Ophthalmology: Grand Rounds

October 15th, 2015

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Presentation

- 52 y/o Caucasian woman presents with painless decreased vision in left eye x 4 weeks
  - 4 weeks ago: patient noticed a bright diffuse flash of light while reading her book in the sun and noticed “narrowing” of vision in the bottom half of her visual field
  - One week after onset of visual loss, also c/o tinnitus with no hearing loss

Patient Care, Interpersonal Communication Skills, Professionalism, Practice-Based Learning and Improvement

History

- PMHx: osteoporosis
- PSHx: sclerotherapy for varicose veins on leg (2 months ago), back surgery (3 years ago), abdominal hernia repair
- POHx: refractive error
- Trauma: remote motor vehicle collision (w/o concussion)
- Social Hx: occasional wine; no tobacco or illicit drugs
- Medications: ASA 81 mg, Calcium/Vitamin D; Krill oil
- Allergies: levofloxacin→ hives
- Family History:
  - Neuropathy- father
  - Idiopathic pulmonary fiborosis- mother;
  - Aortic Aneursym- paternal grandfather (70s), cousin (50s), and aunt (unsure of age)

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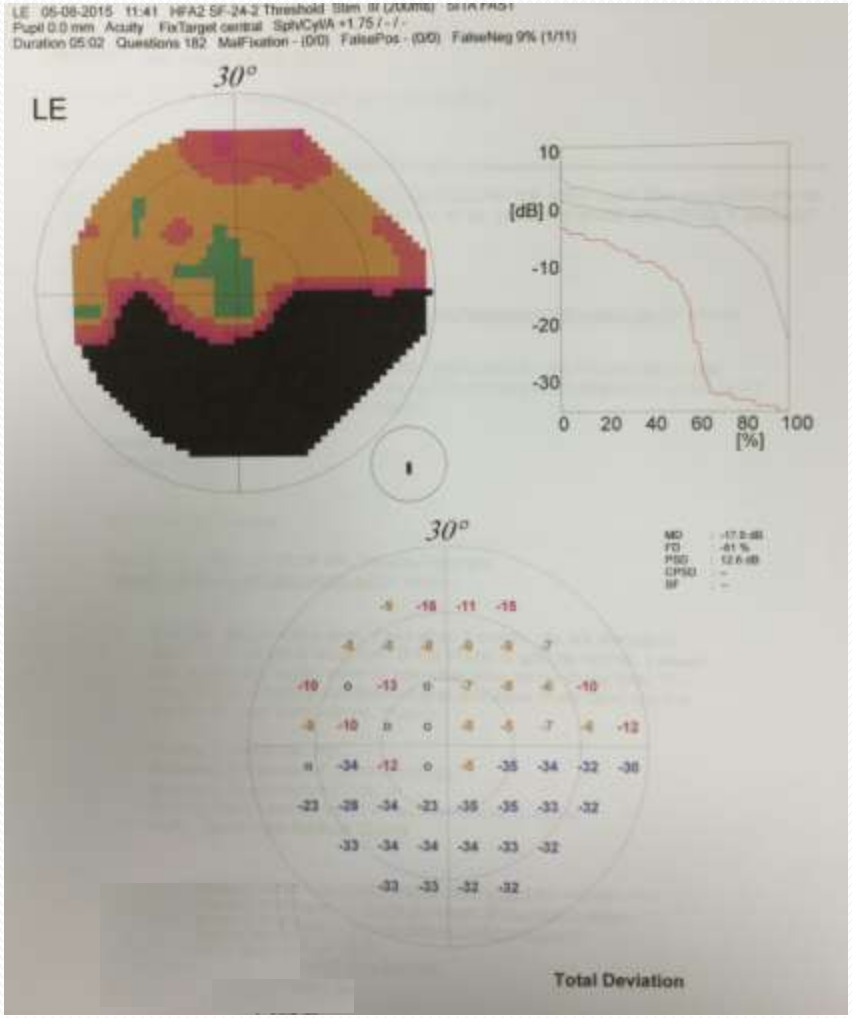
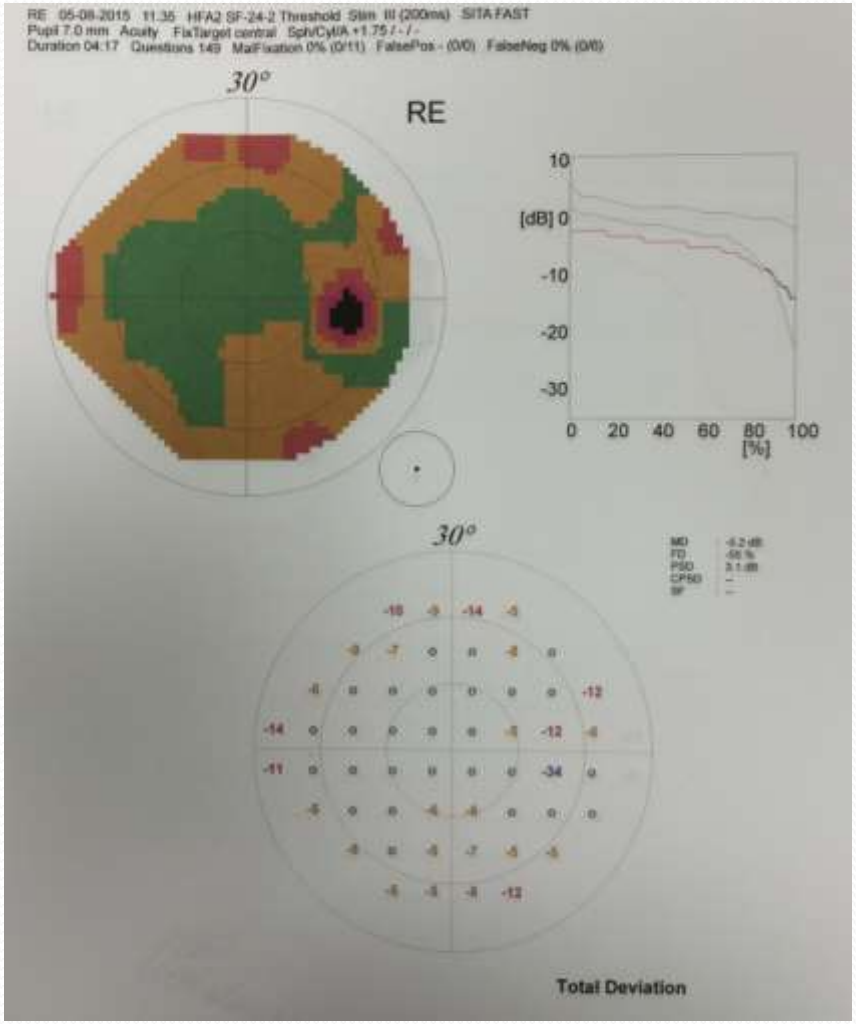
History/Initial Exam

