

Retinal Manifestations of Systemic Disease

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Hypertensive Retinopathy

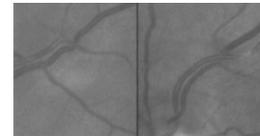
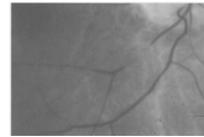
- Typically middle age or older pts
- More prevalent in certain populations
 - AA> Hispanic>Caucasians
- Typically asymptomatic and found on routine exam
- May often be first sign of underlying HTN

Hypertensive Retinopathy

- Clinical findings include
 - Retinal artery narrowing and attenuation
 - Retinal artery nicking and crossing changes
 - Flame shaped hemes
 - Cotton wool spots
 - Rarely retinal or macula edema
 - May have macular star
 - Disc edema

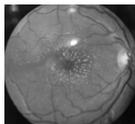
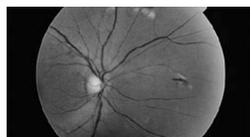
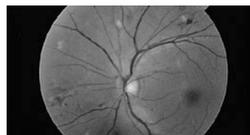
Hypertensive Retinopathy

- Keith Wagner Baker Classification System
 - Grade 1 Hypertensive Retinopathy
 - Retinal arterial narrowing and straightening
 - Grade 2
 - AV Nicking



Hypertensive Retinopathy

- Keith Wagner Baker Classification System
 - Grade 3
 - Retinal hemorrhages
 - Cotton wool spots
 - Hard exudates
 - Macular star



Hypertensive Retinopathy

- Keith Wagner Baker Classification System
 - Grade 4
 - Grade 3 with ONH edema



Hypertensive Retinopathy

- Rare to have either macula edema or optic disc edema unless there is malignant HTN, where BP is elevated in 250/130 range
 - However presentation of macular star and disc edema is almost pathognomonic for HTN crisis
- CWS typically do not appear until diastolic BP is > 110

Hypertensive Retinopathy

- Monitor fundus q 12 months
 - Sooner if severe
- Pt education
- Management involves appropriate tx of underlying HTN, with referral to primary care physician or internist
- If papilledema from HTN, consider medical emergency!!
 - Immediate referral and/or trip to ER!!

What is Hypertension?

- Systolic BP > 140 or
- Diastolic BP > 90
- Affects ≈ 70 million Americans
 - Essential HTN
 - Malignant HTN
 - Secondary HTN

	SYSTOLIC	DIASTOLIC
Normal	<120	<80
Pre-hypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	>160	>100

Essential HTN: >140/90

- Most common type of HTN
 - 90-95%
- Family History common
- Risk Factors include:
 - Sedentary lifestyle, smoking, stress, alcohol intake, **obesity**, high sodium intake, vitamin D deficiency, aging
- Usually controlled with 1 or 2 oral meds

Secondary HTN

- By definition results from an identifiable cause
 - Cushing's Syndrome
 - Hypo/hyperthyroidism
 - Kidney disease
 - Pregnancy (pre-eclampsia)
 - Coarctation of the aorta
 - Certain prescription and illegal drugs

Malignant HTN: BP>210/130

- Ocular findings
 - Papilledema
 - Exudates
 - CWS
 - FSH
 - AV changes
- Systemic Findings
 - None
 - HA's
 - Vomiting
 - Coma

Malignant HTN

- Immediate referral for BP lowering
 - ER or PCP
- MRI to r/o space occupying lesion
- MRA to r/o ‘venous sinus thrombus’
- LP if needed
- 80% of patients with malignant HTN die within 1 year
- 95% mortality within 3 years

Hypertension

- Other Complications
 - **Retinopathy**
 - Left ventricular Hypertrophy
 - Angina
 - Myocardial infarction
 - Heart Failure
 - Stroke
 - Peripheral vascular disease
 - Chronic kidney disease

Hypertension

- Risk
 - Each increase of 20 mmHg systolic or 10 mmHg diastolic doubles risk of complications
- Risk reduction with treatment
 - 35-40% reduction in stroke
 - 20-25% reduction in myocardial infarction
 - >50% reduction in heart failure

