

The Optic Nerve in Glaucoma and Beyond

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Financial Disclosures

- ◆ Nothing to Disclose

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What is glaucoma?

* Glaucoma is a group of diseases that lead to **characteristic damage of the optic nerve**, which in turn results in characteristic effects on vision

Note: IOP not in the definition.....
but.....IOP remains the only easily modifiable risk factor



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Who's at risk for glaucoma?

- ◆ Elevated IOP : Decreased ICP?
- ◆ Family History : Siblings / parents are particularly important
- ◆ African Americans and Hispanics at increased risk. Increasing age is a risk
- ◆ Myopes, OSA, migraineurs
- ◆ Increased systolic BP / decreased diastolic BP: Concept of DPP (diastolic perfusion pressure). DBP-IOP. 40 and below can be an issue
- ◆ Low corneal hysteresis or thin corneas

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IOP considerations

- ◆ Diurnal curve is critical.....fluctuation matters. IOP constantly fluctuates
- ◆ Overnight supine IOP can vary greatly from daytime sitting / standing IOP
- ◆ "Side sleeping" may matter
- ◆ Multiple studies have shown a peak IOP between 3:30 and 5:30 am and a trough around 9:30 pm
- ◆ So some "NTG" is just night-time spike OAG.....or "burned out" glaucoma
- ◆ On a practical basis, very difficult to determine.....often requires time
- ◆ Prostaglandins appear to be particularly good at blunting the diurnal curve
- ◆ The cornea can impact IOP measurement

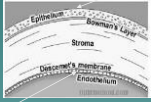
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Measuring IOP

- ◆ **ORA** (Ocular response analyzer): CPT 92145: not covered by Medicare. Also **Corvis ST**
- ◆ **Pachymetry**: CPT 76514: covered once for glaucoma
- ◆ Thin cornea = increased risk
- ◆ ORA measures corneal hysteresis / resistance and provides a "corrected" IOP
- ◆ Low hysteresis = increased risk. May be more indicative than just "thin or thick"
- ◆ Sometimes opposite of pachymetry. Low hysteresis with thick cornea, for example

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Pachymetry: just a distance



- ◆ Uses optical means or ultrasound to measure the distance from the front corneal surface to the back
- ◆ Can assess thin / normal / thick, but not stiffness / rigidity

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ORA: Ocular Response Analyzer Pressure, but much more

- ◆ Non-contact air puff that provides the following information.....
- ◆ Assesses ability to absorb shock
- ◆ Can think of it like stiffness
- ◆ Corneal hysteresis. Average is around 10.5-11.0 (10.7 in one large study)
- ◆ Corneal compensated IOP
- ◆ Estimated Goldman IOP
- ◆ WS: reliability indicator; want 3.0 or above to be acceptable (really good readings often above 8)
- ◆ Can do single puff, or average of 3 puffs

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CH Histogram

- ◆ Puts patient's reading on a bell curve histogram to compare to average CH (peak of histogram)
- ◆ Low end of bell curve at 5.0, high end of 16.0



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ORA

- ◆ Example (low):
- ◆ IOPcc 20.4
- ◆ CH 6.5
- ◆ IOPg 15

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ORA

- ◆ Example (average):
- ◆ IOPcc 16.4
- ◆ CH 10.8
- ◆ IOPg 16

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ORA

- ◆ Example (high):
- ◆ IOPcc 19.7
- ◆ CH 15.2
- ◆ IOPg 26

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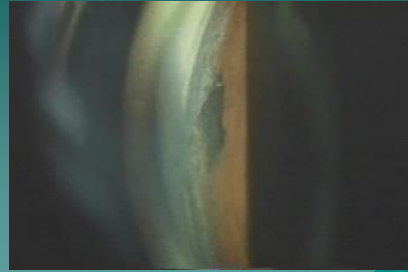
Types of glaucoma

- ◆ POAG / NTG
- ◆ Secondary glaucomas
 - ◆ Narrow angle / acute angle closure
 - ◆ PDS
 - ◆ PEX
 - ◆ Traumatic / angle recession
 - ◆ Uveitic & neovascular
 - ◆ Phacolytic
 - ◆ Phacomorphic
 - ◆ Steroid induced



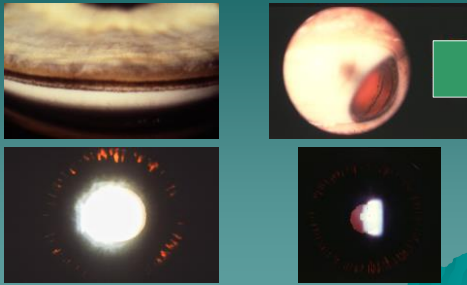
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Angle recession with iridodialysis

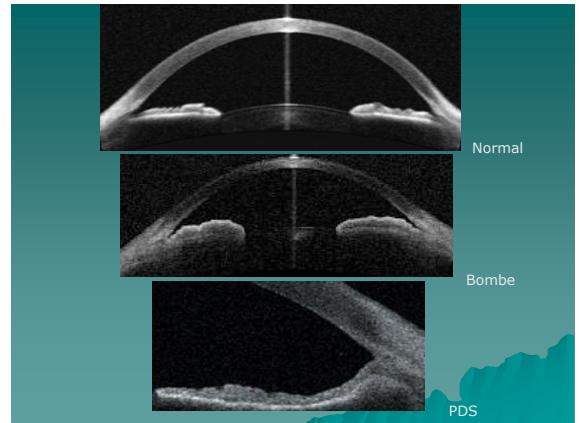


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PDS

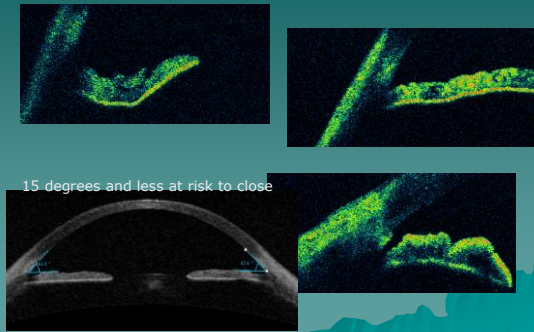


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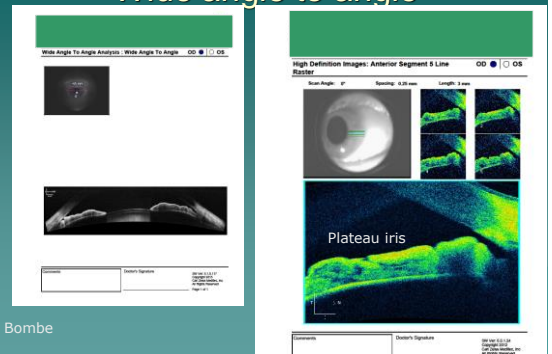
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PDS angle



