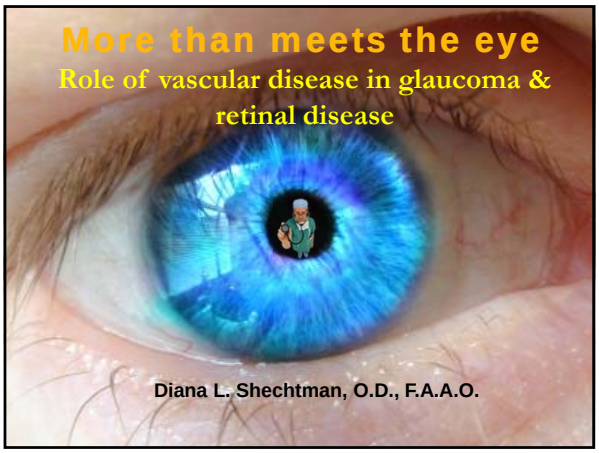
More than meets the eye

Role of vascular disease in glaucoma & retinal disease



Diana L. Shechtman, O.D., F.A.A.O.

The questions that follow

- What's you Dxs or DDx?
- What tests would you order to identify underlying disease?
- How would you manage the glaucoma?
- Are you concern with the decreased vision OD? Would you order a MRI?
- Other in office tests tests?

Financial disclosure

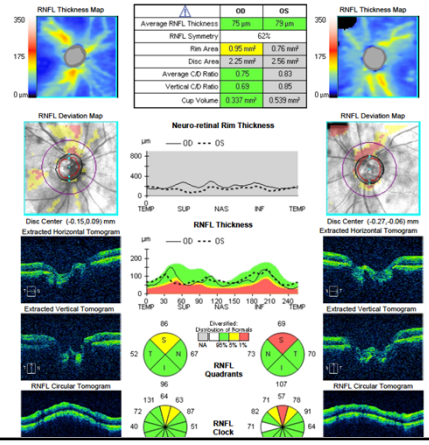
- I have received lecture honoraria or serve on the advisory boards or speaker's bureaus of:
  - B&L, Alcon, Allergan, ArcticDx, Annidis, CZM & Zeavision

68 Jamaican female

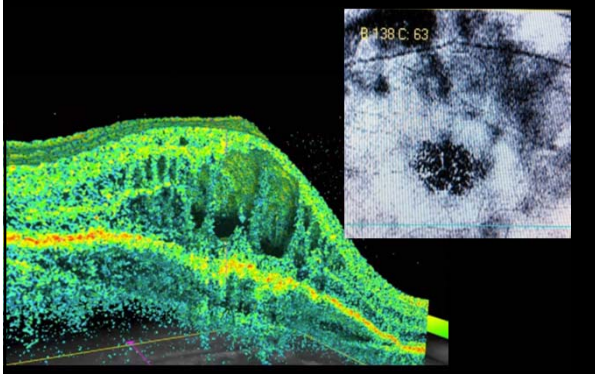
- CC: mild decrease in vision OS X few months
- POHx:
  - ACIOL OS (slight de-centered)
  - Cataracts OD
  - Retinal break OS s/p laser
  - POAG OU (Takes timoptic BID)
- PMHx: PRE-DM X 1 yr
- IOP: 15mmHg OU

51 BM

- Vision decreased OD over the last 2 yrs
- PMHx: unremarkable
- BCVA:
  - 20/60 OD 20/20- OS
- P: (+) APD OD
- IOP: 38mmHg OD 27mmHg OS
- SLE: mild cataracts OU



Advanced visualization

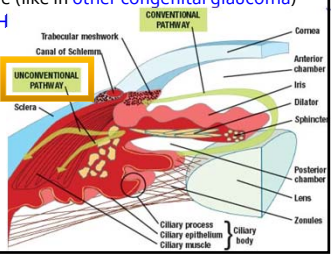


SWS and association with glaucoma

Pathophysiology:

- Abnormal development of anterior chamber
  - Abnormalities within the angle structures may be associated with decrease aqueous drainage (like in other congenital glaucoma)
- Mechanical pressure from CH pressure (onset of OAG late)

Treatment via unconventional path (AH sip thorugh tissue around uvea)



Conventional
TM→schelm canal→ episcleral venous plexus (via limbus)→VV→ophthalmic (leave via sclera)