- Work-up from outside ophthalmologist (4 weeks ago)
  - Vacc: 20/20 OD; 20/20 OS
  - Tapp: 21/20
  - Severe optic disc edema OS
  - Sent to hospital for emergent work up

Visual Field – 8/5/15





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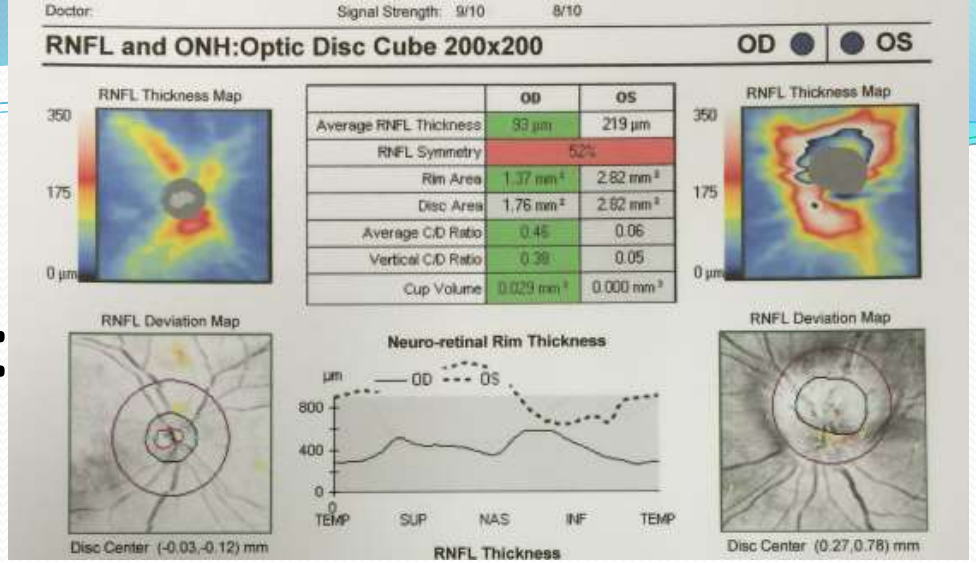
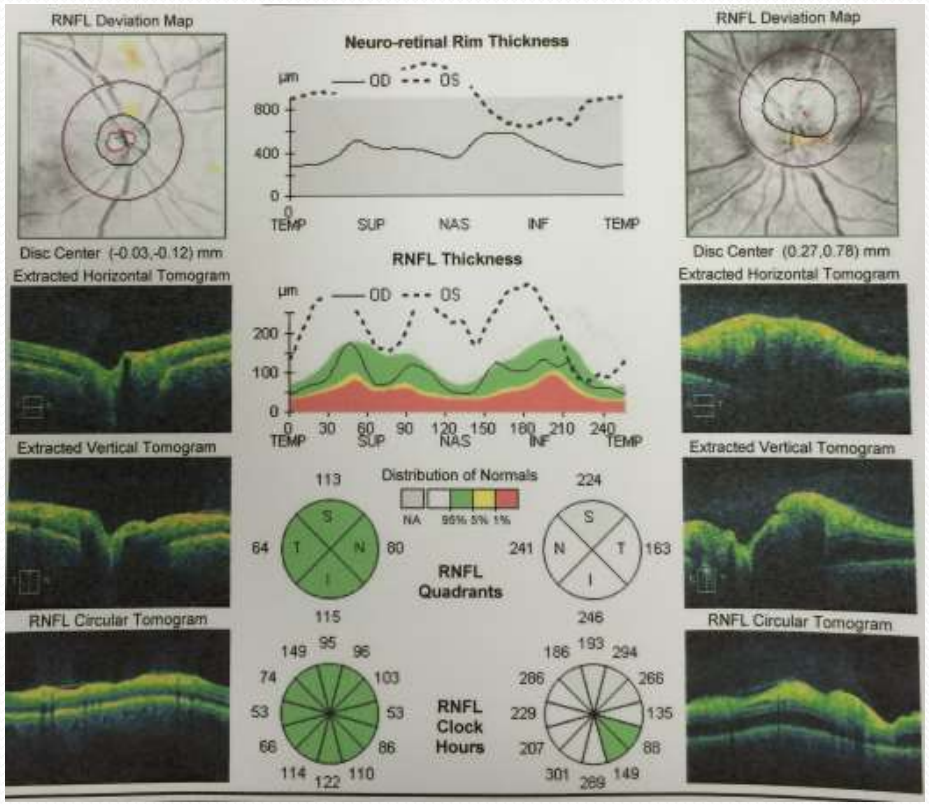
OCT ONH: 8/5/15



Average RNFL:93 OD 219 OS



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Differential Diagnosis:

Differential Diagnosis:

- NAION (Non-arteritic Anterior Ischemic Optic Neuropathy)
- Arteritic Anterior Ischemic Optic Neuropathy (Giant Cell Arteritis)
- Compressive Optic Neuropathy
- Central Retinal Vein Occlusion
- Unilateral papilledema
- Painless optic neuritis

Prior Clinical Course/Testing

- Admitted to outside hospital for treatment with IV steroids for presumed optic neuritis
- Lumbar puncture → CSF studies normal
- Was told by outside ophthalmologist she had a "stroke in eye"

- ESR= 6 (normal)
- CRP < 0.1 (normal)
- PTT, PT/INR, Lipid Profile= normal
- CTA Head and Neck: normal; patent ophthalmic arteries
- MRI Brain and orbits w/ and w/o contrast: normal
- MRA Head and Neck w/ and w/o contrast: normal
- TEE= normal; no vegetations

3 weeks after onset:

- Noticed decreased peripheral vision
- Developing “tunnel vision”
- Still painless
- ROS: negative

Neuro-op Consult Exam

- Vitals: Height= 5’ 2”; Weight 105 lbs; HR 76 bpm (regular rate + rhythm); BP 130/80
- dVAcc: 20/20 OU
- Pupils: 3->2mm OU; 0.6-0.9 log unit left RAPD
- CVF: full OD; deficits in the inferior hemifield and the superonasal hemifield OS
- Tapp: 20 OD, 21 OS
- Motility: full OU, orthophoric; no nystagmus
- Neuro: AAOx3; CN III-XII intact
- HEENT: no masses; no proptosis
- SLE: normal OU