Hypertension Treatment

- Lifestyle
 - Weight reduction
 - BMI goal 18.5-25
 - Diet
 - Sodium restriction
 - DASH diet
 - Dietary Approaches to Stop Hypertension
 - Physical activity
 - Moderation of alcohol consumption

DASH Diet

- Dietary Approaches to Stop Hypertension
 - Proven to lower BP in as little as 14 days
 - Best with moderate or less or pre-hypertension
- Includes whole grains, poultry, fish, and nuts and has reduced amounts of fats, red meats, sweets, and sugared beverages.
- www.dashdiet.org

Hypertension Treatment

- Medical management
 - Thiazide diuretics (hydrochlorothiazide)
 - Work by helping body reduce sodium and water thereby decreasing blood volume
 - Beta blockers (atenolol)
 - Reduce workload on heart, causing decreased heart rate
 - Angiotensin-converting enzyme (ACE) inhibitors (lisinopril, captopril)
 - Help relax blood vessels by blocking the formation of enzymes which narrow blood vessels

Hypertension Treatment

- Medical management, cont
 - Angiotensin II receptor blockers (losartan)
 - Relax blood vessels by blocking action of the enzymes which narrow blood vessels
 - Calcium Channel Blockers (verapamil, diltiazem)
 - Help relax the smooth muscles of the arteries and heart, thereby decreasing blood pressure
 - Renin inhibitors (aliskiren)
 - Newer drug which works on renin, an enzyme produced in the kidneys which starts hypertensive cascade

Retinal Plaques

- Several different types of plaques can often be visualized in the retinal vasculature
- Pt is typically elderly, has HTN, CAD, hypercholesterolemia/hyperlipidemia, and/or atherosclerotic disease
- Often totally asymptomatic and found on routine exam

RISK FACTORS

- Age
- HTN
- Vascular disease
- Past vascular surgery
- SMOKING
- High TOTAL cholesterol
- Men > women

Prevalence

- Beaver Dam Eye Study: 1.3%
 - smoking, HTN and DM
 - 9x more likely after age 75 vs. 43-54
 - after 75, 3.1% prevalence
 - Equates to 1.2 million people with emboli 43-86
 - » 450,000 are 75-86
 - Fatal stroke 3x as likely over 8 years in pts with emboli, adjusting for other factors
 - OD > OS
 - Bilateral very infrequently

Prevalence

- Blue Mountain Eye Study 1.4%
 - HTN, smoking, Vascular disease
- LA Latino Eye Study: 0.4%
 - Smoking, CAD, h/o MI, HTN
- Singapore Eye Study: 0.6%
 - Smoking, high cholesterol, h/o angina

Retinal Plaques

- May present with amaurosis fugax, transient episodes of monocular blindness
- Rarely, may report transient ischemic attack (TIA), which is above with hemiparesis, parasthesia or aphasia

Retinal plaques

- Three different types of plaques, but all share strong association to significant cardiovascular disease
 - HH 80% > fibrino-platelet 14% > calcific 6%

Retinal Plaques

- Cholesterol (Hollenhorst) plaque
 - Most common
 - shiny yellow-orange in appearance
 - from plaque in the ipsilateral carotid artery
 - Rarely causes occlusion, unless multiple
 - Typically occurs at bifurcations
 - Mobile in nature

Retinal Plaques

- Fibrino-platelet
 - Appear as dull white to gray, long plugs
 - Typically within arterioles, not at bifurcations
 - May break-up and dissolve with time
 - May lead to BRAO or CRAO
 - Often associated with carotid disease or mitral valve insufficiency

Retinal Plaques

- Calcific
 - Appears more whitish than HH
 - Dull, non-reflective, white
 - Classically within arteriole, not at bifurcation
 - Typically immobile
 - Most dangerous, as often cause BRAO
 - Often from cardiac atheromas of heart valves