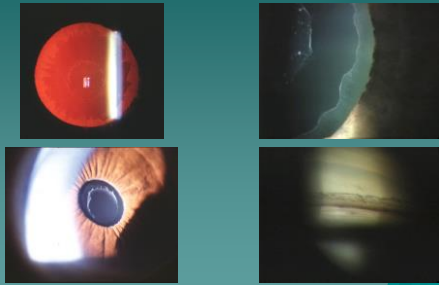
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Wide angle to angle



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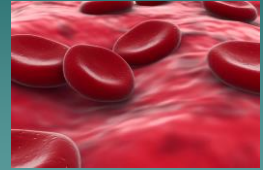
PEX



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Question.....

- ◆ Is PEX associated with anything systemically?
- ◆ Yes, it is a syndrome. Cardiovascular issues, hearing issues, increased homocysteine



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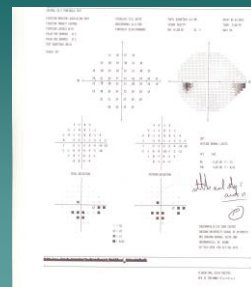
Visual field loss

- ◆ Types of VF loss...
 - ◆ Nasal step
 - ◆ Arcuate defect
 - ◆ Paracentral defect
 - ◆ Altitudinal defect
 - ◆ Bjerrum defect
- ◆ Correspond to damage on the nerve



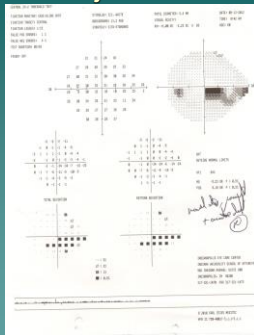
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Nasal step and early arcuate defect



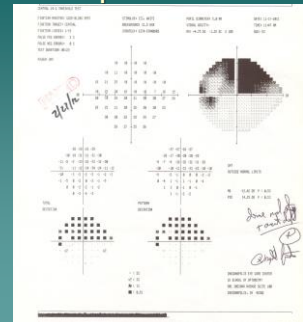
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Bjerrum defect



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Severe arcuate / altitudinal defect with split fixation



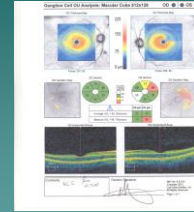
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Paracentral defect on 10-2



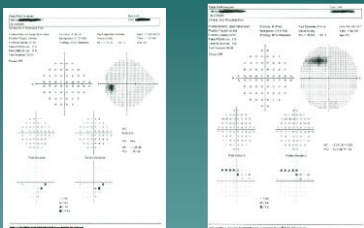
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GCC analysis: eyes like this are good candidates for 10-2 VF



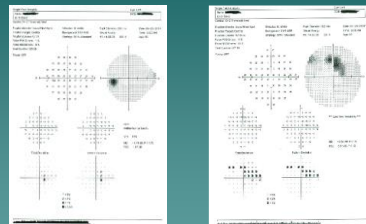
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24-2 vs 10-2 #1



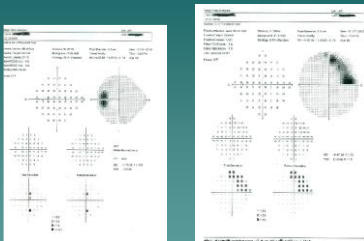
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24-2 vs 10-2 # 2



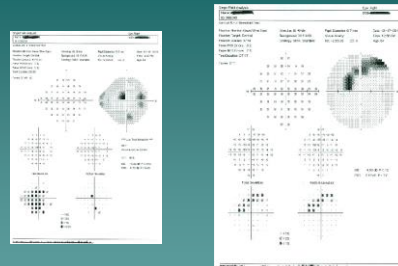
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24-2 vs. 10-2 # 3



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24-2 vs 10-2 # 4



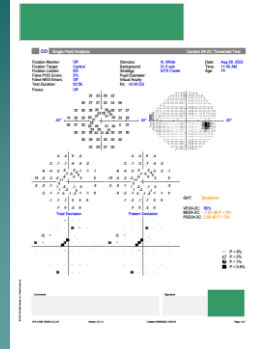
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10-2 VF vs 24-2 VF

- ◆ So what do we do with this information clinically?
- ◆ 24-2 has **12** points in central 10 degrees, 10-2 has **68!**
- ◆ When should we do 10-2?
- ◆ If there is a 10-2 defect, can you stop doing 24-2?
- ◆ Should we "mix and match"?
- ◆ If so, on what schedule?
- ◆ Is a central defect that shows up only on a 10-2 noticeable to the patient? (each point is 2 degrees apart, vs 6 degrees on 24-2)
- ◆ What does this mean for glaucoma staging?
- ◆ What about 24-2 C pattern on HVFA III testing? Adds 10 points to the center portion of the test, so **22**

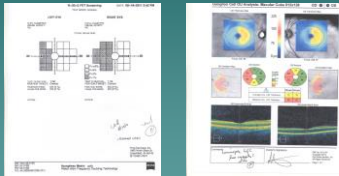
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HVFA 24-2 C Pattern