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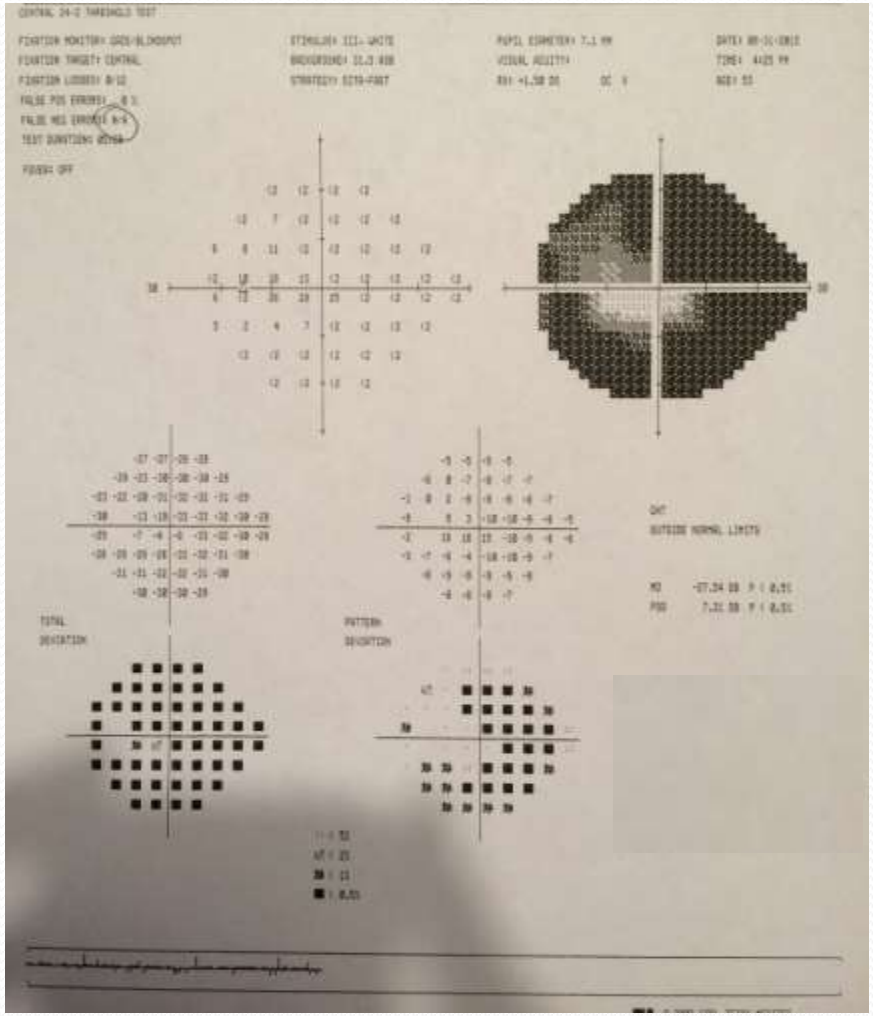
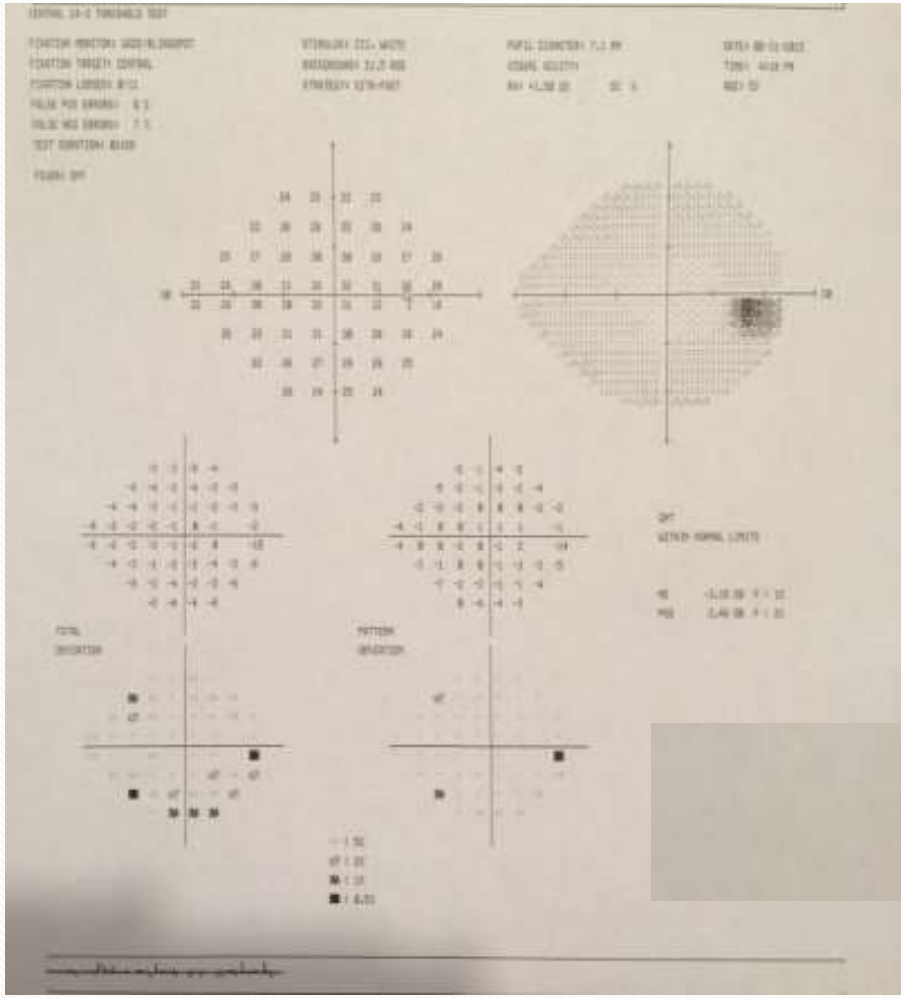
Visual Field 8/31/15





