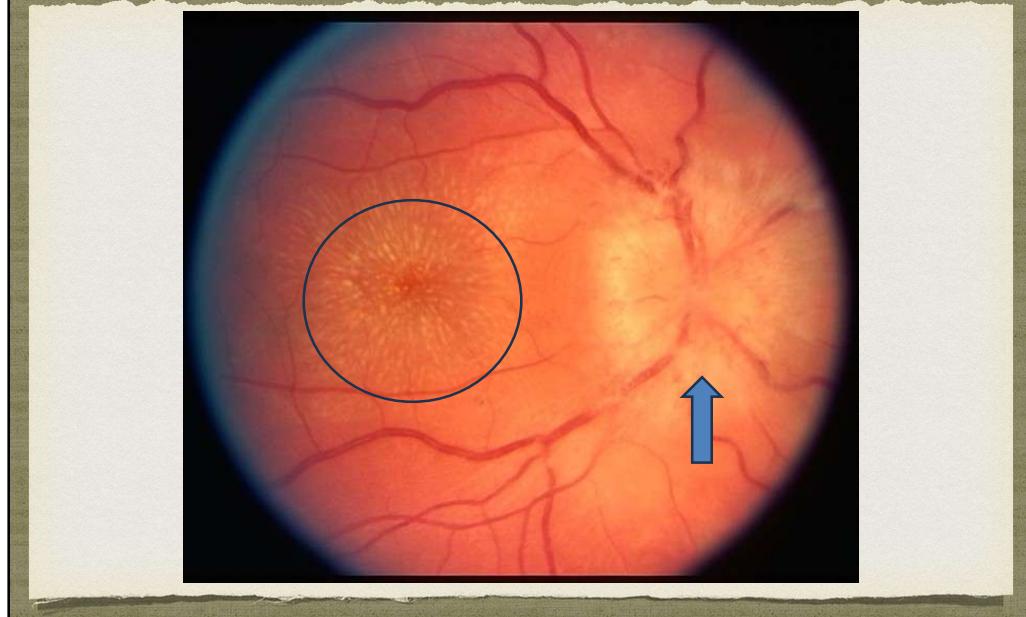
POSTERIOR UVEITIS CHORIORETINITIS



Large active spots of choroiditis near nerve and temporal to fovea, area of chorioretinal scar seen superior to fovea

looks fluffy on slit lamp

POSTERIOR UVEITIS NEURORETINITIS



Neuro+Retina: swollen optic nerve with classic macular star exudates (both are inflammatory). Differential includes cat scratch disease, lyme disease, syphilis, toxoplasmosis.

SYSTEMIC LUPUS ERYTHEMATOSUS

Diagnostic criteria in SLE

S	• Serositis [pleuritis, pericarditis]	B	• Blood [all are low - anemia, leukopenia, thrombocytopenia]
O	• Oral ulcers	R	• Renal [protein]
A	• Arthritis	A	• ANA
P	• Photosensitivity	I	• Immunologic [DS DNA, etc.]
M Malar rash		N	• Neurologic [psych, seizures]
		D	Discoid rash



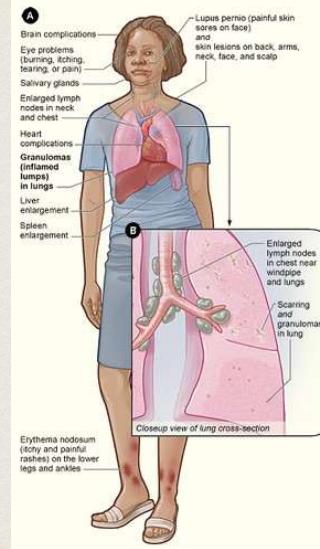
Mnemonic: "SOAP BRAIN MD"

- Chronic inflammatory multisystem disease
- Most common ocular involvement include **KCS, vasculitis**

KCS can affect about 33% of SLE patients. Vasculitis can be visually devastating. Less common ocular findings with SLE: optic neuropathy, uveitis (especially anterior or posterior), ocular motility issues including INO

SARCOIDOSIS

- Idiopathic, multisystemic granulomatous disease
 - Lung and skin involvement (more common in children)
 - African and Scandinavian descent
- OCULAR MANIFESTATIONS:
 - **Most common: anterior uveitis and posterior uveitis**
 - Orbital and eyelid granulomas
 - Keratoconjunctivitis and lacrimal gland infiltration
 - Treatment: local & systemic immunosuppression



biopsy of lacrimal gland to see if can find sarcoid

INFECTIOUS DISEASES WITH SIGNIFICANT OCULAR INVOLVEMENT

- TORCH
- ✖ HIV/AIDS
- Herpetic viruses
- ✖ Syphilis
- ✖ TB
- Candida
- Lyme

- ...too many to list!!

but anything can get in the eye

TORCH in newborns: Toxoplasma, Other (syphilis, hep B, zoster, listeria, parvovirus), Rubella, Cytomegalovirus, Herpes Simplex Virus.