Retinal plaques

- Talc retinopathy
 - Represents an exogenous plaque as opposed to others
 - Appears typically as multiple shiny yellow plaques within capillaries in posterior pole
 - Typically smaller than other plaques
 - Typically seen in IV drug users
 - Rarely cause complications, but reported cases of associated NV and occlusions

Retinal plaques

- No direct management of plaques is needed
- Management is aimed at discovering source of embolus to decrease risk of other emboli, occlusion, or stroke
- Pts need referral to internist for complete physical

Retinal Plaques

- Assess risk factors with PCP
 - DN, HTN, lipid panels
- Carotid ultrasound
- MRA: non-invasive image with 2D/3D
- TEE: invasive, probe into esophagus to image heart valves
 - Helpful with calcific
- CTA: CT scan of arteries construct 3D images

Carotid Ultrasound

- First line screening test
- ORDER WITHIN TWO WEEKS!!
- Identifies flow rate and % stenosis
- Common, internal, and external
- Only ≈20% of asymptomatic emboli will have significant carotid stenosis

Retinal Plaques

- | | |
|--|----------------------------------|
| <50-60% occlusion | >70-99% |
| • ORAL TREATMENT | • SURGICAL TREATMENT |
| – Anti-Platelet <ul style="list-style-type: none"> • ASA | – Carotid endarterectomy |
| – Anti-coagulation <ul style="list-style-type: none"> • Comadin, platelet | – Angioplasty |
| – Cholesterol meds | – Reduces risk of future stroke! |

Retinal Plaques

- After ruling out underlying etiology, see patient regularly, q 6 -12 mos, to evaluate for additional plaques or other disease associated with vascular disease
 - BRVO/CRVO
 - BRAO/CRAO
 - NTG

Is it worth working up these patients?

- 18% of pts with retinal emboli had internal or common carotid stenosis >75%
- Higher incidence of stroke
 - 8.5% with emboli vs 0.8% w/o per year
- Pts with cholesterol HH emboli have 15% mortality at 1 yr, 29% by year 3, and 54% by 7 years

Retinal Vein Occlusions

BRVO

- Second most common retinal vascular disorder
- Often associated with systemic HTN
- Peak incidence in 5th to 6th decades, with no sex predilection

CRVO

- Very visually destructive disease with strong systemic association
- Typically occurs in men > 50
- Vision is typically compromised, ranging from moderate to total vision loss

Retinal Vein Occlusions

BRVO

- Classic presentation is dilated tortuous veins and dot-blot hemes from site of compression to periphery in sector normally drained by that vein
 - Can also see flame-shaped hemes and cotton wool spots as hypoxia develops
 - Lipid can also develop leading to macula edema

CRVO

- Non-ischemic characterized by dot/blot hemes, intra-retinal hemes, and possible macula edema
- Ischemic CRVO presents with dot/blot hemes, flame-shaped hemes, CWS, and gross intra-retinal and macula edema. Also, papilledema commonly present

Ischemic vs non-ischemic CRVO

- IOP often reduced more with ischemic vs. ischemic CRVO
- APD often present with ischemic
- VA generally reduced more with ischemic
 - Rule of thumb: if VA < 20/200 then ischemic.
- In order to know for certain, FA needed
 - Helps to stratify risks, prognosis

Traditional Treatment: BRVO

- Branch Vein Occlusion Study Group concluded that grid laser improves visual outcome in eyes with BRVO and vision 20/40 or worse from macular edema
 - BRVO at least 3 months old
 - VA 20/40 or worse
 - FA within 1 month, demonstrating macula edema and absence of foveal ischemia

Traditional Treatment: BRVO

- Other sequelae of BRVO include neovascularization, either of the retina, disk, or iris (25-30%)
- BRVO study group also concluded that PRP should be administered in eyes with BRVO and Neovascularization
- Results suggest that there may be no advantage to treat to prevent development of NV