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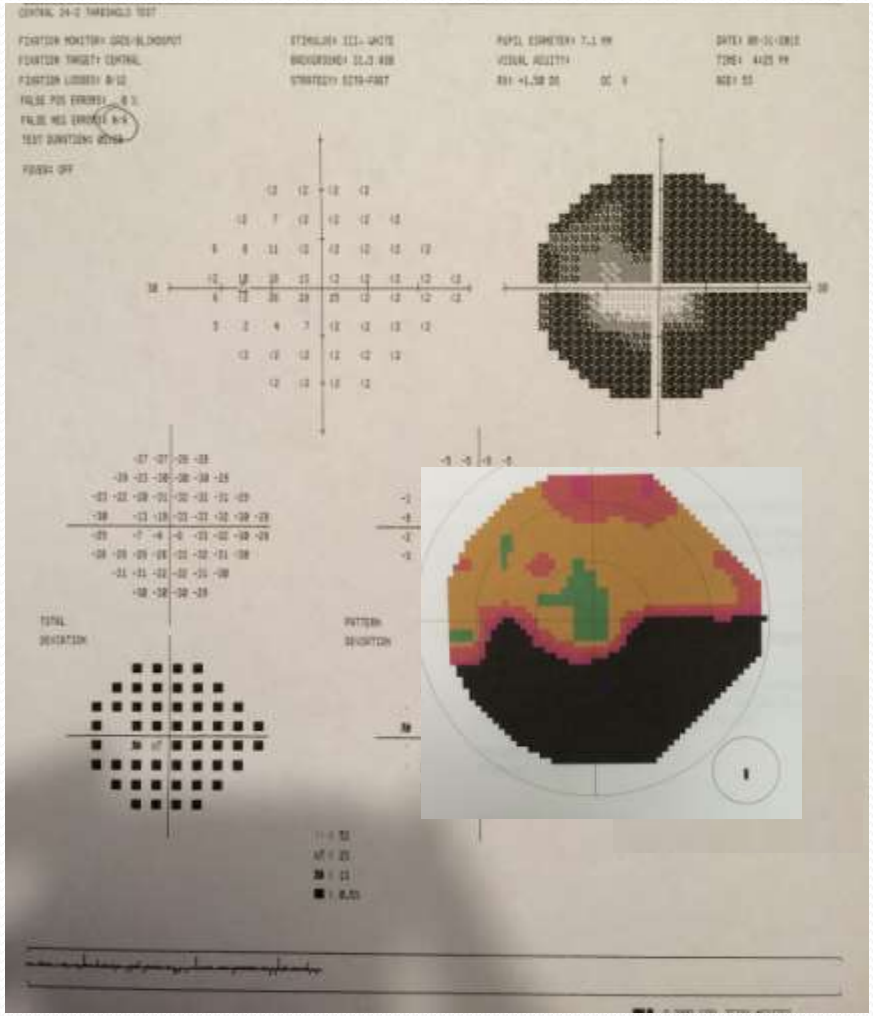
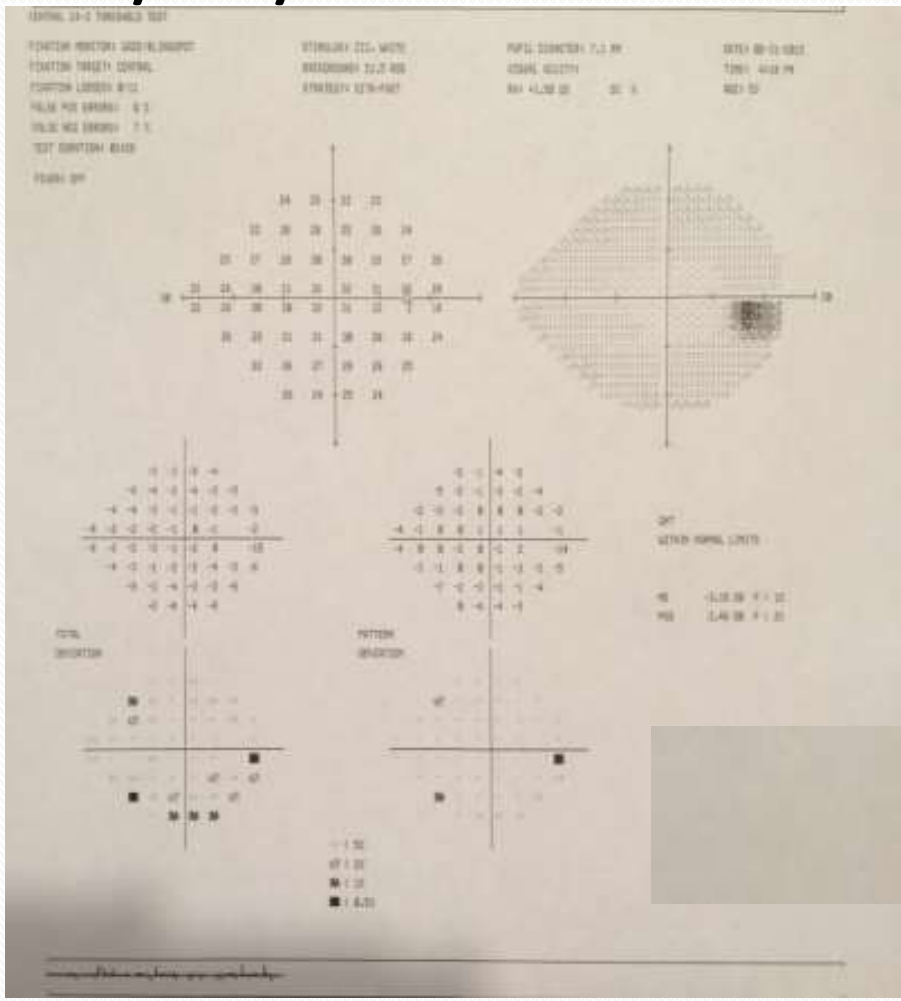
Visual Field 8/31/15