HIV AND ASSOCIATED INFECTIONS

- **Molluscum contagiosum** common in children

- Nodular, umbilicated lesions on eyelids

- Chronic follicular conjunctivitis

- **Herpes Zoster Ophthalmicus**

- Sometimes the first sign of HIV in a young adult

- Can lead to rapidly progressing retinal necrosis

- **Kaposi's Sarcoma lesions on lid / conjunctiva** movie Philadelphia

- **CMV and toxoplasmosis retinitis in AIDS**

if a lot
sometimes will
scrap them

MOLLUSCUM CONTAGIOSUM IN HIV



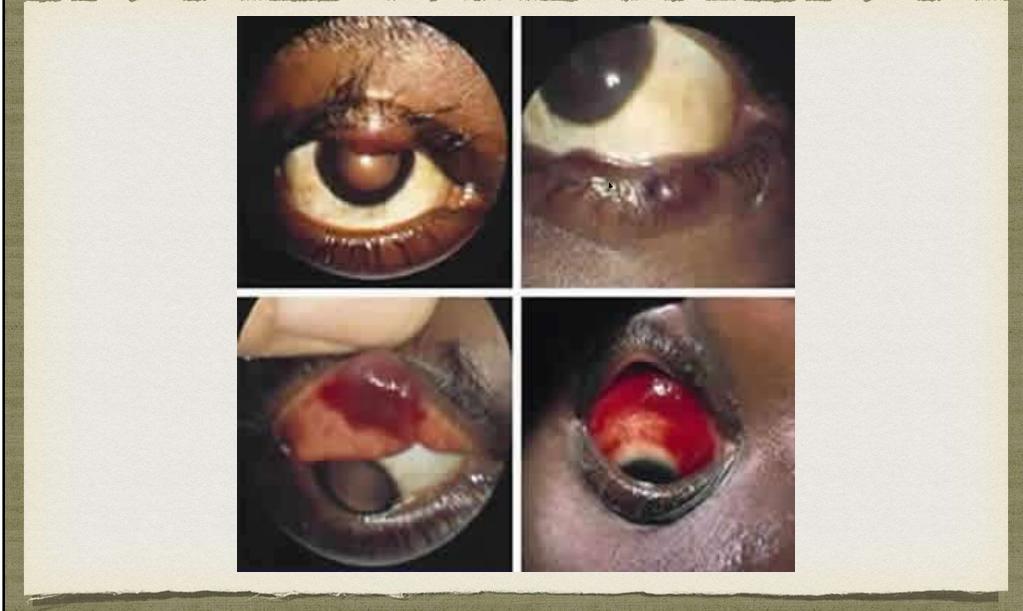
Raised pink-pearl lesions with central dimple. Viral infection. In immunocompromised patients these lesions tend to be larger than the benign infections common in childhood, but size is not a reliable differentiator. Take more history if suspicious of immunocompromise.

HERPES ZOSTER OPHTHALMICUS IN HIV



[zoster in immunocompetent may have some scarring but won't look like this](#)

KAPOSI'S SARCOMA AND HIV



giant blood blisters
make sure to lift the lid

PROGRESSIVE OUTER RETINAL NECROSIS (PORN)

