Retinal Findings with Systemic Disease

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Disclosure

- I have been on advisory boards/a consultant to/received honoraria from/ or been on speakers bureau list of the following:
  - Allergan, Apellis, Arctic Dx, Avellino, Bausch & Lomb, Essilor, Genentech, Luneau Technologies, MDA, Notal Vision, Novartis, Optos, Regeneron, VSP, ZeaVision

These affiliations will have no affect on the content of this lecture

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Antioxidants

- Do you drink coffee?
  - Over 50% of Americans drink coffee
- Is this important?
  - Coffee is leading source (by far) for antioxidant intake in the US diet!![1]
- Neither coffee nor caffeine intake were associated with early AMD per BDES
- Beware:
  - COFFEE and DOUGHNUT Maculopathy[2]

1. As reported by American Chemical Society 8/05
2. Kerrison J.B. et.al. Coffee and Doughnut Maculopathy: Acute Ring Scotomas. BJO.2000 Feb;84(2):158-64.

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The Relationship of Coffee Consumption with Mortality *Ann Intern Med 2008:148:904-14*

- 2 Cohorts
  - 41,736 men Hx Professionals FUp Study – 18 years
  - 86,214 women Nurse's Hx Study - 24 years
- Results
  - After adjustment for age, smoking, other CVDz and CA risk factors

	Men
<1 cup / month	1.07
1 c/m – 4 cups/w	1.02
5-7 cups / week	0.97
2-3 cups / day	0.93
4-5 cups / day	0.80
> 6 cups / day	0.74

P<0.001 for trend and independent of caffeine intake

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How much can diet affect vision?

- Junk food can cause blindness!
  - French fries, potato chips, white bread, processed ham and sausage
- Complaints at age 14 of tiredness
  - Normal BMI, no signs of malnutrition
    - Low B12 and anemia treated and given dietary advice

- Age 15: hearing and vision loss
- Age 17: Blindness
  - Low B12, Vit D, bone density and high Zinc

- Optic neuropathy caused by junk food diet!
  - Some controversy as to possibility of other cause…..
  - BMI isn't everything (as seen in this case)

Harrison et al. Blindness by Junk Food. Annals of Int Med. 9/19

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Course Objectives

- Discuss Ophthalmic tests for evaluating retina
- Discuss systemic conditions that affect retina, and how we factor into patient care
- Discuss findings associated with systemic diseases, both common and uncommon
- Know when to refer, and to whom

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Medical optometry: A different kind of "liability"

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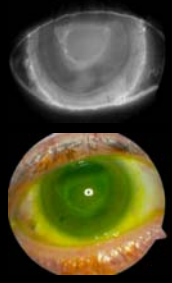
More Than Meets the Eye

- Macula off retinal detachment OD
- LP vision
- Systemic health: good?
- Meds: Valium, Oxycodone, Methadone, Elavil
- Tx: Vitrectomy and Scleral Buckle
- Post op: Corneal Abrasion and HM
- How did the abrasion happen???
- Bottle Top



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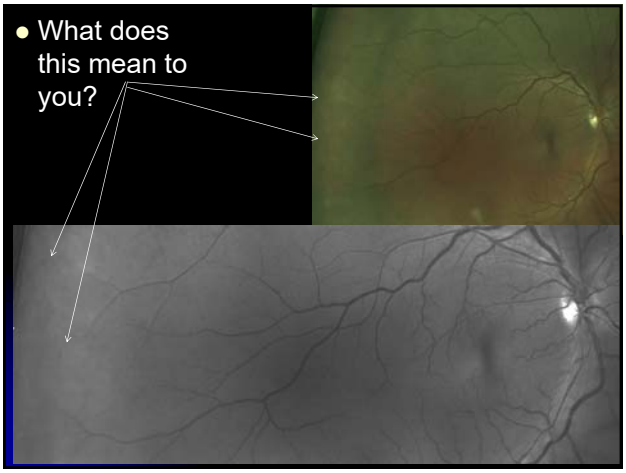
- What does this mean to you?



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Clinical exam

- **BIO best for clinical exam of peripheral retina
- Condensing lens at slit lamp ideal for magnified posterior pole views
- Dynamic clinical exam
- Require examiner to document
- Some things best seen clinically, and unable to be seen with imaging devices

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Healthy patient??...

- 32 yo male
- 2-3 month history of cough, dyspnea, chills, malaise
- Recently returned from International travel
- Lives in Midwest
- Health care professional
- No improvement with antibiotics and PO prednisone
- Abnormal chest x-ray
- Good vision
- Referred to Pulmonologist

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Chest X-ray

- Calc
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  - Ti
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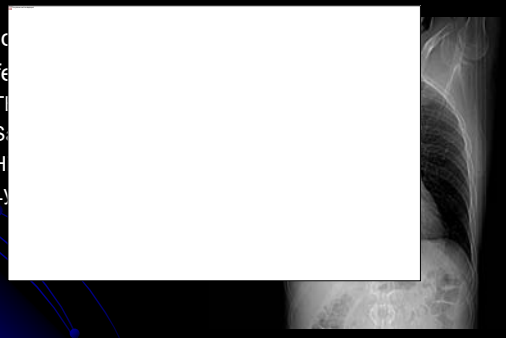
  - Ly



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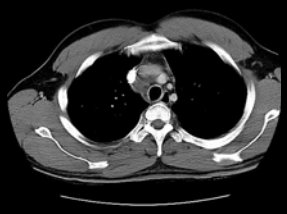
Case continued

- CT ordered with contrast
- Labs ordered
  - CBC Normal
  - Normal Liver function
  - ESR 46 mm/hr
  - Negative TB skin test
  - ACE 44 U/L (7-46)
  - Histo Mycelial Ab Normal
  - Histo Anti H Ab 1:32



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Histoplasmosis

- Treatment:
  - Sporanox (Itraconazole) 200mg BID x 1 mo
  - 100mg BID x 2 mo

Aside:

- Value of prescription drug coverage!
- Importance of good doctor patient relationship!!!
- **In case you were wondering, Histo has remained quiet, with no radiologic changes as of 4/06**

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Systemic Histoplasmosis

- Caused by Histoplasma capsulatum, a dimorphic fungus, that turns into a yeast at body temperature
- Endemic to Ohio, Mississippi, and Missouri River valleys
- Aerosolized fragments result in alveolar deposition
- Most infected people are asymptomatic
- Can involve CNS, liver, spleen, eyes, rheumatologic system, and hematologic system

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Histoplasmosis cont.

- Symptoms can occur 3-14 days after exposure
- Approximately 250,000 infected annually
- Clinical manifestations in less than 5%
- About 90% with acute pulmonary histo are asymptomatic
- Enlarged hilar and mediastinal lymph nodes in 5-10% of patients
- Affects males 4:1
- Progressive disseminated histo mostly occurs in immunocompromised patients ex: AIDS

Good summary article: Trevino & Salvat:Preventing Reactivation of OHS. Optometry 1/06

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Testing

- CBC generally normal
- Sputum cultures yield positive results in only 10-15% of acute pulmonary histo
- Complement fixing antibodies
  - Greater than 1:32 suggests active
    - Positive 5-15% of within 3 wks of exposure
    - Positive 75-95% at 6wks
- Immunoprecipitating antibodies
  - Anti-M detected in 50-80%, and remains elevated for years
  - Anti-H detected in 10-20% and becomes undetectable after 6mos. This antibody is most specific for active histo
- Imaging studies
  - Chest X-ray
  - CT scan
- HLA-B7, HLA-DR2 and may be elevated more in people with CNVM

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Treatment

- No treatment needed if asymptomatic
- Treatment if symptomatic, or progressive
- Treatments
  - Amphotericin B: drug of choice for overwhelming active histo, administered by IV
  - Itraconazole: Fungistatic, very active against Histo, minimal side affects
    - Liver functions must be monitored
    - Approximately 86% success when treating > 2mos
  - Ketoconazole: Fungistatic, well tolerated, does not cross blood/brain barrier