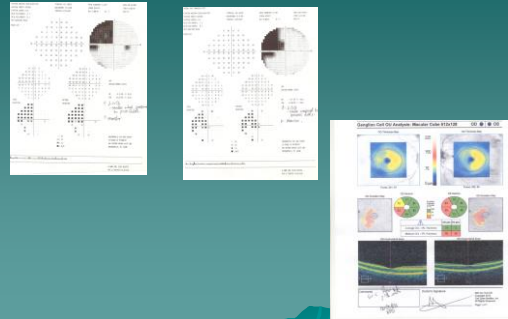
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Another cool OCT / VF correlation: Stroke and GCC loss



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Stroke and GCC loss # 2



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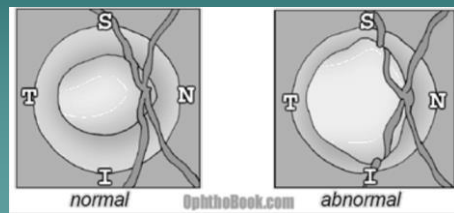
ONH evaluation

- ◆ Overall size of the nerve is **very** important: small nerve should have a small cup, big nerve should have a big cup.
- ◆ ISNT rule
- ◆ Notching
- ◆ Shelving / barring
- ◆ Rim erosion / verticalization
- ◆ Drance hemorrhage / wedge RNFL defects
- ◆ PPA



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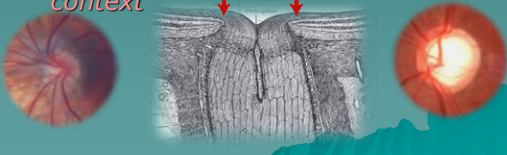
ISN'T rule graphic



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Nerve size is critical

- ◆ Larger discs should have large cups
- ◆ *Small discs should have small cups*
- ◆ *Always consider cupping as it relates to overall nerve size*
- ◆ *CD ratio of little value without context*



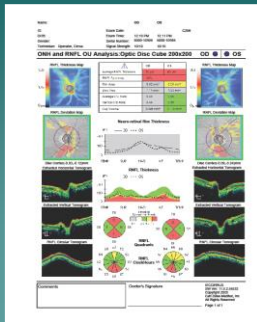
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Average disc size

- ◆ Average optic disc size (area) varies by race
- ◆ Caucasian 2.15 square mm
- ◆ Asian 2.38
- ◆ African American 2.55
- ◆ Hispanic 2.57

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Small nerves: 1.14 OD, 1.33 OS

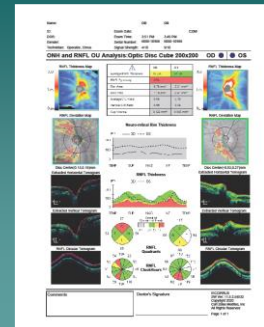


Glaucoma OU

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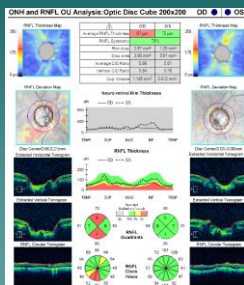
Very small nerves: 1.15, 0.91

CD .6/6 OD, .15/.15 OS
 RNFL AVG. 81 OD, 92 OS
 Traumatic glaucoma OD,
 Normal OS



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Large nerves: 3.90 OD, 3.91 OS

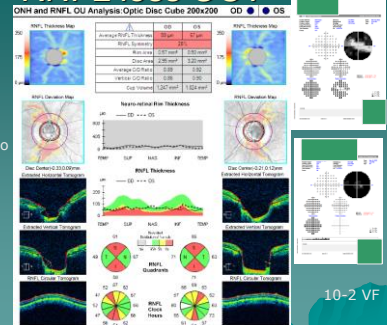


Normal OS

Developed
 Glaucoma OD
 Over time

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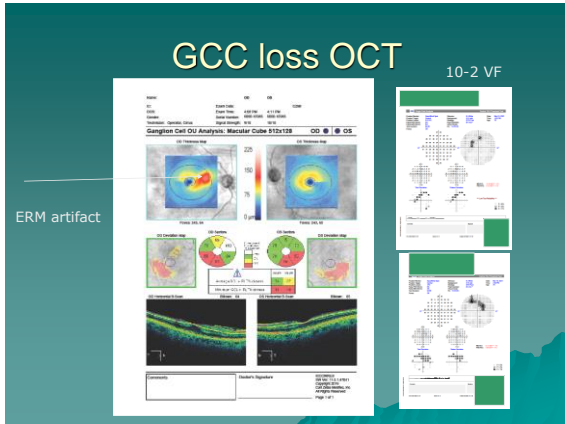
RNFL loss OCT



Large nerves too

10-2 VF

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DISC EVALUATION

- ◆ Glaucomatous damage is focal, not equal concentric enlargement.