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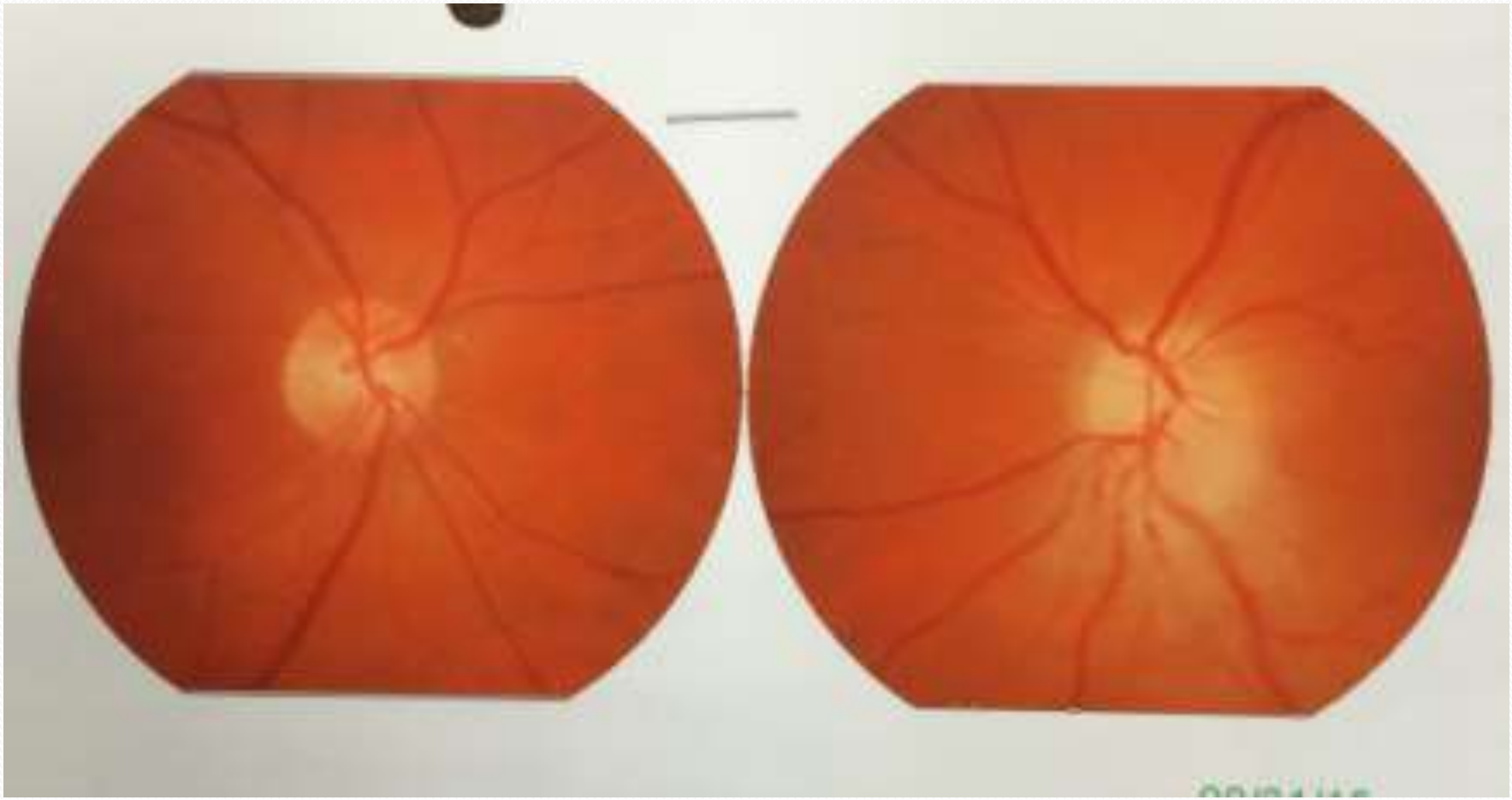
DFE/Optic Nerve Photos – 8/31/15



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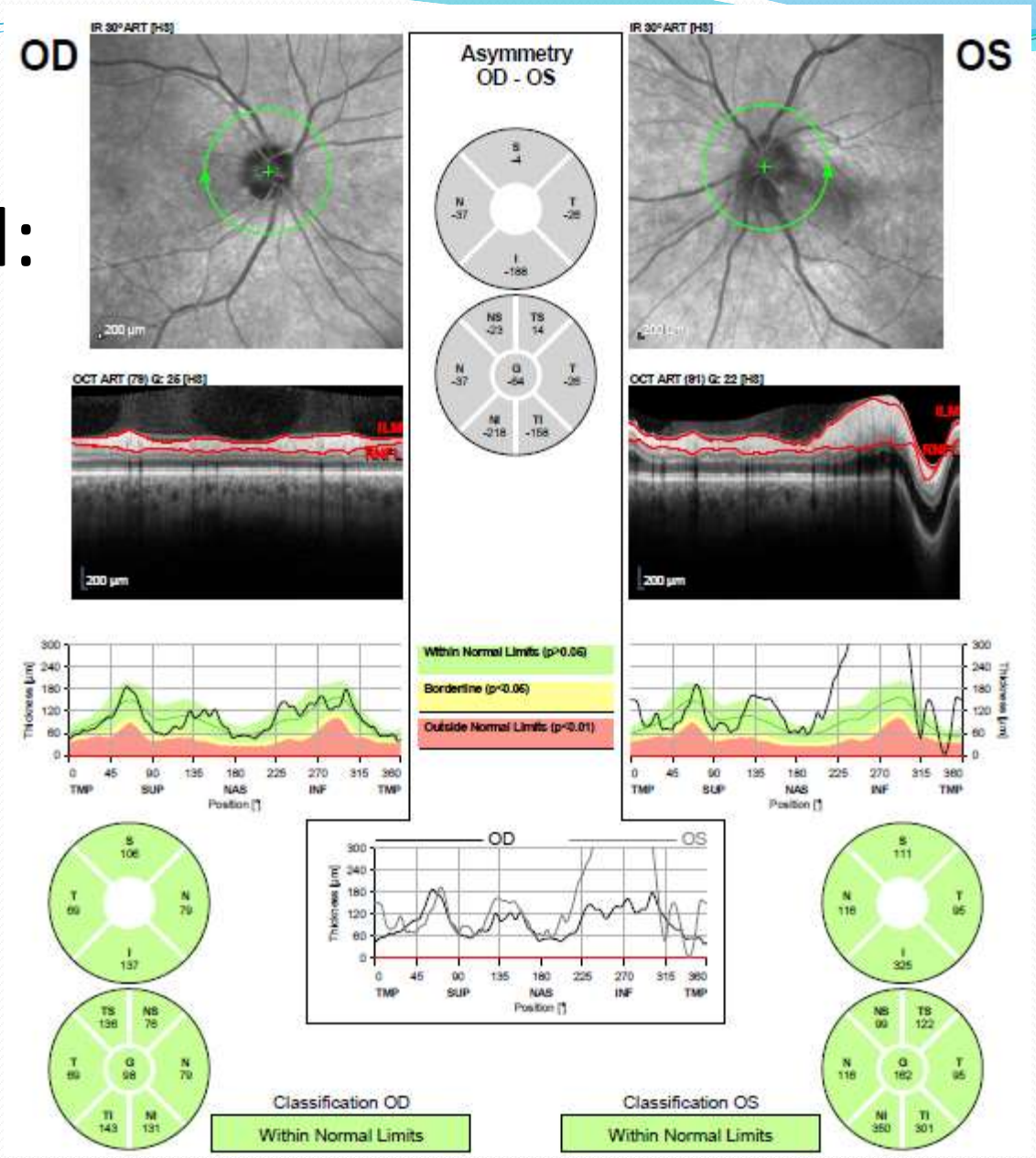