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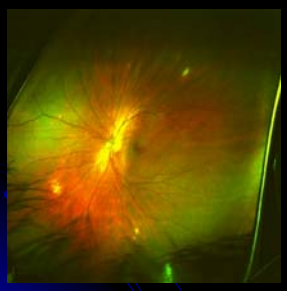
(P)OHS



- (Presumed) ocular histoplasmosis syndrome
- Not previously found post-ennucleation in patients with typical POHS
- Has been found in eye of patients with known Histo
- Approx 1-10% pts. In endemic areas have ocular involvement, usually asymptomatic
- 10% will be bilateral

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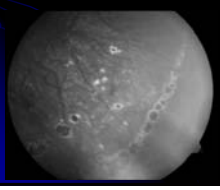
OHS

- Histo Spots
  - Atrophic yellowish white scars from previous multifocal or disseminated choroiditis
  - Can form streaks
- Peripapillary Atrophy
  - May represent atrophied granulomas that formed during active infective stage of
  - Neovascular membranes can form here, and involve macula



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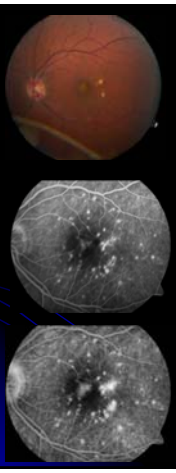
OHS



- Macular Involvement
  - CNVM tend to form in area of pre-existing histo spot
  - May be immune reaction against *H. capsulatum*
  - May be due to weakened Bruch's membrane
  - 10% become bilateral at 5 yrs, and 20% at 10yrs
  - 81% with disciform macular scarring have pulmonary calcifications

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Treating CNVM from Histo

- MPS
  - Argon laser to entire lesion effective if extrafoveal with 8% recurrence
  - Krypton laser if juxtafoveal with 23% recurrence
- Submacular Surgery (SST)
  - Benefit seen in surgical group if entering acuity worse than 20/100 (76% vs 50% same or better)
  - More recently shown beneficial with PPCNVM[1]: different histopath
  - Pt experience no better with surg in any group[2]
- PDT
  - >50% remain equal or show improvement
  - No cases of severe vision loss as has been reported as has been with AMD patients
- Anti-VEGF Therapy

1. Thomas, Matt at Barnes Retina in St. Louis 3/2008 2. Surg vs observ with POHS CNVM. SST group. Arch Ophth 12/08

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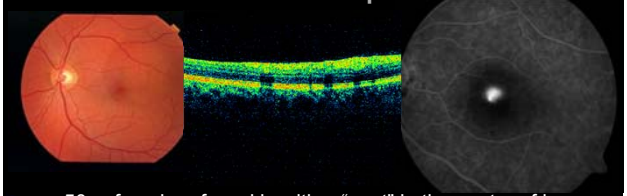
Central "Spot"



- 50yo female referred in with a "spot" in the center of her vision
- Present for 1-2 wks
- Referring OD noticed abnormality
- VA 20/20 OU
- Denies High stress or type "A" personality

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Central Serous Choroidopathy

- Characterized by breakdown of the outer retinal barrier, with leakage of fluid through a defect in the RPE into the subretinal space, resulting in a neurosensory detachment
- Often times associated with high stress +/-
  - ED (Emotional Distress) may be related[1]
- FA or OCT must be done to rule out CNVM
- Other systemic associations
  - Use of corticosteroids* (Well documented in literature), pregnancy, increased adrenaline level, hemodialysis, collagen vascular disease, and hypertension
- Treatment?
- Letter of diagnosis to PCP to make aware

1. Conrad et al. **Alexithymia and emotional distress in ICSC.** Psychosomatics. 2007 Nov-Dec;48(6):489-95

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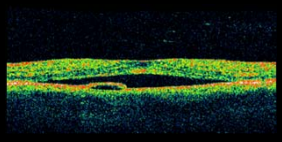
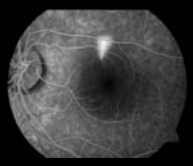
ICSC

- Treatments proposed:
  - PDT
    - Success in multiple studies[1]
  - IVTA
    - May prevent leakage
    - Not study proven and counterintuitive
  - Anti-VEGF
- Is it too easy to be successful with new treatments??





PDT for RPE leaks in CSC. Ober, M et al. Ophthalmology. Dec. 2005.

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Central Serous and Steroids

- How would you know about steroid use?
- What kinds of steroids
  - I have had cases of cream/ointment, oral
- Could hormones have same affect?
  - Patient on Androgel for "Low T"

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ICSC

- Steroids react with mineralocorticoid receptors
- Mineralocorticoid antagonists (counteract or prevent effect steroids)
- Significant reduction in RPE detachment and in choroid thickness in treatment groups vs. placebo groups after 1 month of treatment
- Improved VA in patients with prolonged CSCR after 1 month of treatment versus placebo or eplerenone. Also improved CRF/CRT

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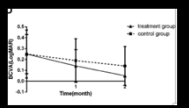
ICSC continued

- Placebo controlled 40mg BID Spironolactone vs control x 2 mos[1]
  - Complete of SRF in 56 vs 8% at 2 mos
  - Statistically significant improvement in central thickness: 75 vs 15 microns
  - VA improved in both; more in Tx, but not stat statist.
- Practical guidelines:
  - Sprionolactone 25-50mg BID
  - Consider K supplementation and kidney function testing



1. Sun et al. BJO. Spironolactone in ICSC. 8/2017.

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Case Study

- 44 yo native-american male
- Recent awareness of central blind spot
- 20/25 OU
- Diagnosis?
  - Solar Maculopathy
- Systemic assoc???

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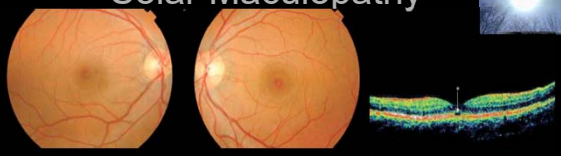
Solar Maculopathy



- Bilateral yellowish spot in fovea with surrounding hyperpigmentation and OCT shows loss of cells at RPE layer
- Retinal phototoxicity vs photocoagulation
- Often happens in patients who use drugs or are on psychotropic meds
  - Sun gazing while "on drugs" or brief exposure with pharm. Dilated pupils
  - No other systemic associations

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Case Study cont.

- Take a closer look at the ONH
- What is this?
- No PEPS
- Idiopathic
- Warned of possibility of future CNVM

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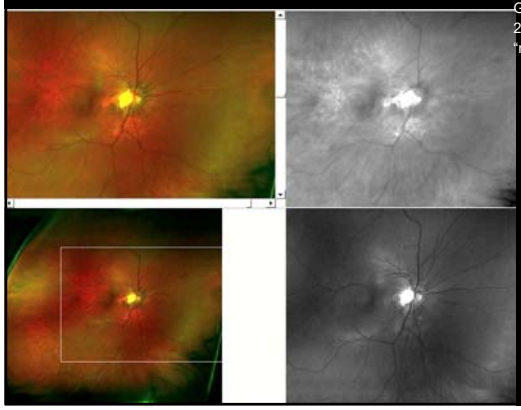
Case study

32yo female
Good health
20/20 OU
"retinal changes"



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Angiod Streaks

- **Diagnosis: Angioid Streaks**
- **Treatment: yearly exams, and home monitor with Amsler grid**
- **Note: proximity of Angioid streak to fovea**
- **Over 50% of Angioid streak patients have associated systemic disorders**

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Angioid Streaks

- Represent breaks in an abnormal Bruch's Membrane that may present spontaneously or as result of trauma
- Eventual RPE and choriocapillaris degeneration
- Generally radiate out from ONH, bilateral
- Color depends on fundus color and degree of RPE atrophy
  - Red: Lightly colored fundi, reflect underlying choroid
  - Brown: Darker pigmented fundi
  - Orange: Specific type of RPE mottling