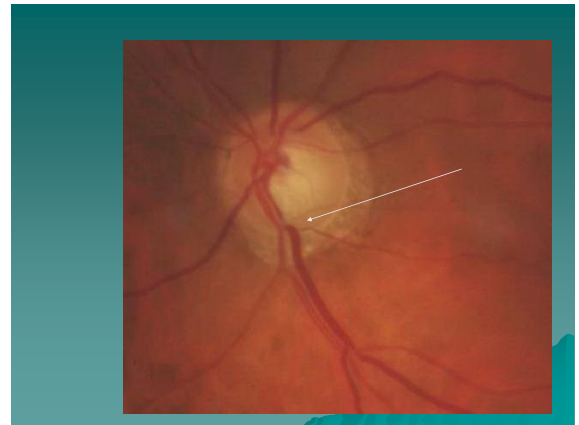
Focal inferior damage

Normal

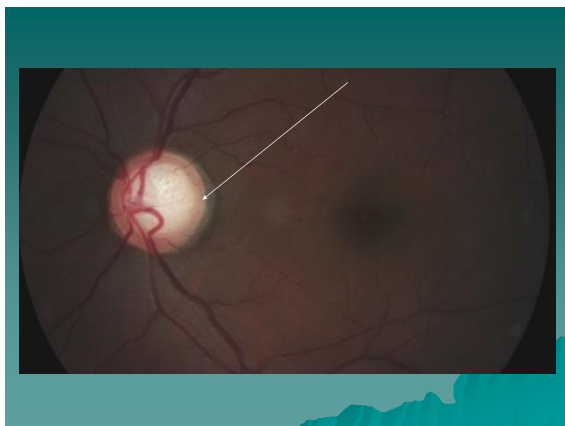
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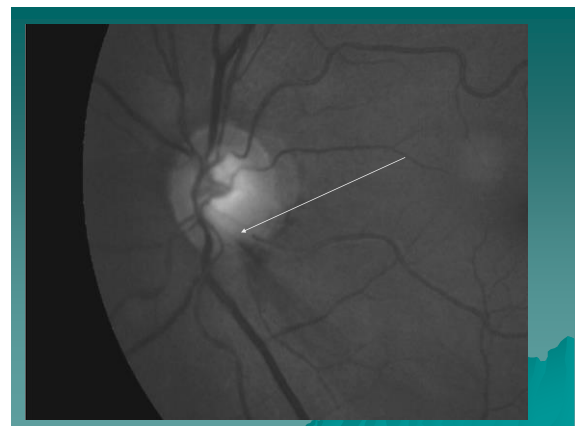
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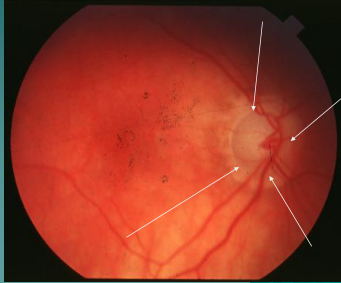


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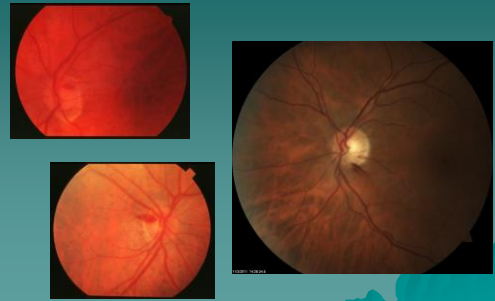
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Glaucoma...but how severe? Where is the cupping?



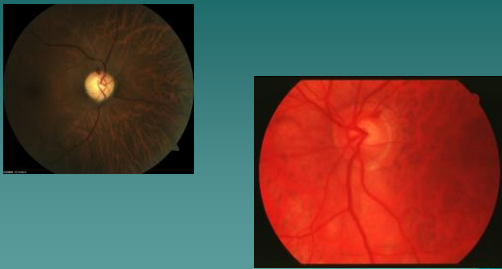
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Drance Hemorrhages



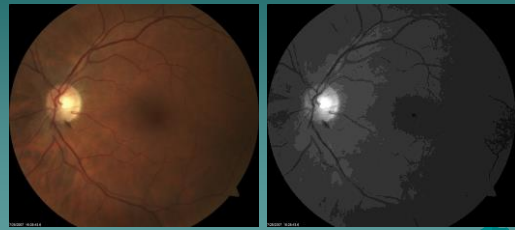
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Drance Hemorrhages



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Drance heme with NFL defect: are they all like this?



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Interesting fact.....

- ◆ In the OHTS, the vast majority of all Drance hemes (84%) were missed on examination
- ◆ Only detected on photographs
- ◆ These were glaucoma specialists



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Critical points.....

- ◆ Glaucoma does not cause pallor of the neuroretinal rim tissue
- ◆ Glaucoma generally does not decrease central visual acuity until late stage. Does decrease contrast sensitivity

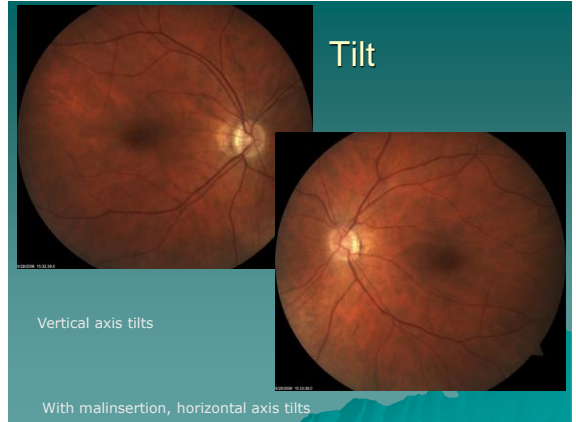


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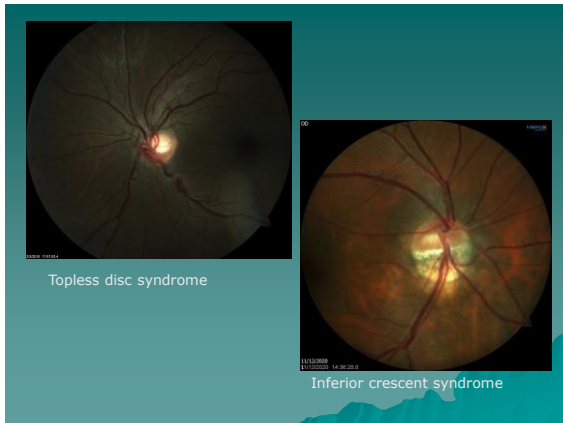
So what about when it is not glaucoma?