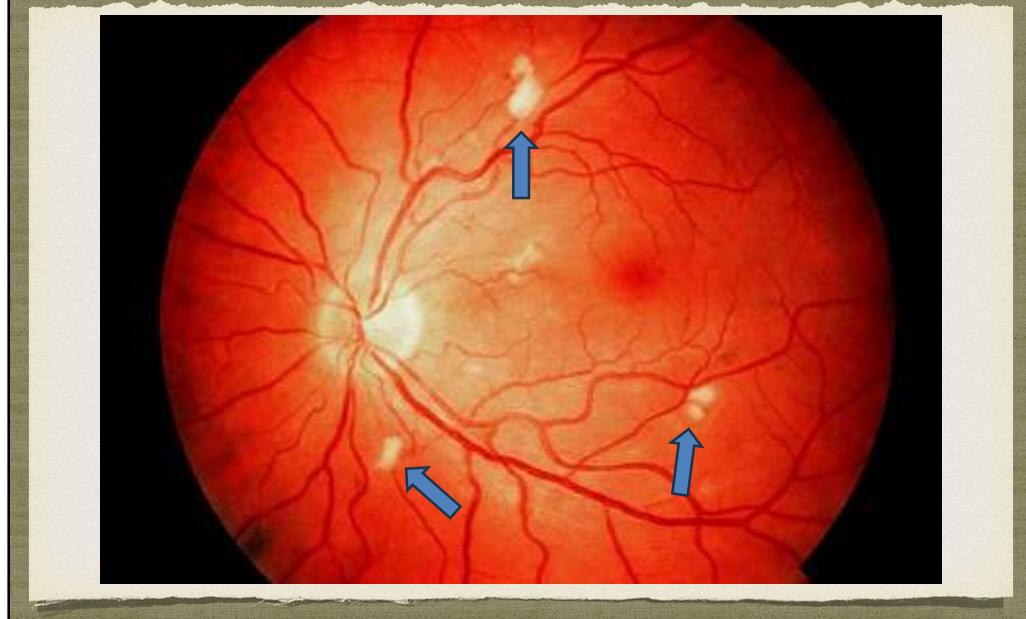


ARN

In contrast to Acute Retinal Necrosis, PORN can be painless and often lacks intraocular inflammation. Both are most commonly associated with varicella zoster or herpes simplex inflection.

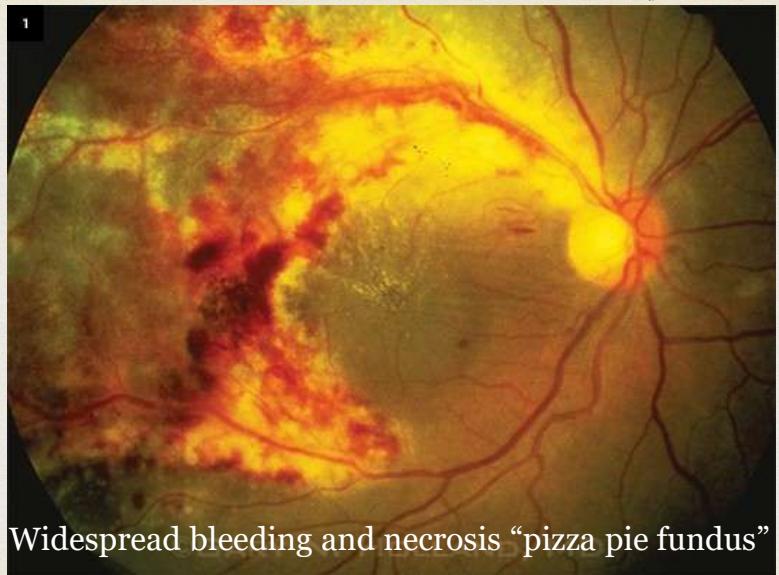
neither PORN nor ARN is good

COTTON WOOL SPOTS



CWS= retinal nerve fiber layer infarction. Commonly seen in HTN and HIV retinopathies

CMV RETINITIS



Widespread bleeding and necrosis “pizza pie fundus”

CMV in guts and doesn't cause this in immunocompetent

ranch and ketchup

as opposed to blood and thunder - which has no necrosis (white part) and blood doesn't look like it's been dropped

OCULAR SYPHILIS

Congenital: interstitial keratitis associated with conjunctival injection and anterior uveitis (5-20 years-old)

Primary: eyelid chancre, conjunctivitis

Secondary: uveitis/iritis, optic neuritis, retinal vasculitis all the inflammation

Tertiary: Argyll Robertson pupils; internuclear ophthalmoplegia

Argyll Robertson pupil is light-near dissociation: pupils fail to constrict to light but will constrict with accommodation during near tasks. Diagnostic marker for tertiary syphilis.