20 HM

- CC: Decreased VA X few weeks OS
  - World looks like a "FISH bowl"
- PMHx: Unremarkable
  - LME 6M (never told to get an "EYE exam")
  - CT at age 1 & sees PCP q12M
- POHx: Unremarkable
  - Last CEE was at age 1
- Amsler: (+) metamorphopsia OS
- BCVA 20/20 OD 20/30 OS

Management of OUR patient

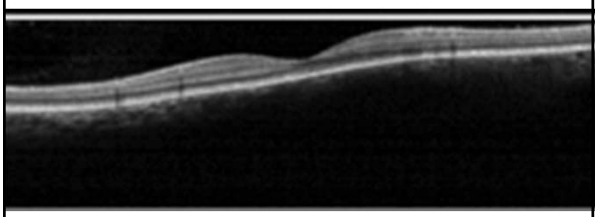
- SWS
  - Glaucoma
    - Glaucoma work-up
    - Cosopt BID initiated
      - PG work well with THIS 2nd glaucoma but why is it NOT an ideal med in THIS case?
  - Retinal detachment/Choroidal menangioma
    - Ultrasound/FA CONFIRMED the Dx
      - FA: hyperFL of large choroidal vessels with Fl staining entire lesion
      - UBM: solid moderate reflective tumor

Sturge Weber Syndrome (SWS)

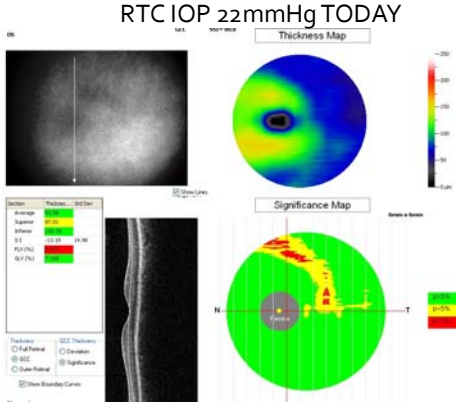
Encephalotrigeminal (facial) angiomatosis
Neuro-oculo-cutaneous congenital vascular hamartomas

- Need not affect ALL 3 systems
  - CNS angioma
  - Choroidal hemangioma (Ipsilateral to PWS)
    - 50% of CH are associated with SWS
    - Most commonly DIFFUSE pattern
    - **Various associated complications**
  - **PWS**
    - Distribution along trigeminal nerve
    - Choroidal hemangioma is more common with lid involvement
      - Also increased likelihood of glaucoma

S/p **AVT** injection affect on permeability
Pt will be undergoing external beam radiation to treat the choroidal hemangioma

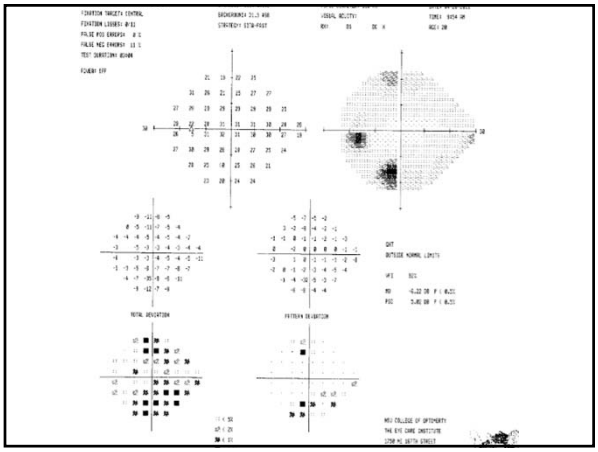


RTC IOP 22mmHg TODAY



54 BM

- Blurred vision at near
- No medical Hx
- BCVA: 20/20 OD, OS
- P: (+) APD OS
- POHx: Trauma OS '04
  - Received stitches to the side of his head
- Gonio: Angle recession OS
- BP: 160/110 mmHg



20/20 and (+) APD…is that possible?