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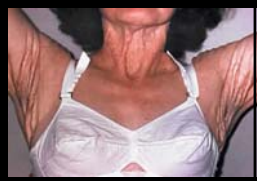
Angioid Streaks: associated systemic conditions

- Pseudoxanthoma Elasticum
  - 80-90% have angioid streaks
  - Degeneration of collagen
  - Most common systemic
- Paget's Disease
  - 8-15% have angioid streaks
  - Metabolic bone disease
- Sickle Cell Disease
  - <6% have angioid streaks
- Ehler's-Danlos Syndrome
  - Skin fragility, joint hyperextensibility
- Diabetes
- Others: maybe coincidental
- PEPSI



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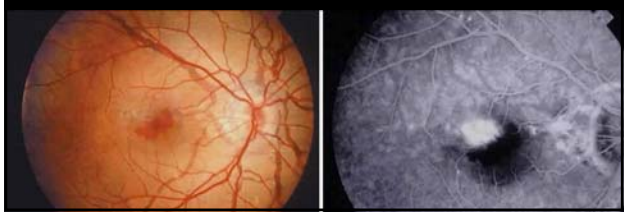
Angioid Streaks

- Not problematic unless get CNVM
- If CNVM, standard is thermal laser, but >75% recur
- Monitor with Amsler grid



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Case of Missing Labs

- RM is a 46 year old Caucasian male
- Referred for retinal changes, questionable macular edema
- Last physical 2-3 years prior
- "No systemic health problems", no medications
- Paramedic
- Note: Not a very healthy looking patient

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"Healthy" Paramedic cont.

- Visual acuity: OD: 20/100 OS: 20/30
- Pupils, CVF, Amsler all normal
- Anterior segment: Normal, no iris changes
- Fundus exam:
  - Widespread microaneurysms, several cotton wool spots, vascular engorgement and crossings, dot and flame hemorrhages in post-pole and equatorially
  - Macular edema present OD, and possibly OS
- Fluorescein Angiogram ordered
  - Above changes noted, significant leakage in OD macula. Limited change to macula OS
- TX: Focal laser recommended
- TX Cont: Letter sent to PCP telling of findings, recommend blood workup for DM and other vascular problems

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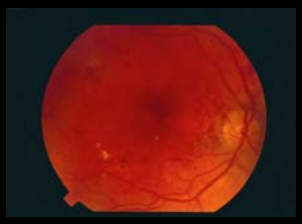
Unhealthy Paramedic

- Vision after focal: OD: 20/70
- Retinal changes: worse
- Pt notes that has been to doctor, and now on meds for DM
- BP checked at visit and was 184/102



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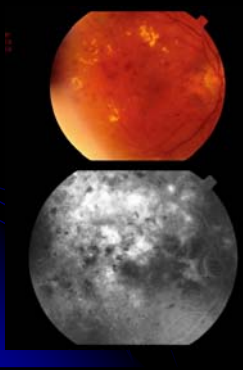
Paramedic



- 2 mos later he notes vision may be a little worse: OD: 20/200 OS: 20/40
- BS poorly controlled
- BP: 156/94
- We called PCP for lab results…….

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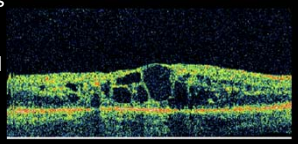
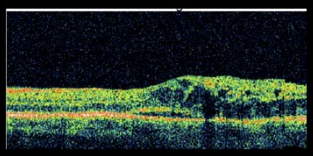
Case of Missing Labs

- MD office had no records of any lab work done!
- Pt self tested while on job, and treatment based on that
- Fairly non-compliant patient
- ? Compliant PCP
- Needs Endocrinologist consult…
- **This patient not only has diabetes, but also hypertension!





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Diabetes

Approximately 9.3% of US Adults!

- 2 types
  - Type 1 (previously insulin dependent)
    - Beta cell destruction leading to absolute insulin deficiency
    - Glucose stays in blood since can not enter insulin dependent tissues
  - Type 2 (previously non-insulin dependent)
    - Peripheral insulin resistance, maybe relative insulin deficiency or secretory defect
    - Treatment to decrease hepatic glucose production &/or decrease peripheral insulin resistance
    - May become insulin dependent

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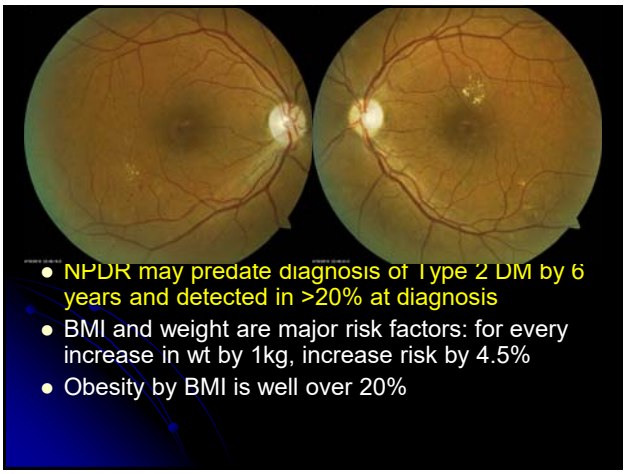

- NPDR may predate diagnosis of Type 2 DM by 6 years and detected in >20% at diagnosis
- BMI and weight are major risk factors: for every increase in wt by 1kg, increase risk by 4.5%
- Obesity by BMI is well over 20%

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Diabetes

- Testing
  - Should be more frequent if obese, family history, birth to large baby, hypertensive or dyslipidemia
- Diagnosis
  - Fasting BG >125mg/dl
  - Symptoms of DM plus casual BG >200mg/dl
  - 2 hour BG >200mg/dl during OGTT
  - Repeat test to confirm
  - ***A1c over 6.5

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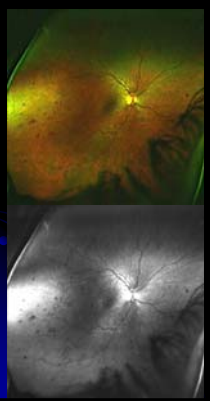
NPDR



- Mild
  - At least 1 ma
- Moderate
  - Hemorhages &/or ma's (2A), CWS, or VB(< 6B) or IRMA (<8A)
- Severe
  - 4/2/1
  - 15% to PDR in 1yr[1]
- Very Severe
  - 2 or severe findings without neo.
  - 45% to PDR in 1 yr[1]

1. As reported by ETDRS

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Proliferative Diabetic Retinopathy

- NVD or NVE
- High risk
  - NVD >1/2 disk area
  - NVD and VH/PRH
  - NVE >1/2 disk area +VH/PRH
- Untreated, can lead to VH or tractional RD
- Without tx, 50% blind in 5 years
- Current treatment: PRP when High Risk, may need vitrectomy

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Macular Edema

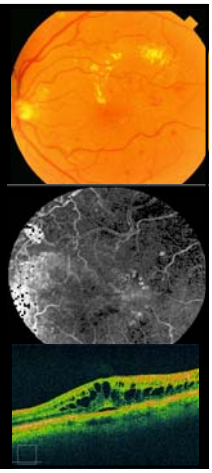
Today's categories of DME

CI-DME: Central subfield involving central 1mm of fovea

Non-CI: Not involving central subfield (1mm of fovea)

CSME not really "used" anymore

Does Vision matter?