Average RNFL
OD: 98
OS: 162

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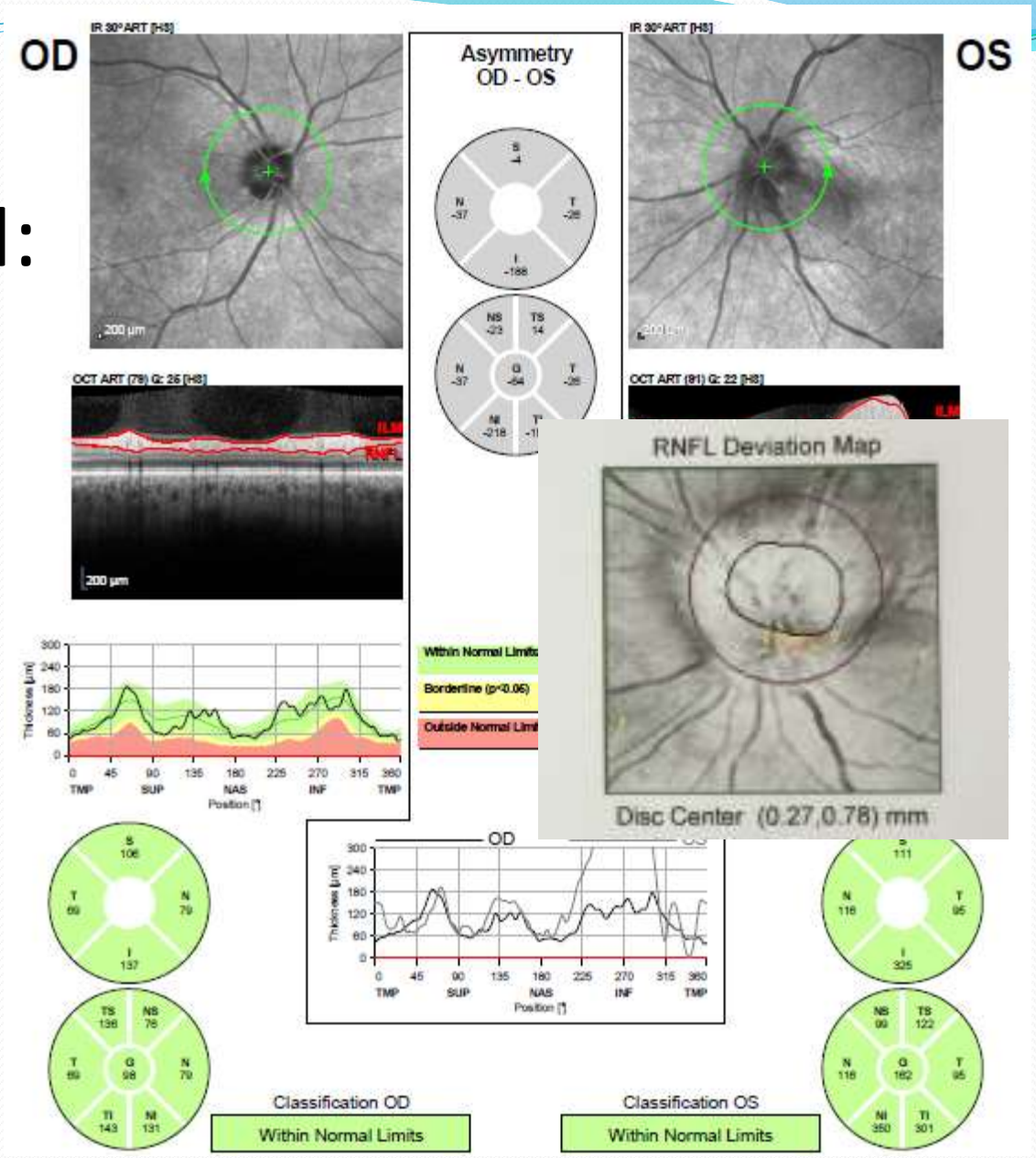

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NAION (Non-arteritic Anterior Ischemic Optic Neuropathy)

- NAION is the most common clinical presentation of acute ischemic change to the optic nerve
- Approximately 2-10 cases per 100,000 in the U.S.
- Average age of onset: 57-65 years of age

Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. Eye 2015; 29: 65-79

Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy. *Survey of Ophthalmology* 2010; 55: 47-63

Presentation

- Acute, unilateral, painless vision loss that evolves over several hours to days
- VA can vary from 20/20 to NLP
- But VA will typically remain 20/200 or better in about 2/3 of patients
- Optic neuropathy
  - RAPD
  - Visual field by automated perimetry will most commonly show altitudinal or arcuate defects.

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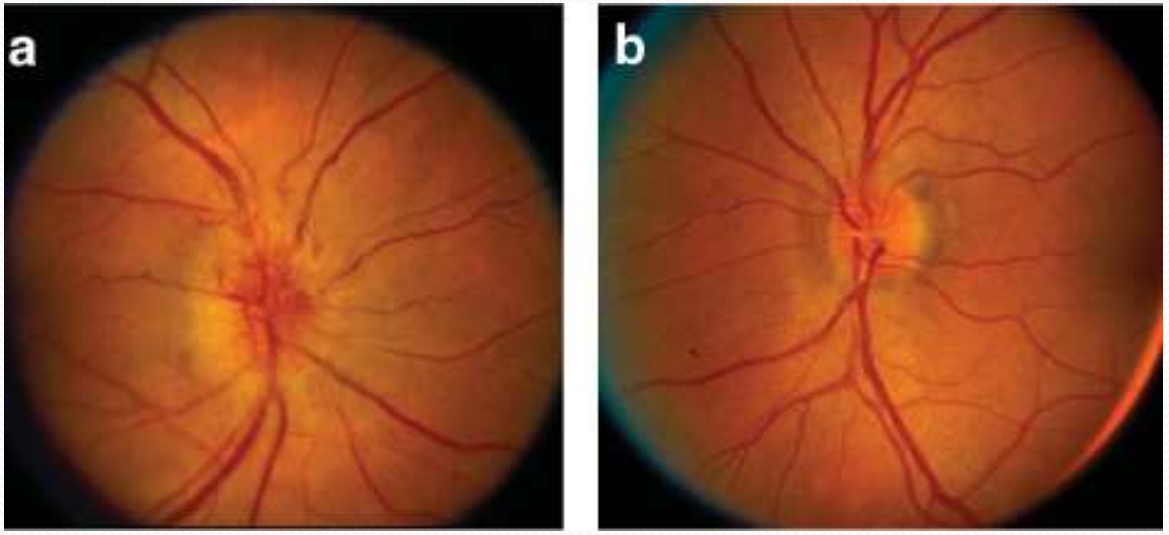
Risk Factors