Traditional Treatment: CRVO

- Patients with macular edema from CRVO typically do not respond well to FML at all
- CVOS Study: Improvement on appearance, but no gain in acuity
- Big concern is risk for NVG
 - NVG in 14-20% of all CRVO
 - NVG almost 60% of the time in ischemic CRVO

BRVO/CRVO

- Management includes diagnosis and management of underlying etiology
- Most often associated with DM and HTN
- However many other possible etiologies
 - Carotid artery disease
 - Hyperlipidemia/hypercholesterolemia
 - Altered platelet function
 - Coats disease
 - Von-Hippel Lindau
 - Eales' disease
 - Trauma

BRVO/CRVO

- At minimum, should have
 - BP evaluated
 - Fasting Blood sugars (FBS)/A1c
 - CBC
 - Lipid profile
- Additional tests might include
 - Carotid artery evaluation
 - Cardiac evaluation
 - Additional blood tests
 - ANA
 - RF
 - FTA/ABS
 - ESR

CRVO

Most common etiologies varied with age at presentation

- Under age 50
 - Head injury
 - Hyperlipidemia
 - Estrogen, esp oral contraceptives
- Over age 50
 - HTN
 - DM
 - Chronic lung disease

New Treatments: Steroids

- CRVO SCORE
 - ¼ patients receiving IVT had a 15 letter or better improvement in VA at 12 months
 - Pts 5x as likely to have VA improvement vs. observation alone
- BRVO SCORE
 - Almost equal number of patients in laser or steroid group had > 15 letter improvement
 - More complications in IVT group

New Treatments: Anti-VEGF

- CRUISE (CRVO) Study:
 - Vision improved > 15 letters in almost 50% of patients vs. 17% with sham at 6 mos
 - mean VA gain of almost 15 letters
- BRAVO (BRVO) Study:
 - Vision improved > 15 letters in over 60% of patients vs. 28% with sham
 - Mean VA gain of approx 18 letters
 - Few side effects in either group

Eylea® (afilbercept)

- FDA approved Sept, 2012 for treatment of macula edema secondary to CRVO
- COPERNICUS and GALILEO studies:
 - % of pts gaining 15 letters or more of BCVA
 - Injection q 2 mos for 24 weeks
- COPERNICUS:
 - 56% vs. 12% with sham
 - 17.3 letters gained vs. 4.0 lost with sham
- GALILEO:
 - 60% vs. 22% with sham
 - 18.0 letters gained vs. 3.3 lost with sham

Ozurdex®

- 0.7 mg biodegradable intravitreal dexamethasone insert
- FDA approved for macula edema from BRVO/CRVO
- 853 patients
 - 20-30% gained ≥ 3 lines vs. 7-12% with sham at 6 mos
 - 7.4 mean letter gain vs. 4.9 with sham



BRVO/CRVO Treatment

Traditional

- Wait and see
 - 3 mos
 - 20/40 or worse
- Laser for BRVO
- No Tx CRVO
- Evaluate underlying disease

Now

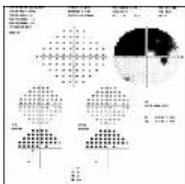
- No advantage to wait
 - 1 week
 - VA limit?
- Anti-VEGF for BRVO
- Anti-VEGF for CRVO
- Evaluate underlying disease

BRAO

- Result of emboli dislodged from elsewhere which travels through the system until a vessel too small for passage is reached
- Arterial occlusion causes anoxia due to lack of oxygenated blood
 - Anoxia causes loss of retinal layers, including NFL through inner nuclear layer

BRAO

- Occurs most frequently in superior temporal region of the retina
- Visual acuity and field loss dependent on location and extent of blockage
 - VF loss is classically a sharp edged defect stopping abruptly at the horizontal raphe



BRAO

- Appearance varies as time progresses
 - Initially, affected arteries narrow and retina becomes hazy
 - Over a few hours, the retinal tissues whitens and appears edematous
 - Segmental optic atrophy may also develop in the affected area