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Diabetic **R**etinopathy **S**tudy

- Randomized, prospective to evaluate PRP
- Primary outcome was severe vision loss defined as 5/200
- Demonstrated 50% decrease in SVL in PRP group
- Recommendation: PRP
- Complication: 11% lost 1 or more lines of acuity, and 5% had visual field loss

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Early Treatment for Diabetic Retinopathy Study

- Evaluated PRP and aspirin in pts with less than HR PDR OU, laser for DME
- Outcome was Moderate VL (doubling of visual angle)
- Results of 3 areas of interest:
  - >50% less MVL with laser for CSME
  - PRP for PDR, not needed earlier, but may be beneficial for Type 2
  - ASA 650mg did not alter retinopathy, VA or VH, or rates of vitrectomy

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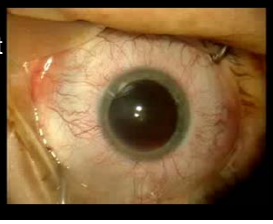
Diabetic Retinopathy Vitrectomy Study

- Is early vitrectomy beneficial?
  - 20/40 was more common in early-vitrectomy group (1-6 mos.)
  - Benefit seen in eyes with most severe disease
  - In regards to VH, clear benefit to type 1, but not to type 2
- Today: 25g vitrectomy



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Lucentis

- DRCR.net investigated Lucentis vs laser and/or steroid n= 691 people (~850 eyes).
  - Grps (success is 20/20 or <250microns @ 1yr)
    - 1: sham injection + prompt laser treatment
    - 2: Lucentis + prompt laser (8/13)
    - 3: Lucentis + deferred laser treatment (≥24 weeks (9/13)
    - 4: IVK + prompt laser (3/4)

  Success: 32%, 64%, 52%, 56%

  Lucentis gained 9 letters vs 3 in laser v 4 w steriod

  Steroid better than laser for OCT, but not VA

  Approx 30% Lucentis + 3 lines vs 15% w laser

Elman et al. Lucentis in DME. Ophthal 4/10

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DRCR

- Protocol T: Any Anti-VEGF will do
- Protocol S: Lucentis not worse than PRP
- Protocol V: NO tx needed for 20/25 mild DME!
- Ongoing studies

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Diabetes Control and Complications Trial & UK Prospective Diabetes Study

- Pts randomized to conventional or intense control
- Showed slower progression for intense control group
- For those with no NPDR at start, if intense, then 76% less devel. of retinopathy
- If A1c down by 2%, PDR would decrease by 50%
- Decrease in A1C by 1 %:
  - 14% decrease in MI
  - 12% decrease in stroke
  - 37% decrease in microvascular dz
  - 21% decrease in any DM endpoint

- DCCT reported relationship of A1C and avg. Glucose

%HbA1C	Avg. Glucose (mg/dL)
4.0	60
5.0	90
6.0	120
7.0	150
8.0	180
9.0	210
10.0	240
11.0	270

Control group in DCCT: 9-10%

Strict control group: 7%

Sources: NEJM 329:977-986 1993 UKPDS: Lancet 352:837-853,1998

53

10 years after DCCT[1]

- 10 yrs later A1c was 8.07% vs 7.98% in the groups
- Prevalence of retinopathy progression or PDR less in intensive group after 10 yrs (24 vs 41% & 6.5 vs 19%)
- Other studies have confirmed retinopathy linked to initial BS control[2]
- Similar effect seen in neuropathy and albuminuria
- Metabolic memory appears to last 10 years, but may wane at some time

1. Prolonged Effect of Intensive Therapy with T1DM. DCCT group. Arch Ophth 12/08. 2. Reichard P. Glycemic thresholds for complications. J Diab Complic. 199:9(1);25-30.

54

What We Need to Know

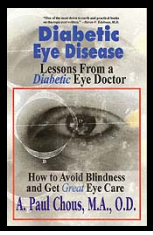
The DPP Ten Years On
- 38% reduced risk of with lifestyle modification
- 17% reduced risk with metformin

- The Diabetes Prevention Program (DPP)
- modifi… …k of
- develo… …isk patients by 58%
- Walkin… …week
- Metform… …0%
  - Exercise was twice as effective as drug

55

Hemoblobin A_1c

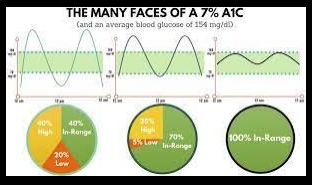
- Importance of A1c monitoring
- Critical to disease control and prevention of problems
- Does a patient know their last reading?
  - Good, bad, or worse response
- In office testing
  - www.a1cnow.com



56

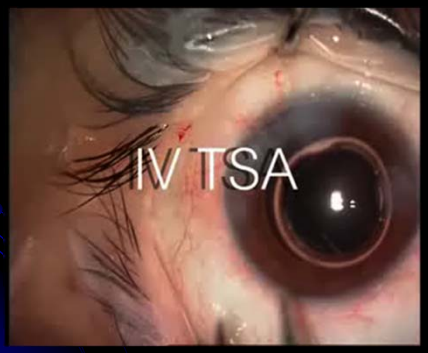
WAY more important than A1c

- TIR w CGM
- 70% TIR dramatically reduces risk of DR or DR progression



57

Intravitreal Steroid



58

The Challenge for OD's in Diabetes Care….

59

Those Who Aren't What We Call Them

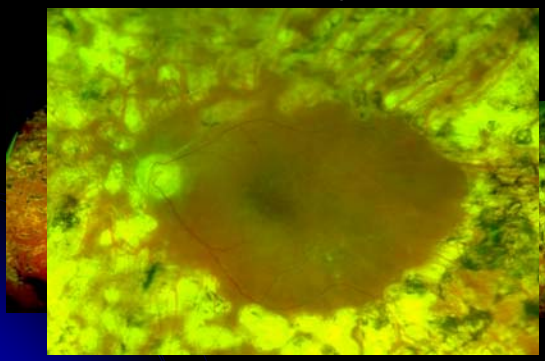
60

You never know..

- Diagnosed with T2DM 2 wks ago
- Vision not good, Endo said due to BS fluctuation
- 20/50

61

And today….



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My favorite student

63

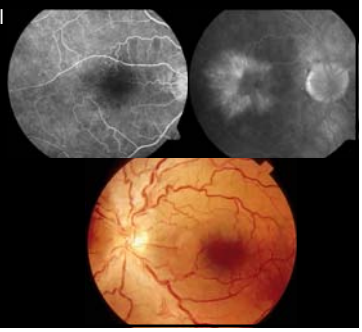
"Paramedic's Friend"

- 65yo male
- Occupation: retired, but used to be field medic in military
- "My optometrist referred me because of my right eye, I am not sure what is wrong"
- "Good general health, my blood pressure runs low"
- My exam…

64

Hypertension??

- Vision: 20/400 OD
- Anterior Segment: normal
- Blood Pressure: 196/120
- What next….
- Sent to PCP directly from office
- Started on HTN meds



65

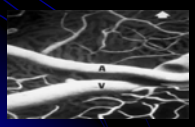
Hypertension

- 50-60 million Americans have systemic HTN (by today's standards)
- Usually asymptomatic, but can lead to MI, PVD, CVA, renal disease, retinopathy
- Significant CVD risk at 140/90, and risk doubles with every increase of 20/10mmHg
- Risk factors include smoking, dyslipidemia, DM, age, family history, race, sedentary, obese, sodium…

66

Hypertension

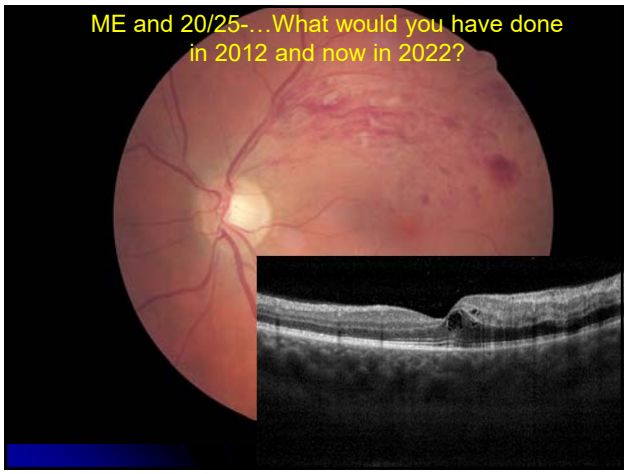
Category*	Systolic	Diastolic
Normal	<120	<80
Pre-HTN	120-139	80-89
HTN		
Stage 1	140-159	90-99
Stage 2	>160	>100
Malignant		>120



- Refer to PCP in timely manner
- Goal of BP reduction to as low as tolerated
- Most patients will require 2 medications
- Lifestyle modification
  - 30 minutes of physical activity >4 days/wk can lower SBP by up to 9mmHg
  - Weight loss of 10kg can lower SBP by 5-20mmHg

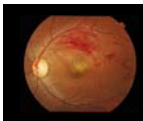
*The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, NIH

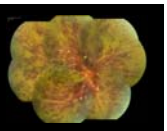
67



68

So pt presents with VO & ME





- First and foremost: Any ME from VO is no longer an "optometric" management: ***There is proven benefit to Tx that are implemented earlier than before***
- Which treatment is best?
  - Not exactly up to us…But sort o

….you choose!