INTERSTITIAL KERATITIS

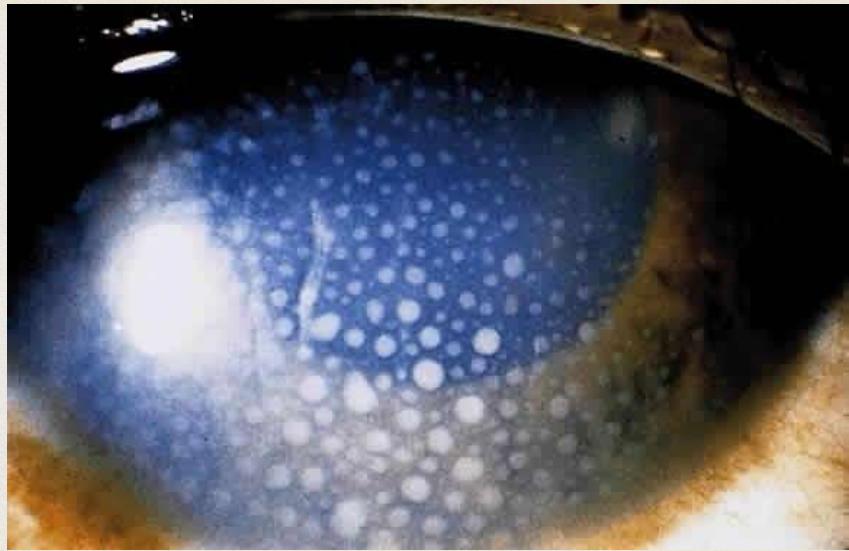


Edward S. Harkness Eye Institute
Columbia University



Intralamellar infiltration of lymphocytes with extensive neovascularization but no overlying ulceration. Late findings include corneal edema (due to damage to the endothelium), ghost vessels (seen in photo on the right), corneal scarring.

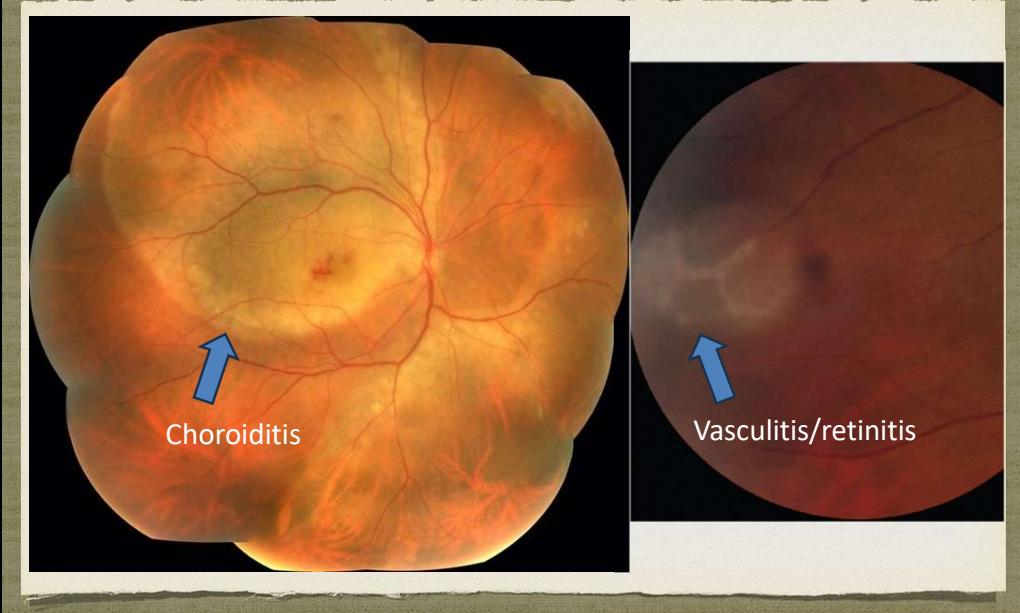
GRANULOMATOUS ANTERIOR UVEITIS



dots of white blood cells

Differential diagnosis includes TB, Lyme, HSV, Zoster, CMV, leprosy, toxoplasmosis, syphilis, COVID-19, sarcoid, MS, juvenile idiopathic arthritis

POSTERIOR UVEITIS



TUBERCULOSIS: THE GREAT MASQUERADE

- Both infectious and inflammatory components
- Triple therapy even if isolated ocular TB
- Treat for TB but will often need topical and/or oral steroid AFTER at least 2 weeks anti-TB treatment
bc of inflammatory response from tx
- High index of suspicion for those from endemic areas