- Occupying ONH lesion
- Optic neuritis
- Neurological VFD
- And…

Relationship b/t glaucoma & vascular diseases (2010 Study)

- N= 76,000 glaucoma
  - 50% had HTN
  - 30% hyperlipidemia
  - 30% had DM
  - Other co-morbidities were also significantly higher in pts with glaucoma than does w/o glaucoma

Glaucoma patients are significantly more likely to have co-morbidities. This can be **life threatening** or can affect the quality of life appreciably. **Glaucoma pts should see PCP q12M**

Herng-Ching Lin Ophthalmology 2010

Follow up for our pt 1M later

- S/p Timoptic BID / Xalatan qhs OU
  - 15 mmHg OU
- BP Dx and managed…
  - Dxed with HTN through a PCP consultation and placed on meds
    - BP today 133/86 mmHg
- F/u q3M

HTN & glaucoma: Pathogenesis

- HTN→arteriosclerosis →constriction of SPCA →ischemia→neural tissue loss
  - This further may cause **dysregulation**
  - Retinal vascular narrowing has been reported among glaucoma pts Beijing Eye & Rotterdam Study
    - Studies have shown that subjects with narrower retinal vessels were more likely to have glaucomatous ON

Deokule Can J oph 2008, Tielsch Arch Oph 1995 & Egna-Neumarkt study 2000

We have all experienced dysregulation…

- Ever felt the following
  - Cold extremities
  - Reduced sensation of hunger OR…
  - Migraines…while working with your kids on their homework
    - OK this one may be SELF induced REGULATION

Systolic BP and Glaucoma

- IOP is positively (but weakly)correlated with BP
  - For every 10mm change in SBP, there is a 0.5mm change in IOP
  - Association between BP and the development of glaucoma is weak

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Glaucoma and OBF

Decrease in OCULAR flow have has been observed in pts with glaucoma & even believe to be associated with progression

World glaucoma association: concluded that vascular dysregulation may contribute to glaucoma pathogenesis

The vascular theory of glaucoma: glaucomatous optic neuropathy may be a consequence of insufficient blood supply

So what is Vascular Dysregulation?

- Impairment of normal autoregulation mechanism
  - Vessels do not constrict/dilate properly in order to provide adequate blood flow
    - It may lead to decrease blood flow into the eye→glaucomatous damage
  - This can be an affect of LOCALIZED ocular disease or OVERALL vascular disease can lead to dysregulation

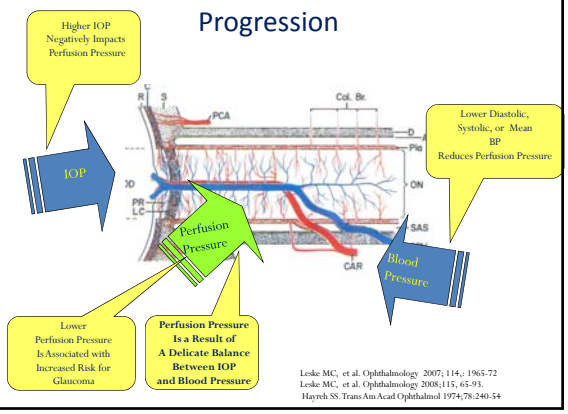
Nicolela Ophth 2007 & Grieshaber Surv Ophthal 2008

Hypotension & glaucoma

- Reduction in systemic BP has a deleterious effect, creating insufficient perfusion pressure to ON
  - Ischemia can lead to glaucomatous damage
    - pts with glaucomatous & associated VLD are more likely to have underlying hypotension, compared to pts with glaucoma & no associated VFD
    - ocular perfusion pressure is associated with decrease blood flow
  - Barbados Eye Study
    - Low SBP was a risk factor for incidence of OAG
  - EMGT: Low SBP was a predictor for progression

STUDIES: Blue mtn, Baltimore, EMGT & Barbados Eye, Latino, Thessaloniski Eye & Grieschaber curr opin ophthal 2005

Ocular Perfusion Pressure and Glaucoma Progression



Leske MC, et al. Ophthalmology 2007; 114,: 1965-72
Leske MC, et al. Ophthalmology 2008;115, 65-93.
Hayreh SS. Trans Am Acad Ophthalmol 1974;78:240-54

OPP in EMGT

- Randomized clinical trial comparing no treatment to treatment for initially diagnosed glaucoma (entire cohort followed for progression)
- In patients with **higher** baseline IOP:
  - h/o CVD increased risk (HR 2.75, CI 1.44-5.26)
  - Lower SPP increased risk (HR 1.55, CI 1.02-2.35)
- In patients with **lower** baseline IOP:
  - Higher systolic BP decreased risk (HR .44, CI .2-.97

Leske MC, et al. *Ophthalmology 2007;* 114, (11): 1965-72

The First Charge

- There is no accurate, repeatable, verifiable method of measuring blood flow to the optic nerve head.
- The instruments purported to do so do not agree.
- We have no means of measuring blood flow to the nerve in a clinically useful fashion

Conclusion

- "The relationship among BP, IOP and development of OAG is complex and requires further investigation."