- ◆ Many conditions that can damage the optic nerve and lead to visual field defects and / or VA loss
- ◆ May have overlapping features with glaucoma
- ◆ Need to properly differentiate and distinguish from glaucoma
- ◆ Anatomical abnormalities: congenital and stable

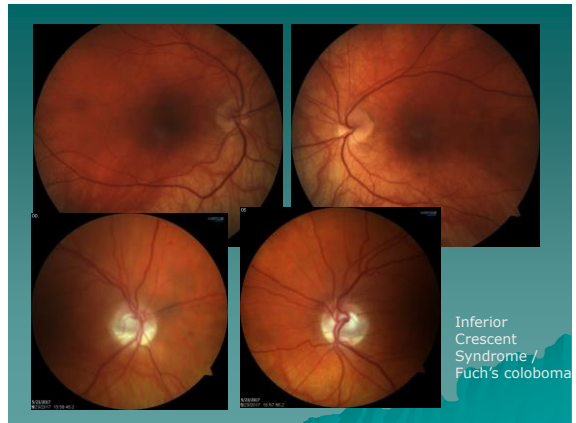
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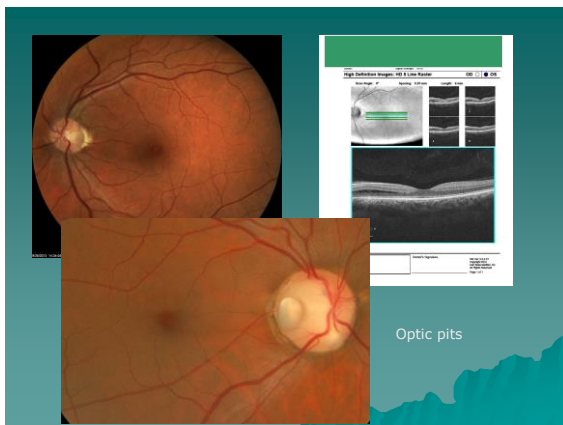
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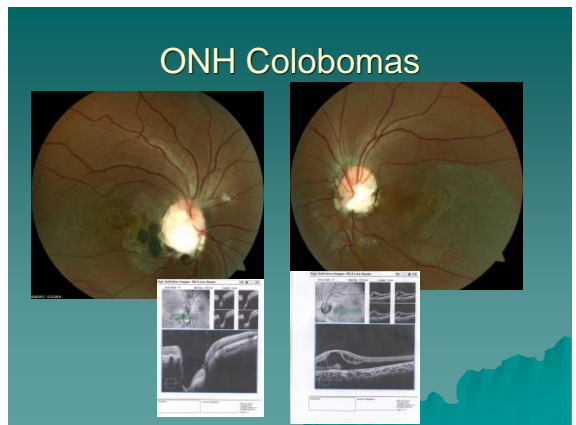
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Chronic IIH induced edema leading to optic atrophy

22-year-old AA F



Light perception

10/700

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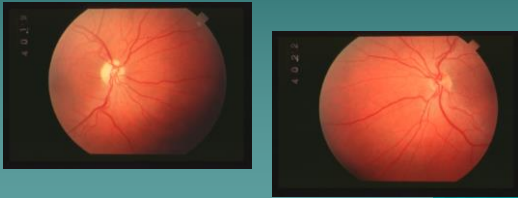
Compressive Optic Neuropathy

- ◆ Compression leads to axoplasmic stasis and retrograde death of nerve fibers
- ◆ Pale, choked, swollen nerve
- ◆ Rarely see hemes; + APD

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Compressive Optic Neuropathy

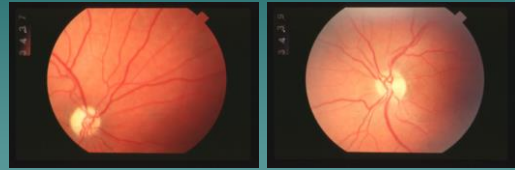
- ◆ Optic atrophy and severe vision loss with time



Pituitary tumor

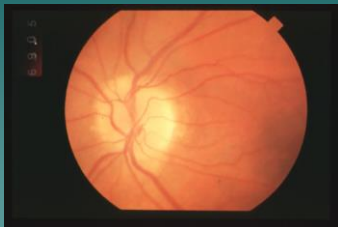
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Pituitary tumor post surgery



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Sphenoid wing meningioma with severe atrophy



Hand motion vision: patient did not know!

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Leber's Hereditary Optic Neuropathy

- ◆ Hereditary mitochondrial disease process affecting the retinal ganglion cells
- ◆ Maternal inheritance pattern (mitochondrial DNA in embryo comes only from the egg)
- ◆ Genetic mitochondrial point mutations that have been fully identified / mapped. 95% of cases due to three genetic mutations: 11778, 3469, 14484
- ◆ Only 20-50% of male carriers and 10% of female carriers get optic atrophy and vision loss
- ◆ Environmental triggers include smoke, excessive alcohol, poor nutrition / vitamin deficiency, trauma
- ◆ Because of inheritance pattern, males can not pass to offspring

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LHON

- Typically strikes in early adulthood but can strike later. 95% prior to age 50, most typically under age 30
- Late onset cases after age 50 have a 5:1 male prevalence
- Most commonly affects one eye followed by the fellow eye within several weeks (75%), but can be simultaneous (25%)
- Possible use of Idebenone. A synthetic drug very similar to CoQ10. Use if within one year of inception and continue for one year after vision plateaus or 18-24 months total. 300 mg TID. About half of people get a modest gain of 7-9 ETDRS letters. Can also stabilize. Approved in Europe, not FDA approved.

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Gene therapy trials

- Gensight Biologics GS010
- Single intravitreal injection using an adenoviral vector to carry information to the mitochondria
- 15 patients in early trial
- 48 weeks after the injection.....
- < 2 years from disease onset, 30 letter average gain in VA
- > 2 years from disease onset, zero letter average gain in VA
- Phase 3 trials Rescue and Reverse: no better than sham at resulting in a 15 letter gain in vision: But.....may have had "cross-over" effect and helped the other eye

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LHON

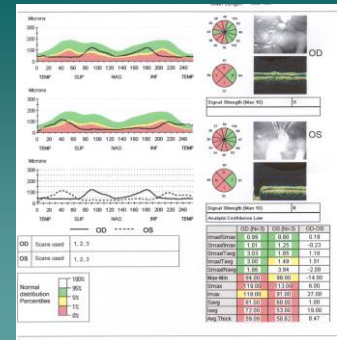
Reported associations

- Can get pseudopapilledema secondary to peripapillary NFL swelling
- Reports of vasculitis (no) and pseudovasculitis (yes)
- Often don't get decreased pupillary responses: sparing of the melanopsin-expressing RGC's that mediate pupil response