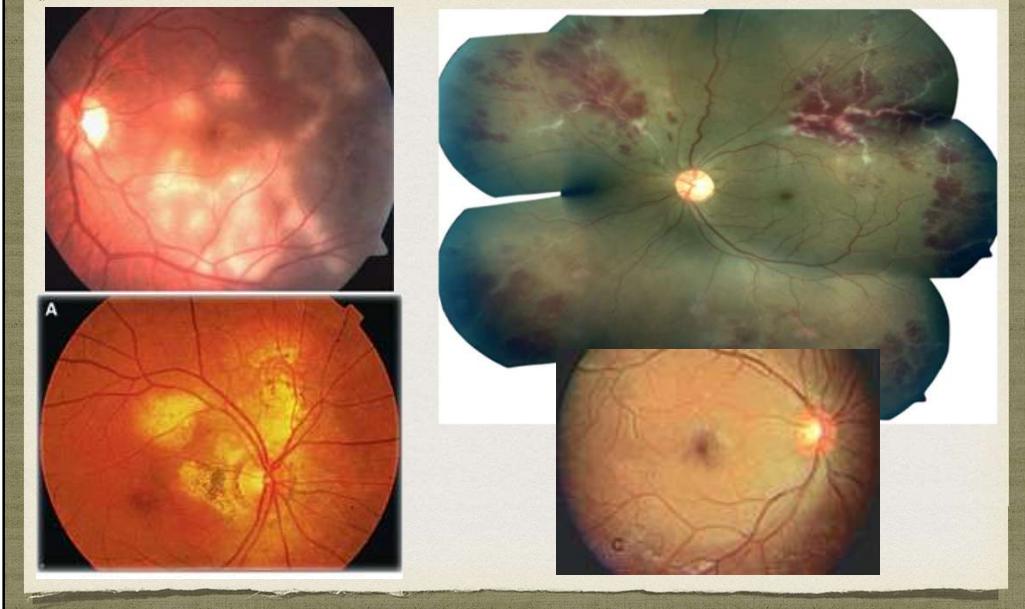
TUBERCULOSIS: THE GREAT MASQUERADE

What else could these be?



Upper Left and upper center: tuberculous granulomas that look like chalazia. Lower left: (tuberculous) uveitis with posterior synechia. Upper right shows interstitial keratitis. Lower right shows phlyctenular keratoconjunctivitis, a form of hypersensitivity to infectious antigens. Prior to 1950's often was tuberculosis, now in USA most commonly due to staph aureus proteins.

TUBERCULOSIS: THE GREAT MASQUERADE



The two left photos show serpiginous-like choroiditis and chorioretinitis. The upper right photo is of chorioretinal necrosis, hemorrhages, and vasculitis. The lower right photo shows vasculitis and macular edema

HERPETIC EYE DISEASE



- For zoster ophthalmicus initiate oral antiviral treatment acyclovir 800mg 5x/day or valacyclovir 1g BID
- **Ophthalmology referral within 24 hrs** to assess other complications such as high pressure, uveitis, retinitis



horse pill but is cheap

ANTERIOR FINDINGS IN HERPETIC DISEASE

know what a dendrite looks like

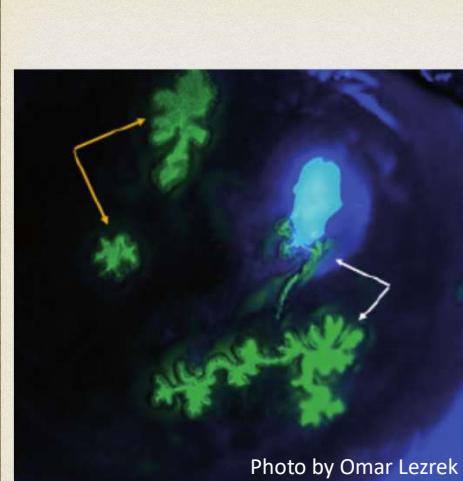
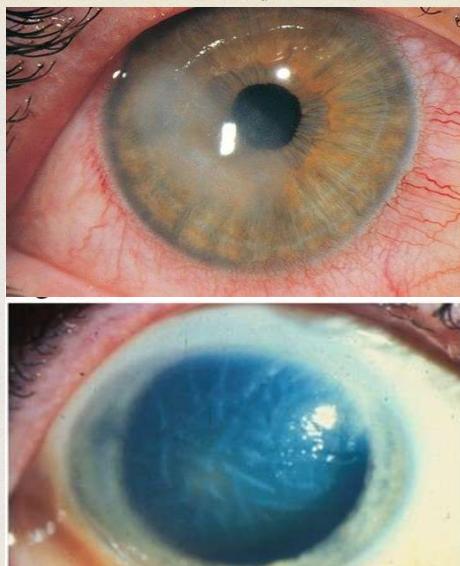


Photo by Omar Lezrek



If there is Keratouveitis, Check for high IOP! Left photo shows dendrites (short arrows) and geographic ulcers (long arrows). Lower Right photo shows stromal keratitis and endotheliitis. Upper Right photo shows stromal (interstitial) keratitis.