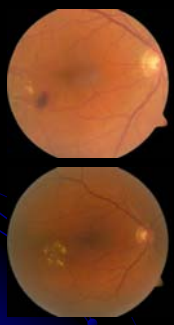
69

Hemorrhage everywhere!

- 68 yo female
- Dramatic decrease in vision 1 wk prior due to Vitreous Heme
- Exam as seen after VH resolution
- Diagnosis and Treatment?
- Hint: Size matters: 100 microns

70

Macroaneurysm



- 1mo and 5 mo s/p focal laser
- VA returned to 20/20
- Blood Pressure at initial visit:
  - 186/98
- Hypertension is prime concern if macro-a seen, secondary concern of diabetes

71

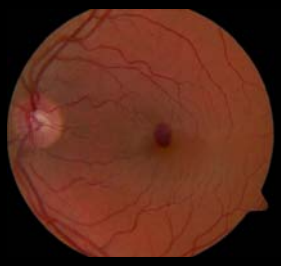
RAM

- Most commonly in 6th or 7th decade of life
- Usually women, and only 10% bilateral
- Hypertension is prime systemic assoc. (2/3)
- Must also rule out cardiovascular disease, including increased cholesterol/lipid levels, and diabetes
- Communication to PCP

72

Dangers of Addiction

- 38 yo male
- Healthy
- No meds, but…
  - Viagra PRN
  - Frequent Alcohol
- 20/20 OD, 20/30 OS
- Ant Seg healthy
- Retina OS as seen
- Diagnosis?



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"Drunken Pumpkin" Valsalva Maculopathy

- Common causes:
  - Vomit, cough, sneeze, constipation, exertion
  - Often seen with alcoholism, bulemia and GI problems
- Tend to resolve on own
- No long lasting damage
- What caused condition in this patient?

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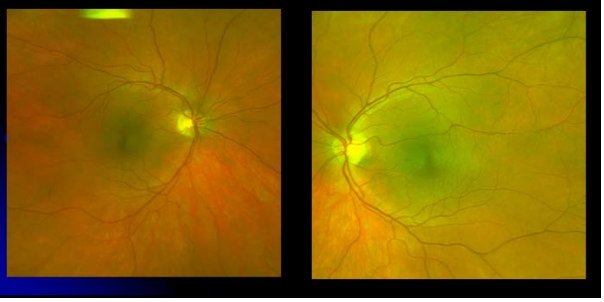
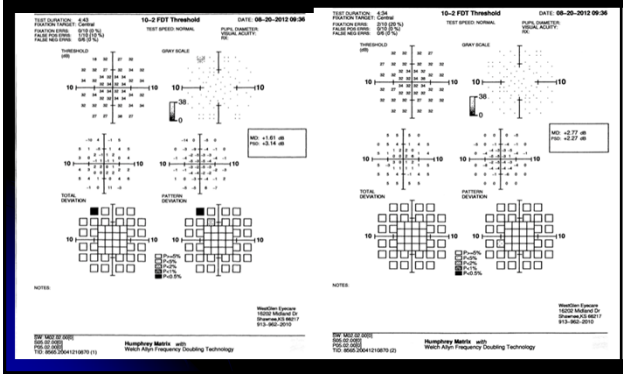
What do you think when you see this clinical image?

OD Macula **OS Macula**



75

How about this Visual Field??



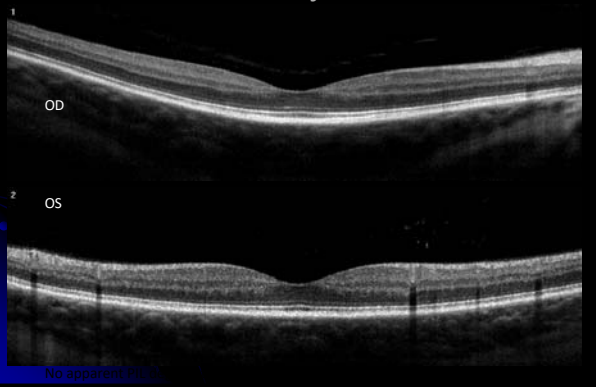
76

Pt. AM exam findings

- Pt AM is a 47yo female that has been on Plaquenil 200mg BID x 1 yr, weights approx 120lbs
- Being seen by request of her rheumatologist for screening for Plaquenil toxicity
- Vision corrects to 20/20 in both eyes
- Pupils and screening Matrix VF are normal
- Contrast is normal at 1.25% OU and color is normal
- MPOD is .31 OD and .38 OS
- IOP 18/17mmHg
- Schirmer is 0mm in both eyes w/ dry eye sx

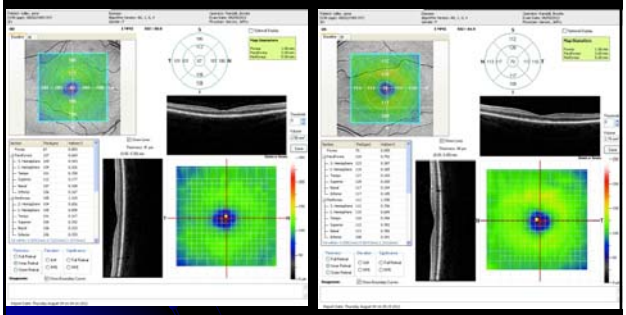
77

Further findings: Cross Hair OCT: Worried yet??



78

Inner Retinal Thickness: Still all normal



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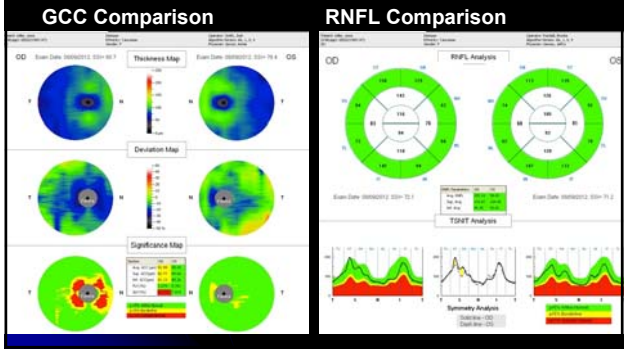
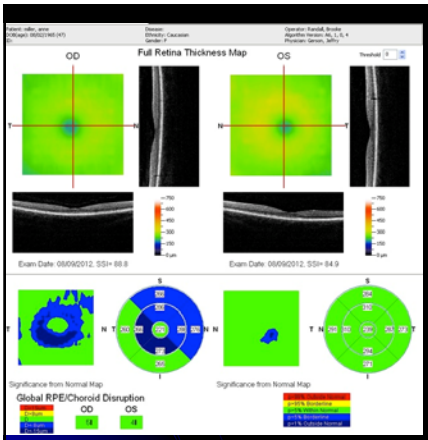
GCC and RNFL