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LHON



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Optic Nerve Head Drusen

- Increased prevalence in small nerves with small cups. Therefore, more common in whites than in AA. Higher incidence in patients with RP (10%)
- Compression of axons leads to stasis of axoplasmic flow and hyaline is excreted then calcifies over time, leading to the formation of drusen
- Nerve appears elevated but no splinter hemes or exudates and the margins are distinct.
- Abnormal vessel branching

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Optic Nerve Head Drusen

- Not always visible! Buried early in life but become visible with time. Creation of more drusen push some forward to the surface of the nerve
- Can cause decreased vision and variable visual field defects. More loss with visible drusen
- Common and under diagnosed

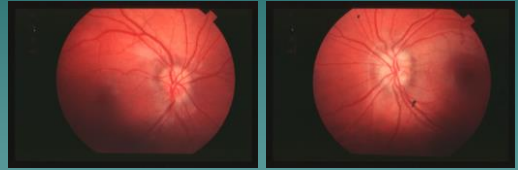
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Optic Nerve Drusen

- ◆ SVP/EVP not affected: APD and color vision loss rare but possible
- ◆ Change with time
- ◆ Use B-scan or OCT to detect buried drusen
- ◆ Also seen with CAT scan, MRI, IVFA, and FAF

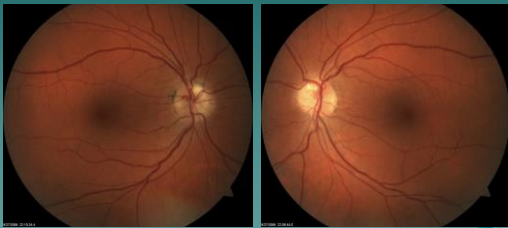
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ONH Drusen



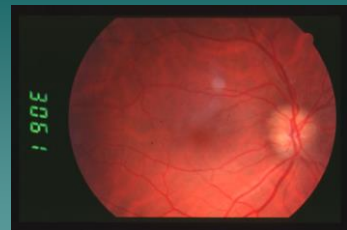
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ONH Drusen



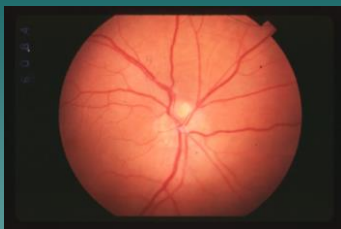
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ONH Drusen



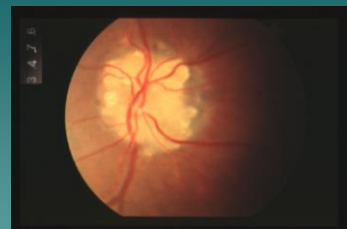
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ONH Drusen



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ONH Drusen



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ONH drusen detection with OCT

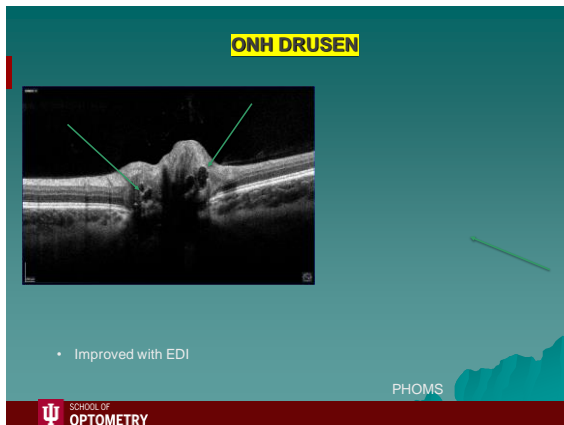
- ◆ Optic Disc Drusen Consortium Consensus.....
- ◆ Always use EDI
- ◆ Blood vessels are more solid, cast a shadow, and can show as figure 8
- ◆ Drusen always prelaminar
- ◆ Drusen always hyporeflective
- ◆ Drusen often have a hyper-reflective border, especially superiorly

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ONH drusen detection with OCT

- ◆ Drusen can conglomerate, and these areas can have some internal reflectivity from borders
- ◆ The old concept of a hypo-reflective fluid wedge at the edge of the nerve in true papilledema DOES NOT APPLY with SD-OCT. Was a time domain OCT artifact.

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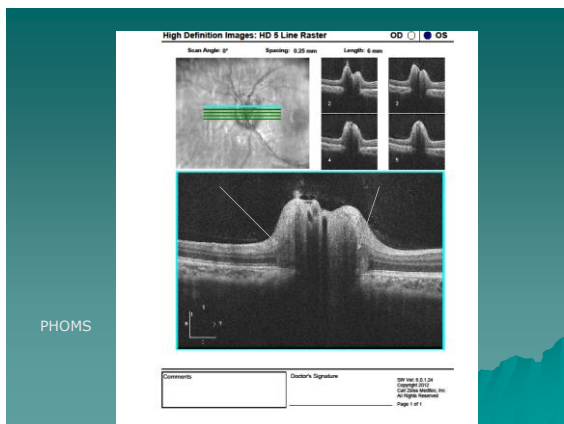


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Peripapillary Hyper-reflective Ovoid Mass-like structures (PHOMS)

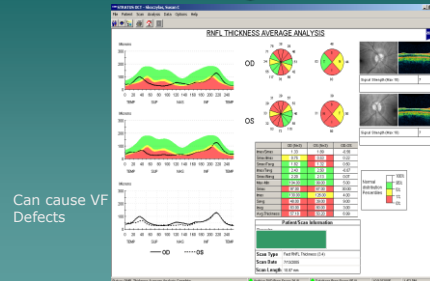
- ◆ "Fomms"
- ◆ Seen best with EDI
- ◆ Only seen with OCT, nothing else
- ◆ Circular innertube like structure around the disc above Bruch's membrane
- ◆ Herniated optic nerve fibers
- ◆ Seen in any condition that leads to nerve swelling or congestion
- ◆ ION, papilledema, disc drusen