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

Consensus Points

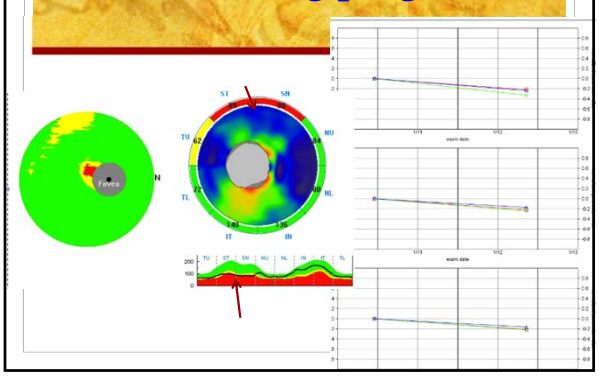
- Blood Pressure is positively correlated with IOP.
- It is unclear whether the level of BP is a risk factor for having or progressing OAG in an individual patient.
- Lower OPP is a risk factor for primary OAG.
- OBF parameters measured with various methods are impaired in OAG, especially in NTG

Weinreb R, Harris A. Ocular Blood Flow in Glaucoma 2009 Kugler Publications

54 WF

- RTC for evaluation of glaucoma
  - Treated with Alphagan BID (highest IOP was 19)
- PMHx: HTN but very compliant with meds
  - Takes systemic b-blocker at night
- BP: 126/60 mmHg
- BCVA: 20/20 OD, OS

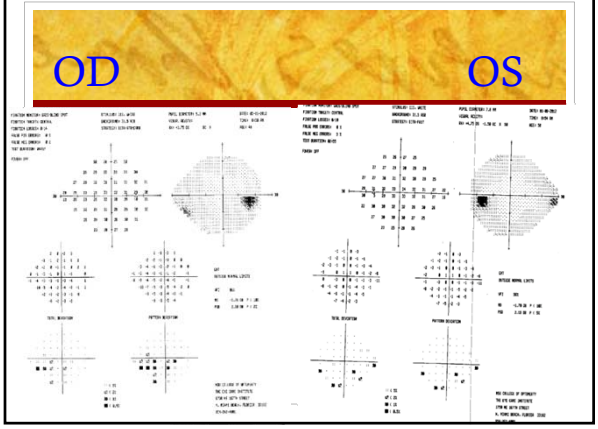
OD is showing progression



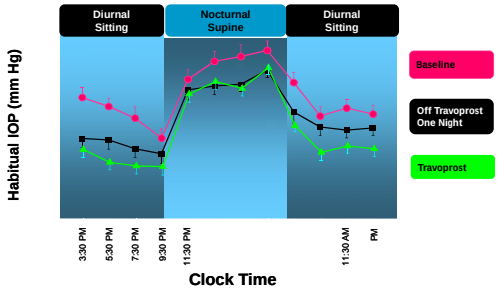
Managing HTN & managing OAG may be challenging

- First, lower IOP (17 is too high for this pt)
- Second, consider increasing perfusion *(but remember that it may be at the consequence of lowered IOP)*
  - Anti-glaucoma meds that affective diurnal/noctunal IOP curves
    - Those who are less likely to have transient spikes
  - ?what about non-selective b-blockers (Timoptic) vs selective (Betoptic)
    - B-blockers may decrease perfusion via vessel constriction
    - How is his systemic b-blocker affecting IOP & should you stay away from ocular b-blocker in these pts?

OD OS

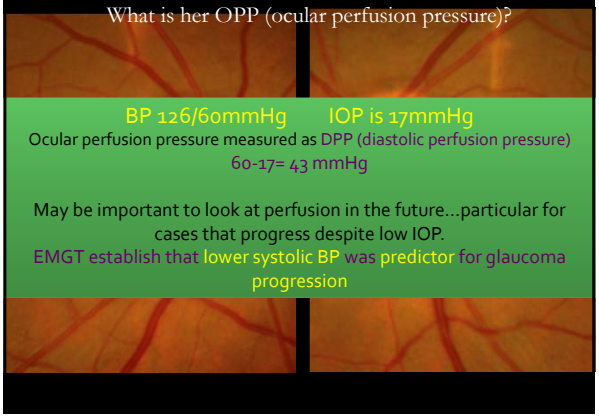


Travoprost Reduces and Sustains Habitual IOP-lowering



Sit AJ, Weinreb RN et al. Sustained Effect of travoprost on diurnal and nocturnal intraocular pressure. *Am J Ophthalmol.* 2006;141:1131-1133.