POSTERIOR FINDINGS IN HERPETIC DISEASE



(inflammatory) Acute Retinal Necrosis: PAINFUL sudden vision loss with red eye, floaters, photophobia

can be painless with PORN

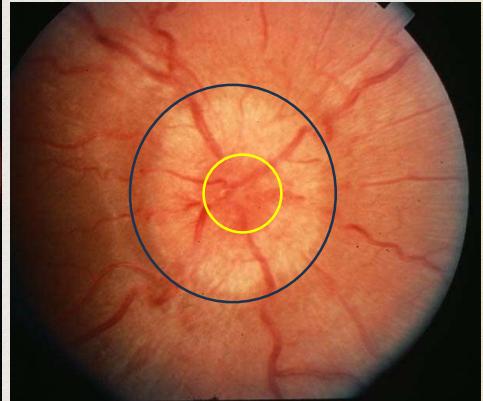
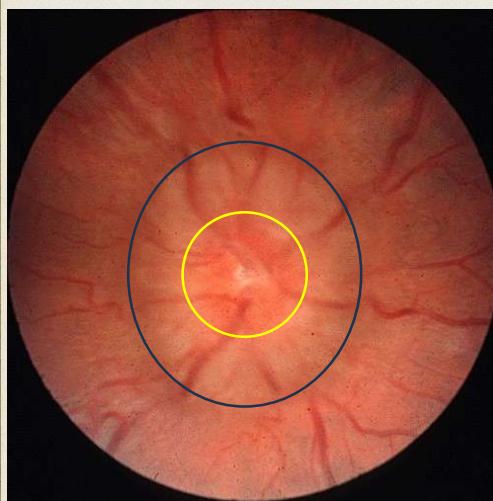
MISCELLANEOUS DISORDERS: PAPILLEDEMA



- Definition: Bilateral **optic disc edema** from **elevated intracranial pressure**
- Causes of elevated intracranial pressure:
 - Intracranial mass
 - Impediment of CSF flow: venous sinus thrombosis, AV malformation, meningitis, subarachnoid hemorrhage, etc.
 - Pseudotumor cerebri (idiopathic intracranial hypertension)
- Other causes of bilateral disc elevation include:
 - Pseudopapilledema (anomalous optic discs)
 - Hypertensive retinopathy (malignant HTN)

whether blood vessels are obscured or not

PAPILLEDEMA



2D pic may not be able to see actual lift but in slit lamp
follow the vasculature

SELECT DRUG TOXICITIES

- Corticosteroids - cataract, glaucoma long term - inhaled for asthma, arth
- INH, ethambutol, sildenafil, cisplatin- optic neuritis
- Amiodarone - corneal deposits, optic neuritis
corneal verticillata that won't stain
- Hydroxychloroquine & Chloroquine - maculopathy
- Topiramate - angle closure glaucoma if causes it never have pt on topiramate again
also a seizure med so cannot just stop
- Dupilumab – anterior ocular inflammation
- Tricyclic antidepressants – pupillary block angle closure

AMIODARONE: CORNEAL VERTICILLATA

know what it looks like and will not stain



Verticillata do not stain with fluorescein. Can also be caused by hydroxychloroquine, chloroquine, indomethacine, phenothiazines. Non drug causes: multiple myeloma, epidemic keratoconjunctivitis, neurotrophic keratitis, corneal deposits of gold, iron, antacids.

PLAQUENIL: BULL'S EYE MACULOPATHY



is dose related

usually comes in 200 mg tablets

Late finding on fundus exam. Better to catch it early on OCT. if <5mg/kg/day then <1% risk of maculopathy in first 5 years and <2% at 10 years, rises to 20% at 20 years. Increase risk if renal disease (eGFR<60ml/min, other drugs with macular toxicity such as tamoxifen, baseline macular disease. Asians may get outer macula RPE deposits not subfoveal. Destruction of macular rods and cones with sparing of subfoveal cones causes bullseye appearance. need baseline OCT screening then annual exam at 5 years and further.

if after 20 yrs don't have any risk only goes up a few percent each year usually present in the earlier stages

prob
won't be
tested on
percentag
es but
good to
know

Cranial Nerve Palsies

Supranuclear causes: check dollshead maneuver!