BRAO

- Prognosis depends upon area affected as well as extent of blockage
- Also depends upon prompt therapy, to lesser extent
 - Some studies indicate that if emboli can be dislodged within 1-2 hours, recovery can be complete
 - After this period, initial acuity is not likely to improve

CRAO

- Mechanism similar to BRAO, but larger embolus causes obstruction prior to lamina cribosa, so entire central retinal artery is obstructed
- Pts typically present with sudden painless loss of vision in an eye that was previously thought to be healthy
- Typically pts from 50-80 years of age

CRAO

- Vision typically in the hand motion to counting fingers range
- Most often present with an APD as well
- If a cilioretinal artery is present, there may be a small island of vision that correlates to the area of vascular supply
 - Present in about 10% of eyes
- Can see an embolus in 20-40% of cases

CRAO

- Early appearance is that of retinal narrowing and haziness of retinal tissue
- After 1-2 hours, retina appears white and edematous, with a “cherry red” macula, representing the choroidal blood supply to the macula
- With time, the arteries may assume a more normal appearance, with irregular narrowing often the only clue
- Optic atrophy may occur, but NVG is very rare

CRAO

- Management often includes attempts to dislodge embolus if pt presents within first 1-2 hours
 - Digital massage, paracentesis to lower IOP, carbogen, anti-thrombotic agents, etc have little to no value
- Management lies in diagnosis and management of underlying systemic disease

BRAO/CRAO

- Immediate ESR needed to r/o GCA if pt over 55
 - Only 2%-5% secondary to GCA in one study
- Most often associated with DM, HTN, and carotid artery disease
 - Many other etiologies including: sickle cell, oral contraceptives, Lupus, Behets disease, Lyme disease, etc

BRAO/CRAO

- Blood pressure
- Lab tests
 - FBS
 - CBC
 - ESR
 - Lipid profile
 - PT/PTT
 - ANA/RF
- Carotid Artery Evaluation
- Cardiac Evaluation
 - Echocardiogram and possible Holter monitor

BRAO/CRAO

- Follow-up
 - BRAO: 3-6 mos after ruling out underlying etiology
 - CRAO: follow closely for first 1-3 mos for NVI, then periodically after
 - If NV, then PRP indicated to prevent NVG

Case

- 67 yo white male
- +DM Type 2 x 5-6 years, HTN
- Here for diabetic check
- Reports good vision
- "other health issues not related to eyes"
- 20/20 OU

Roth Spot

- White centered hemorrhage
- Hemorrhagic CWS
- First described by Moritz Roth, MD in 1872
- Seen in patients with bacteremia

Roth Spot

- CLASSICALLY associated with:
 - Bacterial Endocarditis
 - Leukemia
 - Pernicious Anemia

Roth Spot: Associations

COMMON

- DIABETIC RETINOPATHY
- HYPERTENSIVE RETINOPATHY
- HIV
- ISCHEMIA
- COLLAGEN VASCULAR DISEASE

LESS COMMON

- TRAUMA
- SHAKEN BABY SYNDROME
- MULTIPLE MYELOMA
- RETROVENOUS MALFORMATION
- CARBON MONOXIDE POISONING

Roth Spots: Work Up

- Most common
 - HTN: Check BP (<120/80)
 - DM: A1c (<6.5) or FBS (<126)
 - CBC with white cell differential
 - Anemias, polycythemia, leukemias, bleeding disorders
- Less common
 - PT/INR: for clotting disorders
 - Older pts: ESR/CRP to r/o GCA
 - Younger pts (<40): lipids, aniphospholipids, ANA (lupus)

Cotton Wool spots

- Fluffy, cloud like, whitish deposits in retina
- Typically associated with ischemia
- Differential diagnosis
 - Exudates
 - Drusen
 - Myelinated nerve fiber layer

Cotton wool spots

- DM and HTN most likely cause
- Typically, associated with systemic disease
- One study, pt with CWS and no known medical history
 - Elevated BS (DM) in 20%
 - Elevated BP (HTN) in 50% of pts