80

Full Retina Significance OD and OS

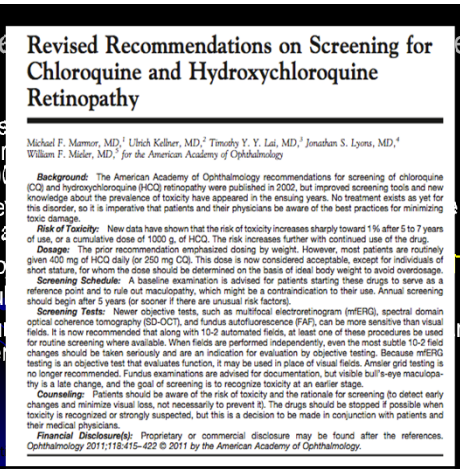


- Note: significantly ring thinning around OD macula

81

Ne

- Ris
- Ne
- Ob
- Su
- Fu



Revised Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy

Michael F. Marmor, MD,[1] Ulrich Kellner, MD,[2] Timothy Y. Y. Lai, MD,[3] Jonathan S. Lyons, MD,[4] William F. Mieler, MD,[5] for the American Academy of Ophthalmology

Background: The American Academy of Ophthalmology recommendations for screening of chloroquine (CQ) and hydroxychloroquine (HCQ) retinopathy were published in 2002, but improved screening tools and new knowledge about the prevalence of toxicity have appeared in the ensuing years. No treatment exists as yet for this disorder, so it is imperative that patients and their physicians be aware of the best practices for minimizing toxic damage.

Risk of Toxicity: New data have shown that the risk of toxicity increases sharply toward 1% after 5 to 7 years of use, or a cumulative dose of 1000 g, of HCQ. The risk increases further with continued use of the drug.

Dosage: The prior recommendation emphasized dosing by weight. However, most patients are routinely given 400 mg of HCQ daily (or 250 mg CQ). This dose is now considered acceptable, except for individuals of short stature, for whom the dose should be determined on the basis of ideal body weight to avoid overdosage.

Screening Schedule: A baseline examination is advised for patients starting these drugs to serve as a reference point and to rule out maculopathy, which might be a contraindication to their use. Annual screening should begin after 5 years (or sooner if there are unusual risk factors).

Screening Tests: Newer objective tests, such as multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF), can be more sensitive than visual fields. It is now recommended that along with 10-2 automated fields, at least one of these procedures be used for routine screening where available. When fields are performed independently, even the most subtle 10-2 field changes should be taken seriously and are an indication for evaluation by objective testing. Because mfERG testing is an objective test that evaluates function, it may be used in place of visual fields. Amsler grid testing is no longer recommended. Fundus examinations are advised for documentation, but visible bull's-eye maculopathy is a late change, and the goal of screening is to recognize toxicity at an earlier stage.

Counseling: Patients should be aware of the risk of toxicity and the rationale for screening (to detect early changes and minimize visual loss, not necessarily to prevent it). The drugs should be stopped if possible when toxicity is recognized or strongly suspected, but this is a decision to be made in conjunction with patients and their medical physicians.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

Ophthalmology 2011;118:415–422 © 2011 by the American Academy of Ophthalmology.

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Revision to SOC

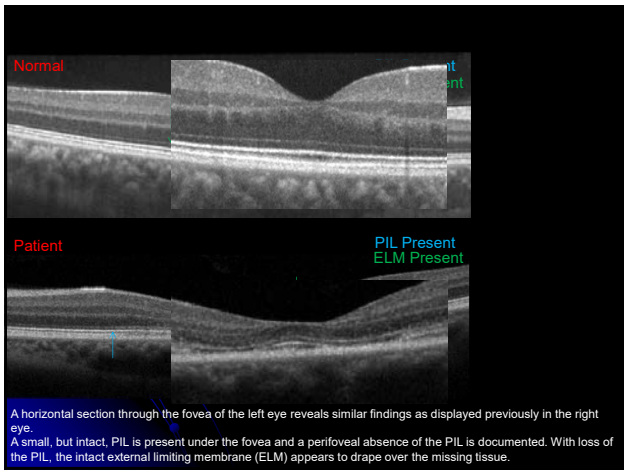
- Published in Ophthalmology in 2016 again by Marmour
- Main changes:
  - OCT and 10-2 are main tests
  - MfERG and FAF in Asians
  - Goal of <5mg/kg of real body weight
  - Risk of toxicity at 5/10/20yrs is 1/2/20%

83

This is the question

- When looking at the scans for this patient, can we tell if this is Plaquenil toxicity vs other macular abnormality?
- Is it likely to see such asymmetric changes due to Plaquenil?
- Cumulative dose is low, at only approximately 150,000mg (well below hypothesized “tipping point” of 1,000,000mg)

84



A horizontal section through the fovea of the left eye reveals similar findings as displayed previously in the right eye.
A small, but intact, PIL is present under the fovea and a perifoveal absence of the PIL is documented. With loss of the PIL, the intact external limiting membrane (ELM) appears to drape over the missing tissue.

85

Importance of VF

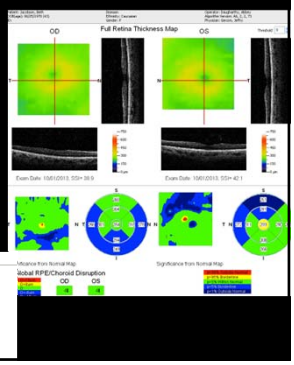
- VF should be 10-2 and performed along with objective test
- Even though SDOCT is objective and more specific: 10% w early toxicity will show significant VF defect and "normal" OCT (in patients w 1000g cumulative)
- Compared VF to OCT profile and thickness….no GCC measurement

Marmor M, Melles R. Disparity btwn VF and OCT w Hydroxychlorouine. Ophth. 6/14

86

Why is baseline so important

- 43yo female w Rx for Plaquenil
- Wants eyes checked before staring
- h/o autoimmune and neurologic disorders w multiple meds



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Drug Induced Maculopathies

- Tamoxifen
- 1-6% incidence
- Related to total dose (10g) or daily dose
- Can happen very acutely
- Often improve after discontinue drug

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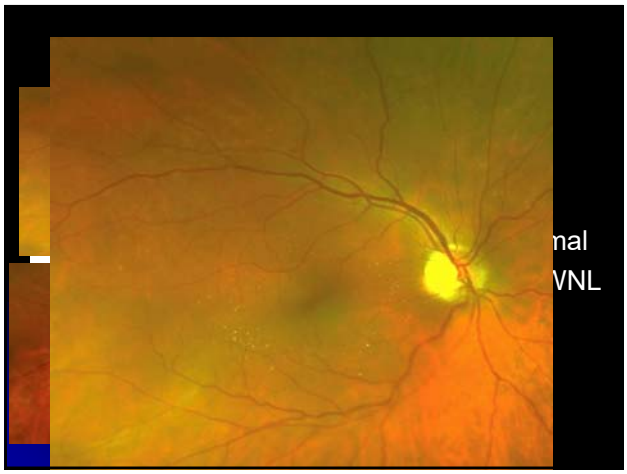

mal
VNL

89

Nevus

- Usually flat lesions of choroid, may have minimal elevation
- May develop drusen
- Estimated to be in 6-10% by Blue Mountain Eye Study
- Recent pub. stating 2.1%[1]
- May be pigmented or amelanotic
- Observation for growth critical
- Ophthalmology Oct 2005 Singh et al
  - Estimate 8.64 million in US with nevus
  - Estimate conversion to melanoma to be 1/8845

1. Greenstein et al. Prevalence of nevi. Ophthal. 12/11.

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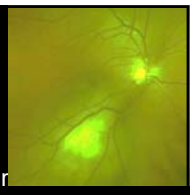
Metastatic Disease