Nuclear causes of CN palsy: consider stroke, compression, aneurysm

Internuclear palsy: INO, most commonly ischemic or demyelinating

Infranuclear palsy:

CN 3: most commonly microvascular

CN4: most commonly traumatic

CN6: in children consider neoplasm, trauma, infection, inflammation
in adults most commonly microvascular, trauma

1 blood vessel in LR most others have 2

Supranuclear: progressive supranuclear palsy (PSP), Parkinsons, Parinaud (dorsal midbrain syndrome)

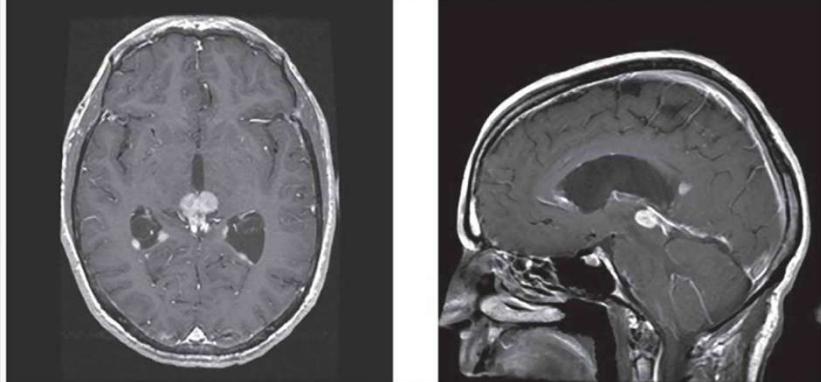
bilateral and young - demyelinating

weird so good
test question

Parinaud Syndrome

Upgaze palsy, convergence retraction nystagmus, light-near dissociation, bilateral lid retraction. 40% due to pineal region tumor

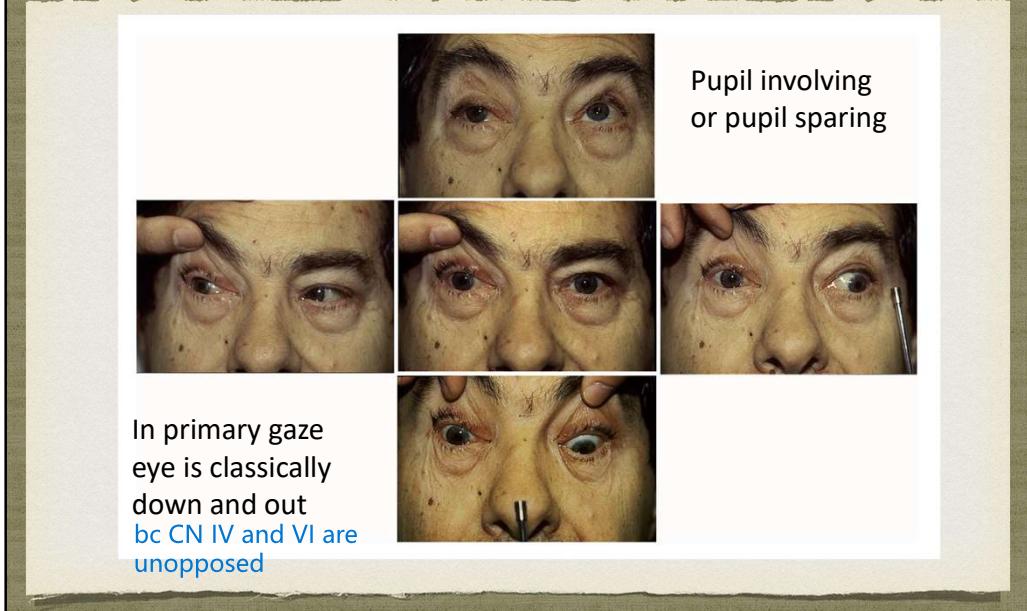
cannot upgaze



Downturn preference = setting sun sign

Cranial Nerve 3 palsy

may see a series
of photos like
this



may be pupil sparing

Shown is a right CN3 palsy, would have partial (if evolving) or complete ptosis of the upper eyelid. Infranuclear causes: Microvascular (DM, HTN) or aneurysm of posterior communicating artery, posterior cerebral. Contrast this to a Horner's syndrome (small pupil on affected side, very mild 1-3mm ptosis of upper lid, no motility paralysis) and myasthenia gravis (variable over time, better with cold, usually partial ptosis and strabismus not gaze paralysis.)