Cotton Wool Spots

- Ischemic
 - VO, OIS, anemia, hyperviscosity/hypercoagulation, acute blood loss, radiation
- Immune
 - SLE, scleroderma, polyarthritis nodosa, GCA
- Infectious
 - HIV, cat scratch, Rocky Mountain Spotted Fever, leptospirosis, onchocerciasis, bacteremia/fungemia
- Embolic
 - Carotid/cardiac emboli, endocarditis, deep venous emboli

Cotton Wool spots

- Neoplastic
 - Lymphoma, leukemia, metastatic carcinoma
- Medication induced
 - Interferon, chemotherapeutic agents
- Miscellaneous
 - Trauma, high-altitude retinopathy, Purtscher Retinopathy
- Idiopathic

Cotton wool spots workup

- Most common
 - HTN: Check BP (<120/80)
 - DM: A1c (<6.5) or FBS (<126)
 - CBC with white cell differential
 - Anemias, polycythemia, leukemias, bleeding disorders
- Less common
 - PT/INR: for clotting disorders
 - Older pts: ESR/CRP to r/o GCA
 - RF
 - Cardiac Risk factors

DME

- ETDRS
 - 3711 pts, 22 centers, 10 years
 - Established focal macular laser (FML) as treatment for CSME
- PROS:
 - Reduced risk of moderate vision loss by 50%
 - 95% chance of maintaining vision when guidelines followed
- CONS:
 - 12% lost >15 letters at 3 years
 - <3% gained 15 letters
 - Diffuse, chronic, lipid deposits respond poorly

Steroids for DME

- Early 2000's, before anti-VEGF, IVT was looked at treatment for DME
 - Inhibit reduction of PGs
 - Decreases permeability
 - May Decrease VEGF proliferation
- DRCR.net *Ophthalmology* September 2008
- 848 eyes with CSME and VA from 20/40 to 20/320 were evaluated
 - At 2 yrs, laser is more effective and has fewer side effects than either 1 or 4 mg intravitreal triamcinolone

antiVEGF

- Lucentis, Avastin, Eylea
- Shown in multiple studies to be beneficial for DME
 - RISE
 - 18.1% of pts in sham gained ≥ 15 letters vs. 44.8% (0.3 mg) or 39.2% (0.5 mg)
 - 2.6 letters gained in sham vs. 12.5 (0.3mg) or 11.9 (0.5mg)
 - RIDE
 - READ
 - VISTA
 - VIVID

Protocol -T: Lucentis vs Avastin vs Eylea

- One year
 - Eylea gained 13.3 letters
 - Lucentis 11.2
 - Avastin 9.7
 - No statistical difference
- If VA was 20/50 or worse
 - Eylea gained 18.9
 - Lucentis 14.2
 - Avastin 11.8

Protocol -T

- 2 year results
 - No statistically significant difference between 3 drugs, even in those worse than 20/50
 - But better acuity with Eylea
 - Bottom line:
 - It may matter which drug
 - May matter more with worse vision
 - Economics may dictate
 - In order to justify use of lucentis/eylea vs avastin, price would have to decrease by 70-80%

PDR

- ETDRS
 - Established benefit of immediate PRP in patients with PDR
- PROS
 - Showed an overall reduction rate of severe vision loss (ie 5/200) of approximately 50% in treated vs. untreated eyes
 - <4% chance of severe vision loss in 5 years w/ tx
- CONS
 - Decreased VF
 - Decreased night vision
 - CME

Protocol S

- Non-inferior study evaluating Lucentis vs. PRP
- 55 sites, 203 pts with PRP, 191 with Lucentis, as frequent as q 4 weeks
- At 2 years:
 - VA improved 2.8 letters with Lucentis vs. 0.2 with PRP
 - More VF loss with PRP: . 531db vs. 213db loss
 - More vitrectomies in PRP group: 15% vs 4%

Protocol S

- Bottom line:
 - Longer Study needed
 - Economics may dictate
 - May be best with concurrent DME
 - Pt must be complaint
 - Perhaps combo of both treatments will be best?
 - Role in severe NPDR?