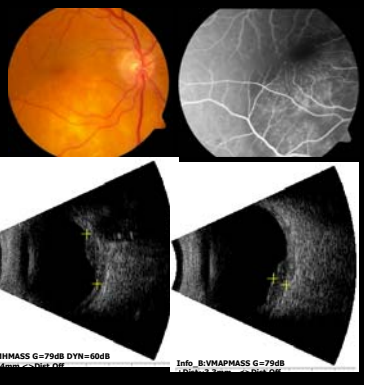


- Cancer is 2nd leading cause of death in US
- Choroidal met is most common ocular malignancy
- As high as 34% with choroidal met, have no previous dx of cancer
- Most common primary site is lung, followed by breast
- Despite rise in dermal melanoma, no rise in choroidal melanoma seen
- PET/CT scans most effective for detecting systemic met. BJO Sept. 2005

91

Metastatic

- Most common primary sites:
  - Men
    - Lung 26-50%
    - Unknown 6-29%
    - GI 3.5-12%
    - Prostate 3-12%
  - Women
    - Breast 68-85%
    - Lung 8-12%
    - Unknown 4-12%



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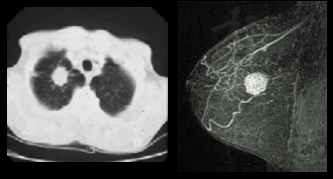
Metastatic Disease

- Most common sites of Choroidal Metastasis
  - Breast 39.7 – 65%
  - Lung 14-29.5%
  - GI 2.6-6.3%
  - Skin 2.0-4.5%
  - Prostate 1.3-3.6%
  - Kidney .9-4.0%
  - Unknown 4-18.3%
- Thorough systemic work-up needed in cases of ocular malignancies



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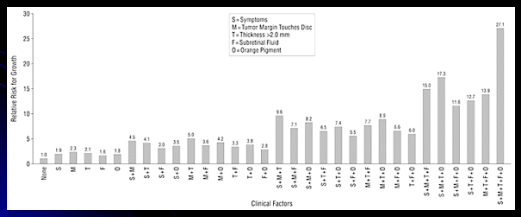
Ocular Melanoma

- Early recognition of signs of small lesions likely to prove to be melanomas: symptoms, tumor margin touching disc, thickness > 2.0 mm, subretinal fluid, orange pigment



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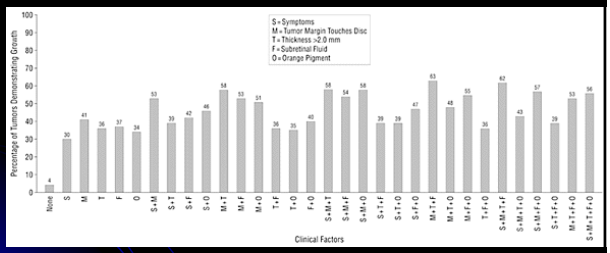
Percentage of Small Tumors that Grew



C Shields et al. Arch Ophthalmol 2000; 118: 360-364

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Easier Plaque Design Low Profile

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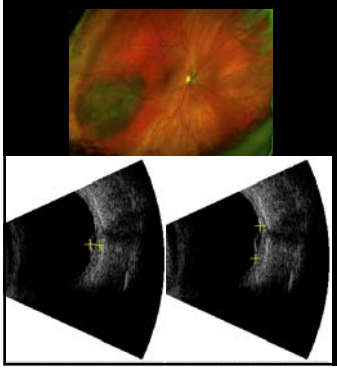
Choroidal Melanoma



- 53yo caucasian female
  - HTN and hypecholest.
- Referred by OD
- 20/20 OD 20/25 OS
- Suspicious lesion OD
- Sent for systemic w/u

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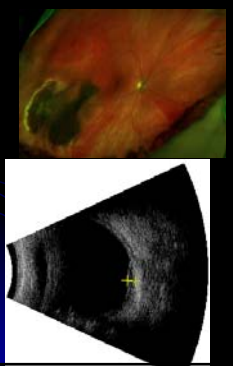
Post treatment



- Systemic workup negative for metastasis or other ca
- Brachyplaque therapy
- Vision to 20/50 post tx
- CE and vision to 20/40
- Spread/mortality
  - Tumor configuration
  - Histology
    - Spindle
    - Mixed
    - Epithelioid

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Life Expectancy

- High likelyhood of metastatic disease
  - 25% at 5 yr and 34% at 10yr
  - If metastasize, poor prognosis
    - Death rate of:
      - 80% at 1 yr
      - 92% at 2 yrs
      - Approx. 1% survive 5 yrs
- Difficult to predict survival
  - Not related to tumor size or treatment modality

COMS group. Devel. Of Metastatic Dz in COMS. Arch Ophth 12/05

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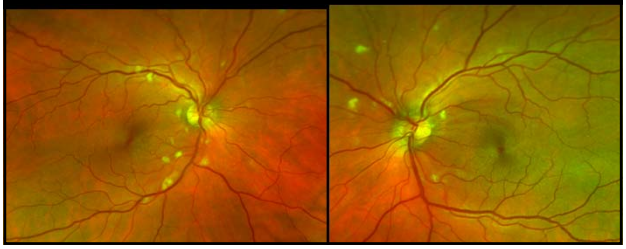
Routine exam finding

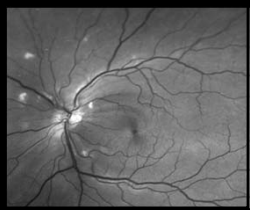
- 54yo male in for routine exam
- 20/20 vision
- h/o Melanoma



100

Drug induced retinopathy

- Interferon treatment for 5 mos
  - Infusions 1/mo and injections 3/wk
- Typical onset 1-5 mos
- Often resolves w d/c Tx
- More common w HTN



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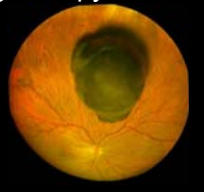
Quality of Life after Tx

- Significant difference in vision for 1st year (plaque > enucleation), fading after 5 yrs
  - Most notably driving and peripheral vision
- Patients treated with plaque had increased psychological distress following therapy
  - This faded after survival rates announced
  - Still distress in both groups



Melia et al. Quality of Life: 5 yrs after Tx in COMS. Arch Ophth 2/06

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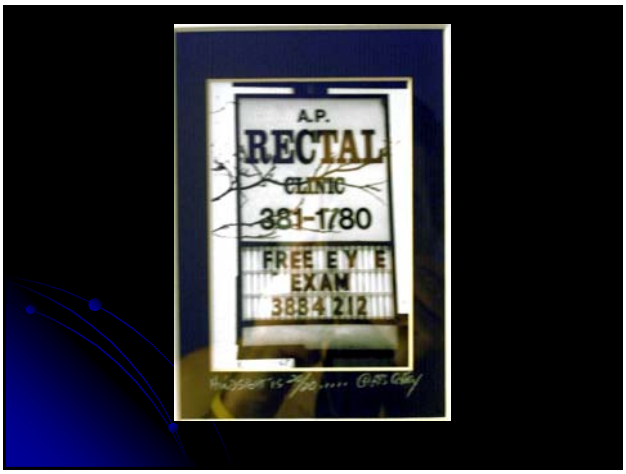
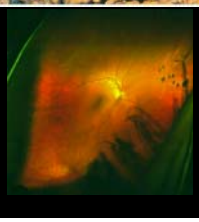


103

Familial Adenomatous Polyposis (FAP)

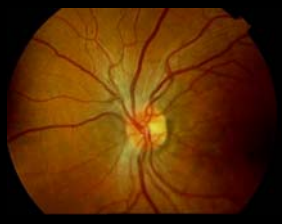
- Rare: 2.3-3.2/100,000
- Avg onset at 16yo
- Without Colectomy, colon cancer inevitable
- Autosomal dominant 75-80% have affected parent
- 78-88% have 4 or more fundus lesions



104

Retinal Consult

- 37 year old female
- Vision 20/40 OS
- No pain or pain with movements
- No APD
- Normal Anterior segment exam
- Recent ER visit for LOV
  - Then went to Ophthal.
    - Either MS, Diabetes or nothing…wait and see



Further History:
Previous episodes of vision "Graying"
Unable to take hot showers
Electric like impulses through arms/back
Numbness in fingers
Clumsy walking
Decreased contrast/color OS

105

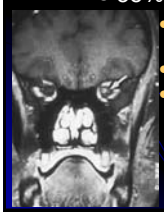
Optic Neuritis

- What is the normal visual outcome?
- Will this recur?
- What is risk of MS?
- What is eye treatment?
- What is Systemic Treatment?
- What tests are needed?