- Hypotension- Systemic hypotension combined with a “disc at risk” and a nocturnal dip in blood pressure
  - Phosphodiesterase inhibitors
- Hypertension
- Diabetes mellitus
- Hyperlipidemia
- Anemia
- Obstructive sleep apnea
- Smoking
- Optic disc drusen: crowding of optic disc
- Thrombophilia

Exam

- Fundoscopy shows:
  - optic disc edema, commonly with peripapillary flame-shaped hemorrhages in the acute setting then optic disc pallor in 4-6 weeks
- Contralateral eye (b) will commonly show a “disc at risk”
  - Small diameter
  - Crowded optic disc with small to absent physiologic cup



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Model for NAION – Berstein and Miller – Japanese Journal of Ophthalmology (May 2015)

- NAION is believed to be due to a compartment syndrome initiated by optic nerve head (ONH) capillary dysfunction
- Rat model: Rat optic nerve (ON) shares many structural similarities to the human ON

Methods:

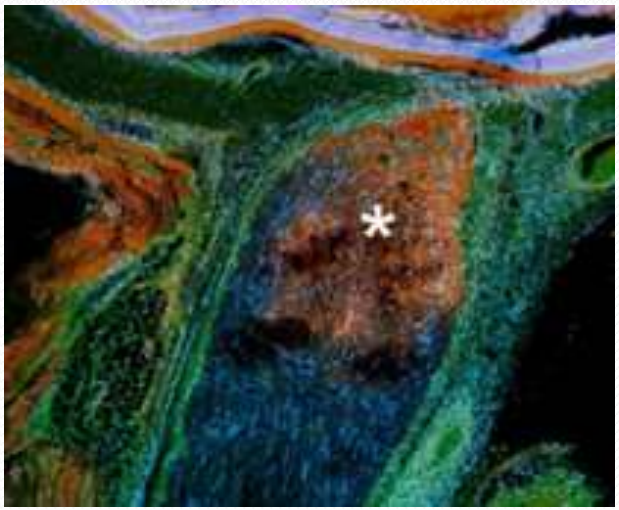
- Inject photosensitive dye (ex: rose Bengal)
- Used a low-intensity laser light focused on optic nerve (ON):
  - Generated dye-induced superoxide radicals to form in the ON capillaries
- Photochemical reaction→ created regions of the capillary endothelial damage

Findings:

- Rat model shows findings similar to human NAION
  - Progressive anterior ON edema and regional blood brain barrier breakdown
- Inflammation = a key factor in early damage in rodent models of NAION
  - Inflammatory cytokines are released after induction of photochemical reaction in rodents
  - Cellular inflammation: sequential involvement of neutrophils and macrophages are seen
- Differences in rodent model and human
  - NAION model-induced ON edema resolves much faster in rats
    - Resolution of edema= complete by 5 days in rats vs > 40 days in humans
  - Differences in speed must be considered in both treatment and disease responses

Confocal micrograph of rat ON Post-photoablation day #1

- Rat was injected with fluorescein-linked bovine serum and rhodamine-dye-linked dextran then euthanized
  - Accumulation of both molecules in the anterior ON with edema shows localized breakdown of the blood brain barrier



Berstein SL, Miller NR. Ischemic optic neuropathies and their models: disease comparisons, model strengths and weaknesses. *Jpn J Ophthalmol* 2015; 59: 135-147

Prognosis

- Visual Prognosis in the **affected eye**:
  - In most cases, vision remains stable after NAION
    - In progressive form of NAION, the vision worsens over 2 weeks to 2 months then remains stable over time
  - VA does not appear to worsen once the disc edema has resolved
  - 20/200 or worse in 31-42% of eyes
- Recurrence of NAION in the **affected eye**:
  - < 5%
  - Lower rate of recurrence with proposed mechanism of action:
    - Atrophy of the optic nerve after an NAION event relieves the crowding (previous “disc at risk”).
- Risk of involvement in the **contralateral eye**:
  - 15 % of patients developed NAION within 5 years

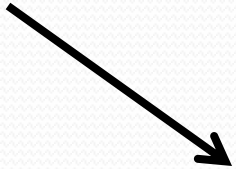
Treatment:

- No general accepted treatment for NAION
  - No consistent beneficial medical or surgical treatment for NAION
- The therapeutic window is considered 2-3 weeks
  - The Ischemic Optic Neuropathy Decompression Trial (IONDT) specified a 2-3 week window for surgical decompression

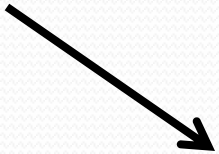
Systemic Steroids

Proposed Mechanism of Action:

- Foulds et al. in the Transactions of Ophthalmological Society of the UK (1970)
- Steroids would decrease capillary permeability, thereby allowing faster resolution of disc edema



- Reduce compression of capillaries in the optic nerve head



- Improve blood flow and restore the function of the surviving axons that were exposed to the insult

Systemic Steroids

- Hayreh et al – Graefe's Archieves of Clinical and Experimental Ophthalmology (2008)
- Methods:
  - 613 patients
    - 312 were treated with systemic steroids
      - 236 patients treated with steroids had treatment within the first 2 weeks
    - 301 had no treatment
  - Steroid= PO prednisone
    - 80 mg once a day x 2 weeks
    - Tapered every 5 days to 70 mg→ 60 mg →55mg→ 50 mg→ 45 mg → 40 mg until the optic disc edema was no longer present
    - After disc edema was resolved, the prednisone was quickly tapered