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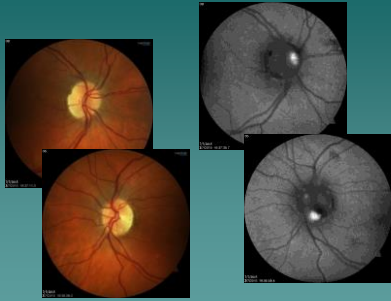
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NFL loss with ONH drusen: looks like glaucoma loss



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FAF ONH Drusen



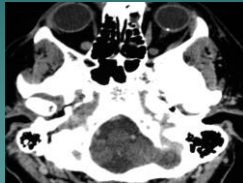
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FAF ONH Drusen



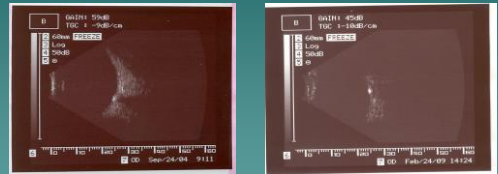
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ONH drusen MRI



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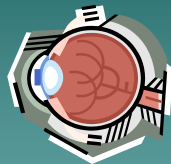
ONH drusen B-scan



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ION

- ◆ Nonarteritic
- ◆ Arteritic



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Nonarteritic ION

- ◆ Swollen, hyperemic nerve with splinter hemes and exudates
- ◆ Often sectoral
- ◆ Ischemic / hyperfusion event caused by interruption of micro-vascular circulation, often at night.
- ◆ Highly associated with sleep apnea (75-90% in several studies)
- ◆ NAION has 5x risk of sleep apnea, 8x risk in women

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NAION

- ◆ No systemic symptoms; normal ESR / CRP
- ◆ Most common cause of ONH swelling over the age of 55 (2-10 cases per 100,000 per year)
- ◆ 45-60 year olds (any age possible) with no sex predilection; C > AA

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Nonarteritic Etiologies

- ◆ 1) Sleep apnea! Up to 90%
- ◆ 2) Hypertension (med related?)
- ◆ 3) Idiopathic
- ◆ 4) Diabetes
- ◆ 5) Atherosclerosis
- ◆ 6) Migraine
- ◆ 7) Increased Homocysteine / Decreased vitamin B6
- ◆ 8) HIV infection

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Nonarteritic ION

- ◆ Idiopathic cases (and others) are more common in disc at risk patients.
- ◆ Approximately 15% of cases will involve the fellow eye in 5 years (more common with VA < 20/200 in first eye, diabetics, and platelet polymorphisms). Repeat attacks in same eye < 5%

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NAION

- ◆ VA varies widely from normal to severe loss: 45% 20/40 or better but 33% 20/200 or worse
- ◆ VA loss progresses over 2-4 weeks
- ◆ VA improves by up to three lines at six months in 40%
- ◆ In patients under 50 years of age, there is a higher rate of bilateral involvement and more visual recovery

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Nonarteritic ION

- ◆ Often APD , color vision usually normal
- ◆ Most frequent visual field defect is inferior nasal / partial altitudinal but may get essentially any type. FDT may be more sensitive and often shows spillover of loss in to "non-affected" hemifield
- ◆ After swelling resolves the nerve is pale but often not cupped-cupping may occur, however
- ◆ Why does area of swelling not always match VF defect? Because we are often catching "secondary" swelling.

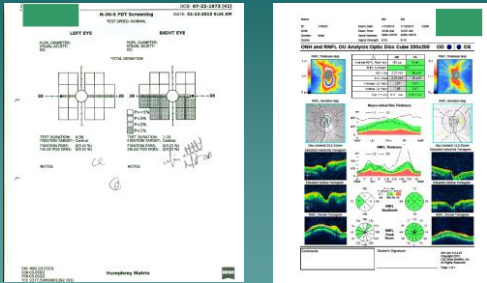
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NAION 2 weeks after onset of symptoms



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NAION



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Nonarteritic ION Treatment

- ◆ No treatment other than managing the underlying cause has proven to be consistently effective
- ◆ Blood thinners may debatably protect the fellow eye but will not alter the course of recovery.
- ◆ Order CBC , ESR and CRP , lipid profile , hemoglobin A1C. Check BP
- ◆ Check for sleep apnea!

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Steroids?:

- ◆ SS Hayreh: 2008 study utilizing oral steroids....
- ◆ If VA 20/70 or worse, oral prednisone resulted in VA improvement (3 or more lines) in 70% of treated patients, only 40% of untreated
- ◆ Beginning dose of 80mg for 2 weeks with slow taper.
- ◆ Not commonly offered, no definitive evidence of benefit

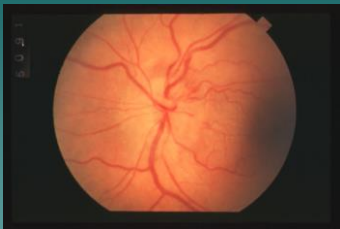
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Incipient ION

- ◆ Early swelling, but no impact yet on VA or VF
- ◆ May resolve without loss of vision of VF, may become full blown NAION with loss
- ◆ Can only impact by treating underlying condition

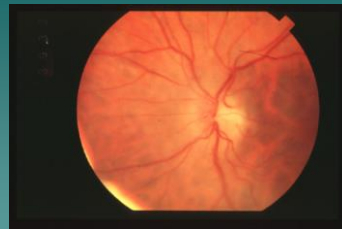
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NAION



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NAION



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NAION



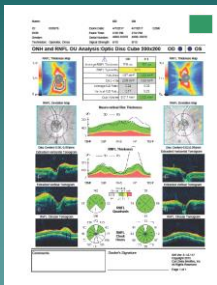
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NAION



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NAION secondary to OSA



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HIV induced optic neuropathy



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Another HIV induced optic neuropathy