106

ONTT, CHAMPS and ETOMS

- All 3 agree, and confirm likelyhood of progression to further demyelinization
- Recurrence of Optic Neuritis:
  - 28% at 5 yrs
  - 35% at 10 yrs



- Recurrence more frequent in those that eventually developed MS
- Single occurrence not associated with poor vision
- Multiple occurrence associated with worse vision, approx. 25% were 20/400 at 5 years

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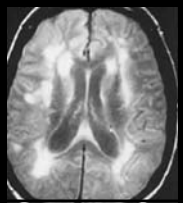
Optic Neuritis and MS

- 15-20% of MS present with ON
- 38-50% of MS will develop ON
- Most predictive factor in who will develop MS is presence of white matter abnormalities (demyelinating lesions) on brain MRI
- *Overall 10-year risk of MS 38%
  - no baseline MRI lesions 22%
  - ≥ 1 baseline MRI lesions 56%*



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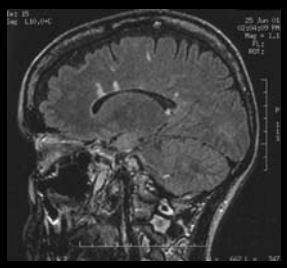
Treatment?

- Oral steroids alone not affective
- At 3 years, MS risk for IV vs PO vs Placebo 17% vs 21% vs 25%
- IV methylprednisilone x 3 days followed by 11 days of oral pred.
- Treatment with IMA?
  - 12,000/yr with wkly/daily injections and side effects
  - Interferon Retinopathy[1]
  - *NEW ORAL TX!!!**



Retinopathy of MS on Interferon. Saito.et al. MS: April 07

109

ON predictive factors

- When no brain lesions were found, the following were not present in any cases of CDMS (clinically definite MS)
  - Severe disc swelling, painless, NLP, retinal exudates, disc or peripapillary hemorrhage

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OCT: Predictive value

- RNFL thickness may be able to be predictive as to MS or level of vision loss
- RNFL thickness signif. reduced in MS eyes
- Disease free thickness>MS = fellow of ON > MS w ON
- Lower visual function with less RNFL
- Avg. RNFL thickness declined with increased neuro. impair. and disability

Fisher et al. RNFL in MS. Ophthal 2/06

111

Lattice Degeneration…

- 30 year old male referred for evaluation of lattice degeneration and atrophic holes
- Very healthy athlete, no medications
- Exam findings:
  - VA: 20/20 OU
  - Anterior segment healthy
  - Peripheral retina: Lattice with holes
  - Posterior pole..

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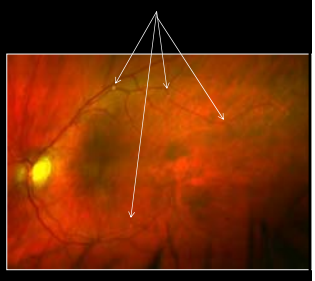
Plaques

- Several *Hollenhorst* Plaques
- Further questioning: No cardiovascular or carotid disease
- Treatment: Laser to lattice and holes
- Referral: To PCP for cardio and carotid work-up
- Pt lost to follow up



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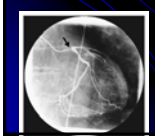
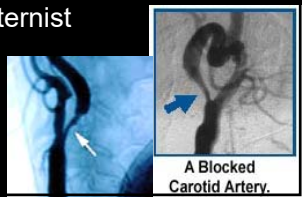
Hollenhorst Plaques

- Landmark article in AJO January 1973
  - Carotid disease and heart disease about same incidence at time of plaque seen
  - Patients 4x more likely to die of MI than CVA
  -
- Referral to PCP or internist





A Blocked Carotid Artery.

114

Artery Occlusion

- Historically felt than 5% develop NV
  - Duker et al 1991: 18.2% NVI, 15.2% NVG
  - Hayreh: mean to NVI 5.5 weeks
    - Can develop NVI without carotid disease
  - Inner retinal cell death, but outer layers spared, and have high O_2 demand
- Treatment
  - PRP when NVI
  - Acute treatment
    - AC paracentesis, massage, carbogen…
    - Accupunture[1]: marked visual improvement in 25%
    - TPA (EAGLE study in Europe)
  - Referral to PCP or internist for treatment of underlying systemic disease
- Article in Sept 06 AJO by S.S. Hayreh

1. Zheng J, Chen Z, Wang W, Xia S: Acupuncture in retinal arterial occlusion. Chin Med J (Engl) 94: 175, 1981

115

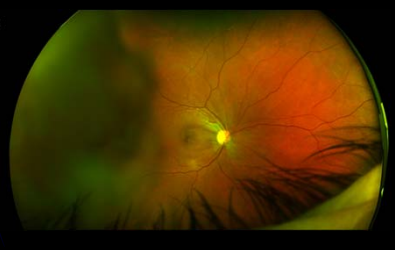
Recent patient

- 64yo Hispanic female
- Sudden LOV 5 hrs ago
- Good health

OD: NLP OS: 20/

What else do you want to know?

260/150



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What's the most important thing to do with an acute artery occlusion?

- HINT: Not eye related!!
- THESE ARE SICK EYES IN SICK PEOPLE
- Study of 103 pts screened after CRAO
  - 37% critical carotid disease and acute stroke
  - 33% HTN emergency, 20% MI,
  - 25% surgical intervention, 93% medicine change[1]
- Immediate referral to ER/Stroke center and Diffusion weighted MRI

1. Lavin et al: Stroke risk and risk factors in AO. AJO in press 9/18

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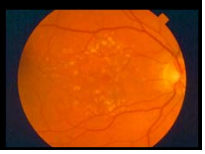
Is AMD strictly an ocular disease with no systemic associations?

- NO
- Several different theories and factors that point to AMD being systemically related
- "Systemic" treatments may be beneficial
- Nutrition modification is an easy way to treat systemically



118

CVD and AMD share many common risk factors

"sick eyes may occur in sick bodies related to smoking, obesity, inadequate nutrient intake, and other unhealthy behaviors".

Seddon JM et al. C-reactive protein and homocysteine are associated with dietary and behavioral risk factors for age-related macular degeneration. Nutrition 22:441-43, 2006.
Seddon JM et al. Evaluation of homocysteine and risk of age-related macular degeneration. Am J Ophthalmol 141:201-3, 2006.
Seddon JM et al. Progression of age-related macular degeneration: prospective assessment of C-reactive protein, interleukin-6, and other cardiovascular biomarkers.Arch Ophthalmol 123:774-82, 2005.

119

Remember Pablo….Vision is important

- Can we allow our patients to see like this…regardless of ocular pathology?

120

So now you are ready to "treat" systemic disease, but…..

- What is the most important thing we can do for our patients (in their "eyes")
- CORRECT VISION!
  - That is why they come to us
    - Majority of vision impairment in diabetes is from lack of refraction![1,2]
- Practice the "Optometric Model"
  - Combining medical and optical "treatment"

1. Klein et al. VI Prevalence (WESDR) Ophth. 10/09. 2. Zhang et al. DM and VI. Arch of Ophth. 10/09.

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Thank You

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Thank You

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Online Resources

- www.retinalphysician.com
- www.pubmed.com
- www.optometricretinasociety.org
- www.optos.com

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