Is decreases perfusion the cause for progression? What is her OPP (ocular perfusion pressure)?



BP 126/60mmHg IOP is 17mmHg

Ocular perfusion pressure measured as DPP (diastolic perfusion pressure)

60-17= 43 mmHg

May be important to look at perfusion in the future…particular for cases that progress despite low IOP.

EMGT establish that lower systolic BP was predictor for glaucoma progression

Managing HTN & managing OAG may be challenging: Continuation

- Exercise can increase blood flow
- Talk to PCP about HTN medications
  - Can pt take Medications during the day rather than at **night ???**
    - **May have a (+) affect on OAG BUT (-) affect on CVD**

REview

- Lower IOP improves OPP
- Higher systemic BP improves OPP but don't necessarily want to raise BP
  - Stroke #3 cause of death in US behind CVD and CA!
- Avoid drugs that lower systemic BP beyond patient's desired systemic control
- Avoid nocturnal hypotension

Take Home Points

- The role of blood supply as a risk factor in glaucoma is poorly understood and remains controversial
- Be aware of vascular health issues in our glaucoma patients
  - Blood pressure
  - Sleep apnea
  - dyslipidemia

MAPEC 2011

- The thought behind the study
  - Previous large population-based, long-term outcome studies found that sleep-time BP level is more sensitive predicator of risk of dying from CVD THAN BP level measured during the daytime
  - Some pts do not experience 10-20% decrease in BP at night (**NON-DIPPERS**)
- 5 yr study used 48hr ambulatory BP monitoring perform in yearly intervals to determine **if AM vs PM dosing would affect CVD/BP**
  - **There are variable BP measurements in AM/PM**

Take Home Points

- Encourage good lifestyle habits
  - Diet
  - Exercise
  - Avoid headstands with yoga
  - Stop smoking
- Refer for appropriate evaluation and management of possible risk factors
  - Blood pressure: avoid nocturnal hypotension
  - Sleep apnea
  - Vasospasm

MAPEC study

- RESULTS: There should be a shift from taking **HTN meds at night** instead of AM in order to protect (CVD) the pt
  - PM dosing:
    - Kept BP in normal range throughout the day
      - Pts had normal daytime BP
    - Provided protection against CVD complications
      - A decreases risk of cardiovascular related death, myocardial infarction and stroke were noted among pts taking PM dosing
        - **Pts with PM dosing had 1/3 the # of CVD related complications**

58 AA Female

- PMHx: T2DM X 6 yrs
- POHx: LEE 2 yrs ago
- IOP: 25mmHg OD 22mmHg OS
- Pachs: 500 OD 508 OS

Overall conflicting clinical evidence for a relationship between diabetes & glaucoma

Out of 15 epidemiological studies

Increased risk (6 studies)	No difference in risk (8 studies)	Diabetes is protective (1 study)
Beaver Dam Eye Study (1994)	Bedford Eye Study (1967)	OHTS (2002)
Rotterdam Eye Study (1996)	Framingham Eye Study (1977, 1980)	
Blue Mountains Eye Study (1997)	Baltimore Eye Study (1995)	
Barbados Eye Study (2003)	DARTS, Scotland (2000)	
Nurses' Health Study (2006)	VIP (2003)	
Latino Eye Study (2008)	EGPS (2007) + OHTS (2008 reanalysis)	

3% of pt reporting DM at baseline developed POAG compare to 8% who did NOT report it

So, why is DM a possible risk for POAG?

- Microvascular damage from DM impairs blood flow to ON, resulting in ON damage
  - Vascular tone depends on pericytes
- DM pts have concomitant CVD risk factors, affecting blood flow to the ON
- The ON of a pt with DM may be more vulnerable to elevated IOP

Piltz-seymour JR Optic nerve blood flow is diminished in eyes of primary open-angle glaucoma suspects. *AJO* 2001

Why the discrepancy?

Varying approaches for
- diagnosis of condition (i.e. diabetes, glaucoma),
- assessment criteria, and
- statistical approaches.