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Old NAION OD



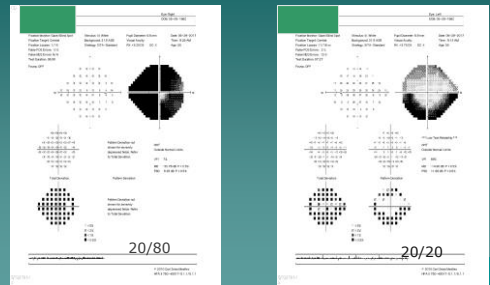
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Bilateral NAION secondary to OSA (40% blood oxygen level)



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Accompanying VF



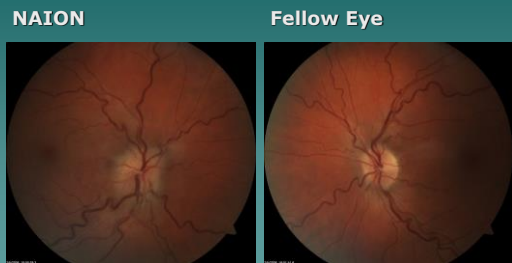
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NAION OD and fellow eye



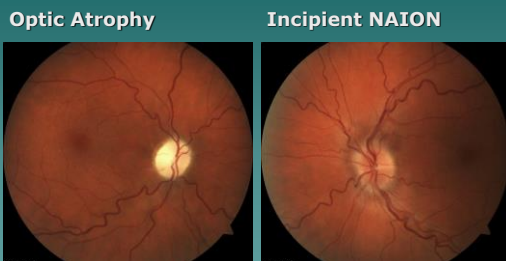
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NAION OD: The Beginning



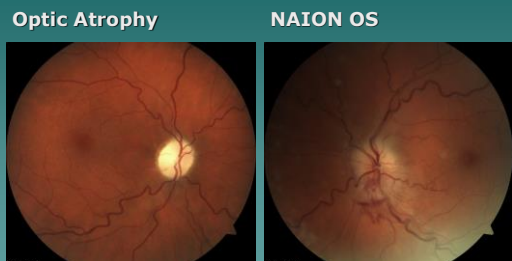
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Optic atrophy / incipient ION



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NAION OS



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Optic atrophy OU

Post NAION

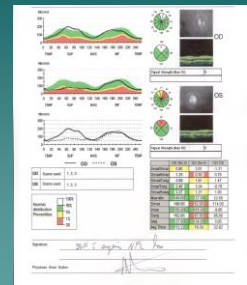
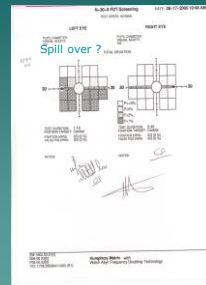


Post NAION



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ION OS with matching VF / NFL loss



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Arteritic ION

- ◆ Pale disc swelling with splinter hemorrhages
- ◆ Average age 76 (80% over 70), F>M 3:1
- ◆ Increased ESR, C-Reactive protein, platelet
- ◆ ESR normal in about 25%!
- ◆ VA 20/200 or worse in 60% of cases
- ◆ Traditional thinking from past studies of a high predilection for Caucasians, but a large 2019 study showed only a slight predilection for Caucasians over African Americans.

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Arteritic ION

- ◆ Sudden, painless loss of vision with APD
- ◆ Altitudinal VF loss most common, others possible
- ◆ Symptoms of GCA but about 1/3 are symptom free
- ◆ Very high five-year mortality rate

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Giant Cell Arteritis

- ◆ GCA is a disease of unknown etiology (emerging evidence that zoster may be involved, but other studies have refuted this) affecting the large and medium arteries including the temporal, ophthalmic, and posterior ciliary arteries
- ◆ Symptoms include HA, scalp tenderness, jaw claudication, malaise, fever, and fatigue

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GCA

- ◆ May also see CWS, CRAO, and amaurosis fugax
- ◆ 20% of cases with ocular involvement are CRAO, 80% ION
- ◆ Obtain stat Westergren ESR, CRP, CBC with platelets

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Giant Cell Testing

- ◆ Normal ESR is age/2 for men and (age +10)/2 for women
- ◆ C-Reactive protein testing is not specific for GCA but it is nearly 100% sensitive so very useful test
- ◆ Temporal artery biopsy when indicated

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Giant Cell Arteritis

- ◆ 25% of untreated patients develop AION
- ◆ 2/3 will develop in the second eye within weeks if not treated, up to 50% within one week
- ◆ Rheumatology referral



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Giant Cell Treatment

- ◆ IV hydrocortisone followed by long term oral prednisone. Maintenance dose of 10mg daily for years. Follow ESR, other markers
- ◆ Average cumulative steroid dose over course of treatment.....over 5000 mg of prednisone!

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Temporal (Giant Cell) Arteritis

- ◆ FDA approved treatment
- ◆ Subcutaneous Tocilizumab (Actemra)
- ◆ Used with steroids (not in place of): makes steroid dose much lower
- ◆ Immunosuppressant
- ◆ Risk of infections, no live vaccines
- ◆ Delivered IV
- ◆ Also used with RA and other forms of arthritis

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Viagra / Cialis / Levitra and NAION

- ◆ Most reported cases Viagra. ? Under reported
- ◆ These medications also occasionally used for pulmonary HTN
- ◆ Visual loss most often noted upon awakening the morning after use
- ◆ Is the association real or coincidence?
- ◆ Likely the "straw that broke the camel's back" in those with risk factors. But.....

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ED drugs and NAION

- ◆ Very interestingly, has been reported in a 7-month-old infant, 28-year-old, and 33-year-old, presumably all taking them for pulmonary HTN
- ◆ At those young ages, not as likely to have other NAION risk factors
- ◆ Also, 2 reported cases of PION with Sildenafil, one in a 39 YO female with pulmonary HTN

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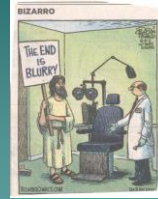
Viagra / Cialis

- ◆ What is the proposed mechanism? Nitrous oxide release actually dilates vessels.....but drops blood pressure.
- ◆ Do ION patients have faulty autoregulation?
- ◆ Ask all males with NAION about ED drug use. D/C if using to protect fellow eye.



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The end!



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