complete - can't adduct, look up, down looking for microvascular and DM and HTN aneurysm of post. cx artery

Right Cranial 4 Palsy

- Vertical & torsional diplopia more severe in...
 - Downgaze - eating, reading, walking down stairs
 - Lateral gaze toward contralateral side
- Contralateral head tilt
- Ipsilateral hypertropia

Congenital

- Usually do not complain of diplopia early in life
- Decompenstate later in life → acute onset diplopia
- Can have very large hypertropias in primary gaze (>10 prism Diopters)

Acquired

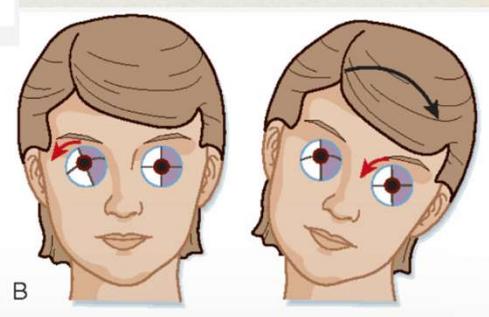
- Patient history is important - microvascular disease, trauma, past medical history
- Acute onset diplopia at start



SO muscle originates at apex goes through trochlea and attaches behind the equator of the eye

intort the eye and down gaze

B



R CN IV have L head tilt bc gets rid of double vision

Right Cranial 6 Palsy



almost microvascular
see a lot esp in DM
nothing to abduct the eye
don't like looking right bc get double vision in pictures
will resolve on own but as it improves the vision becomes closer and
becomes more disturbing
can just cover one eye - but take extra care bc will not have normal
depth perception

Multiple CN palsy

The diagram on the left shows a cross-section of the brain base. The left side displays normal anatomy with labels for the Superior Optic Nerve, Superior Cavernous Sinus, Internal Carotid Artery, Tentorium Cerebelli, and Inferior Petrosal Sinus. The right side shows the dura removed to reveal the trigeminal ganglion. A yellow line indicates the plane of section for the adjacent anatomical drawing. This drawing labels the Cavernous Sinus, Internal Carotid Artery, Optic Chiasm, and Cranial Nerves III, IV, V₁, V₂, and V₃. Below the diagrams, a purple box contains the text "Periorbital Edema Chemosis".

Clinical

- High fever
- Periorbital edema and chemises (conjunctival Edema)
- Cranial nerve palsies (CN VI most common)
- Decreased visual acuity

Dx

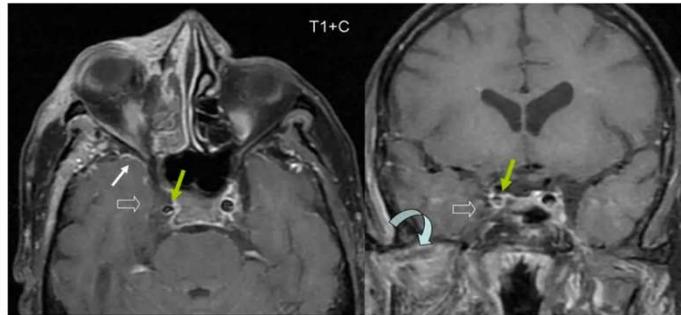
- CT scan
- MRI

Bad

huge stroke

if can't move CN III, IV, sensation = look at cavernous sinus
cavernous sinus syndrome may also have a high fever

Cavernous Sinus Thrombosis



An adult diabetic man presented with sudden right facial swelling, proptosis and complete ophthalmoplegia. He had undergone upper tooth extraction on same side four days previously. Contrast enhanced MRI shows the following changes on right side:

- 1-Ethmoiditis.
- 2-Periorbital inflammation (edematous enhanced skin and subcutaneous tissues).
- 3-Proptosis.
- 4-Meningeal enhancement consistent with meningitis (White arrow on axial).
- 5-Enhancing pterygoid muscles consistent with masticator space infection (curved arrow on coronal).
- 6-Swollen non-enhancing cavernous sinus = cavernous sinus thrombosis (open arrows).
- 7-Narrowed internal carotid artery (green arrows).

Credit: Dr Ahmed Haroun

complete ophthalmoplegia - couldn't move eyes at all

Questions?