Examples:
- Redefinition of primary open angle glaucoma: Rotterdam Eye Studies
  Dielemans et al 1996 vs. de Voogd et al 2006
- Ocular Hypertension Treatment Study (OHTS)
  Gordon et al 2002, Coleman & Miglior 2008

1. Patient self-reported assessment on history of diabetes and medication
2. Exclusion criteria

Comments and reanalysis of OHTS data reported by Gordon et al, *Arch Ophthalmol.* 2008; 126, 280

Controversies about the direct correlation b/t glaucoma & DM

- Longer duration of DM could make pt at risk for POAG
- Could it be that DM pts (compare to those w/o DM) get their EYE examine more often and consequently are more likely to have their glaucoma detected?
- Could it be related to the fact that DM pts have higher IOP but not exactly POAG?
  - Studies shown greater increase in IOP among DM pts compare to those w/o DM (Barbados, Rotterdam & Blue mountain)
  - OHTS found DM pts to have thicker corneas

Quigley Arch Ophth 2009

OHTS results:
Could DM be a good thing for glaucoma?

- OHTS study methodological issues
  - Pts **self** reported their DM
- Selection was bias towards overall healthy DM population
  - EXCLUSION criteria was ANY sign of DR

OHTS in 2007 (OHTS prediction model applied to European Glaucoma Prevention Study control patients) concluded that Diabetes did NOT decrease or increase risk in EGPS

OHTS Study Group,EGPS Study Group. Oph 2007; 114:10-19

49 BM

- Decreased VA X 4 days OD
- PMHx: unremarkable
- BCVA: 20/40 OD 20/25 OS
- BP: 135/80 mmHg
- P: +1 APD
- IOP: 20mmHg 26mmHg

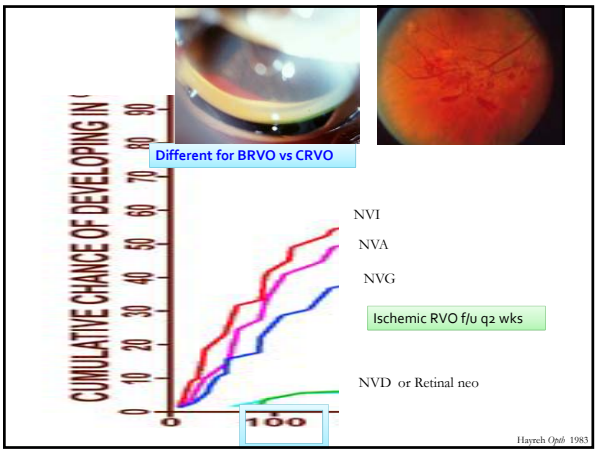
SO WHAT TO DO?

PCP work up
(PMHx: unremarkable)

Evaluation to retinal specialist for ?tx ME
(VA 20/40)

Treatment of glaucoma OU (IOP 19/23)

Ischemic or non-ischemic
(VA 20/40 & retinal presentation but +APD)



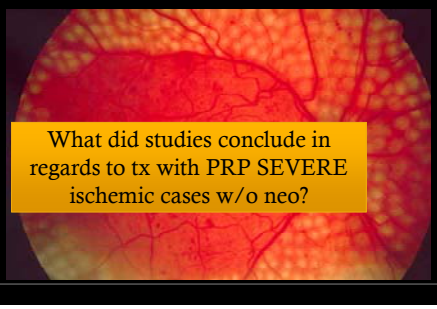
Is POAG a complication of VO: Fact or Fiction

- Studies report low incidence of POAG developing **AFTER** the RVO onset
  - Blue Mtn eye & Beaver Dam Studies & OHTS
- Pts are typically Dx with POAG or have risk factors (like large cups) prior to onset of RVO
  - The eye disease case-control study 1998, Hayreh 2000 & Luntz 1980

Hence, it would seem that with regards to the relationship b/t POAG & RVO that the glaucoma was the **PRIMARY** event

Hyphema in angle→ **heading for NVG**

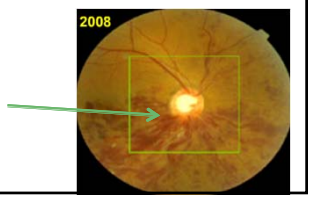
Scattered PRP decreased risk of NVG development



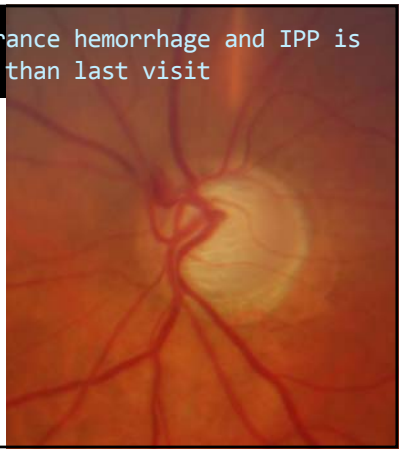
What did studies conclude in regards to tx with PRP SEVERE ischemic cases w/o neo?

Glaucoma & RVO: Pathophysiology

- Glacomatous damage at the level of the LC can result in a collapse CRV
- Increase in IOP can elicit pressure upon the CRV



OS Shows a Drance hemorrhage and IPP is 5mmHg higher than last visit



Disc Hemorrhages in OHTS

- Purpose:
  - To compare the rates of detection of ON hemorrhages by clinical examination and by review of ON photos
  - To assess the incidence of and the predictive factors for ON hemorrhages
  - To determine whether ON hems predict the development of POAG in OHTS

Budenz DL, Anderson DR, et al Ophthalmology. 2006 Dec;113(12):2137-43

ANALYSIS

- Take stereo photos & review them
- If a ON heme appears in patient with OHTN
  - consider the patient to be at higher risk of developing POAG & det if initiate treatment
    - YOU HAVE TIME
  - If a ON hem appears in patient with OAG consider pat. at higher risk of progression
    - But don't necessarily have to increase treatment…again you have time

Repeat test more often & reassess target IOP of need to start or change trt

Results: Disc Heme in OHTS

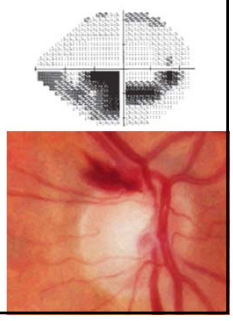
- ON heme detected BEFORE POAG endpoint
  - 16% of hemes detected by exam
  - 84% of hemes detected by review of photos ALONE
- Presence of ONH increased risk of POAG developing by 6-fold
  - Median time to development of POAG after hem appears is 1 yr

64 BM

- CC: Pain X 1 wk OD
  - 3 day follow up on uveitis Dx
  - Been taking PF X 3days q1-2hrs
  - In office homatropine given
- POHx: DR
- PMHx: DM & HTN X 10 yrs

What the Drance Hemorrhage tells you…

- **PATHOGENESIS?**
- Likely indicates active disease
- There may also be an increase likelihood of progression
  - Commonly associated with pre-exiting VFD
  - True prevalence among glaucoma pts is not known
    - Reports of <10%
    - MORE COMMON IN LTG

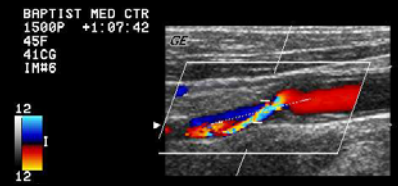


Case Presentation

- BCVA: 20/100 OD 20/40 OS
- IOP: 12mmHg 18mmHg
- SLE:
  - K: **mild endothelial folds** OD
  - *trace* C/F OD
  - NS OD > OS
  - ***Look at injection distribution…***

What did the doppler show?

Carotid stenosis



Clinical picture

Anterior

IOP typically low

Idiopathic uveitis

Cataract

Corneal edema

Dilated episcleral vessels

Neovascularization (in absence of DR)

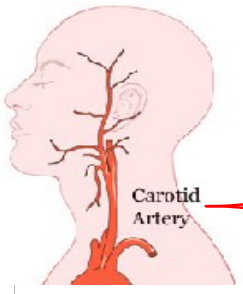
Posterior

Hemorrhages & CWS
Dilated veins
Macular edema

Asymmetrical DR

Embolic events
- **AION**
- **Artery occlusion**
- **Retinal emboli**

NVG can occur in these pts



OIS:

Ocular ischemic syndrome

OIS is commonly associated with carotid artery disease

DDx: may have common underlying risk factors

but DIFFERENT w/u

OIS	CRVO
▪ Mid-peripheral	▪ Posterior pole
▪ Dilated NON-tortuous veins	▪ Dilated tortuous veins
▪ Scares dot blot hemorrhages	▪ Confluent superficial and intra-retinal hemorrhages
▪ Associated anterior segment