Hayreh et al – Graefe's Archieves of Clinical and Experimental Ophthalmology (2008) – Systemic Steroids

- Results:
  - Median time to optic disc edema resolution was 6.8 weeks in the group that received steroids within 2 weeks compared to 8.2 weeks in the untreated cases ($p < 0.0001$)
- Weaknesses
  - Patients were not randomized
  - Untreated group has more vascular risk factors
  - Selection bias: diabetics were less likely to be treated with steroids
  - Previous publications by Hayreh show that optic disc edema persists longer in diabetics

Ischemic Optic Neuropathy Decompression Trial (IONDT) – JAMA (1995)

- Randomized, single-blinded, multi-center trial
- Methods:
  - 119 patients had optic nerve decompression surgery within 2 weeks [treatment group]
  - 125 patients had no surgical intervention [control group]
- Theorized Mechanism:
  - Reducing CSF pressure within the perineural subarachnoid space could relieve the "compartment syndrome" caused by optic disc edema
  - Improvement of local blood flow and enhancement of axoplasmic flow within the damaged axons in NAION

IONDT

- Results:
  - Visual acuity improved at least 3 Snellen lines in 32.6% of the surgery group vs. 42.7% in the non-intervention group
  - Visual acuity worsened by 3 or more lines in 29.3% of patients in the surgery group vs. 12.4 % in the non-intervention group
- Data and Safety Monitoring Committee ceased the trial early due to increased morbidity
- IONDT concluded than optic nerve decompression surgery for NAION may not only be ineffective but also harmful

Aspirin and Reducing Second Eye Involvement in NAION

- Retrospective study by Salomon et al. in *Eye* (1999)
- Suggested that **Aspirin 325 mg/day** may be effective in reducing the frequency of second eye involvement in NAION
- Measured mean time between first and second eye involvement
  - Mean time = total time at risk (time between first and second NAION)/ number of cases of bilateral involvement

Aspirin and Reducing Second Eye Involvement in NAION

- Results:

Aspirin treatment	*n*	Second eye involvement		Mean interval between first and second events (months)
		n	%	
None	16	8	50	63.4
Aspirin 100 mg/day	8	3	38	80.3
Aspirin ≥ 325 mg/day	28	5	18	156.5

  - None of the observed differences reached any statistical significance
    - Most likely from small sample size
  - No statistically significant differences in disease prevalence were found in the 3 different treatment groups

Sustained Neuroprotection From a Single Intravitreal Injection of PGJ_2 in a Nonhuman Primate Model of Nonarteritic Anterior Ischemic Optic Neuropathy

Neil R. Miller,[1,2] Mary A. Johnson,[2] Theresa Nolan,[3] Yan Guo,[2] Alexander M. Bernstein,[2] and Steven L. Bernstein[2]

- Major mechanism of action of PGJ2:
  - Limits inflammation:
    - Acts as an antagonist for cytokine-related inflammation and cellular inflammation

Methods:

- 5 rhesus monkeys (10 eyes) had NAION induced in one eye then had an:
  - Intravitreal injection of PGJ2 [treatment arm]
  - Sham saline [control arm]
- Assessments at:
  - 1 day, 1 week, 2 weeks and 4 weeks after induction
- The contralateral eye then had NAION induced and either intravitreal PGJ2 or sham saline was injected

Results

- Statistically significant reduction in clinical, electrophysiological and histologic damage in treatment arm eyes compared with control eyes.
- Majority of PGJ2-treated eyes had reduced ON and peripapillary RNFL edema in follow-up
  - No statistical significance between the pattern visual evoked potential (VEP) and the pattern-evoked electroretinography (PERG) N95 amplitudes in PGJ2-treated eyes compared with their baseline values
- This suggests that PGJ2 is strongly protective in eyes with induced NAION in comparison to controls

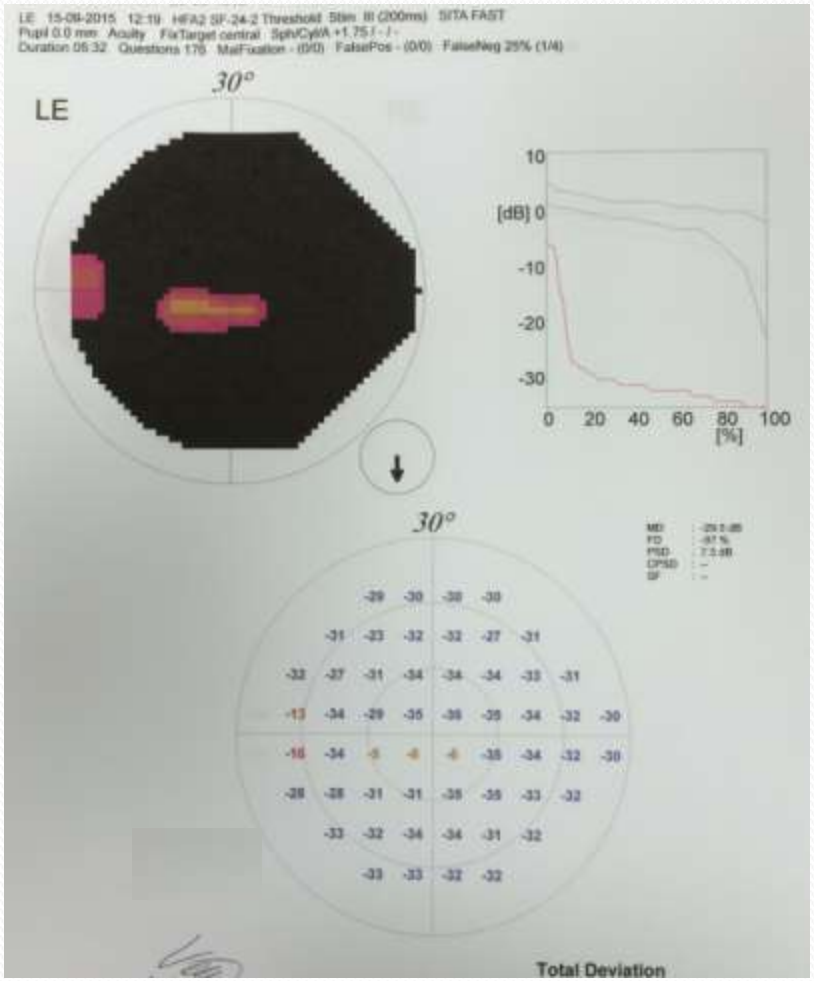
Conclusion:

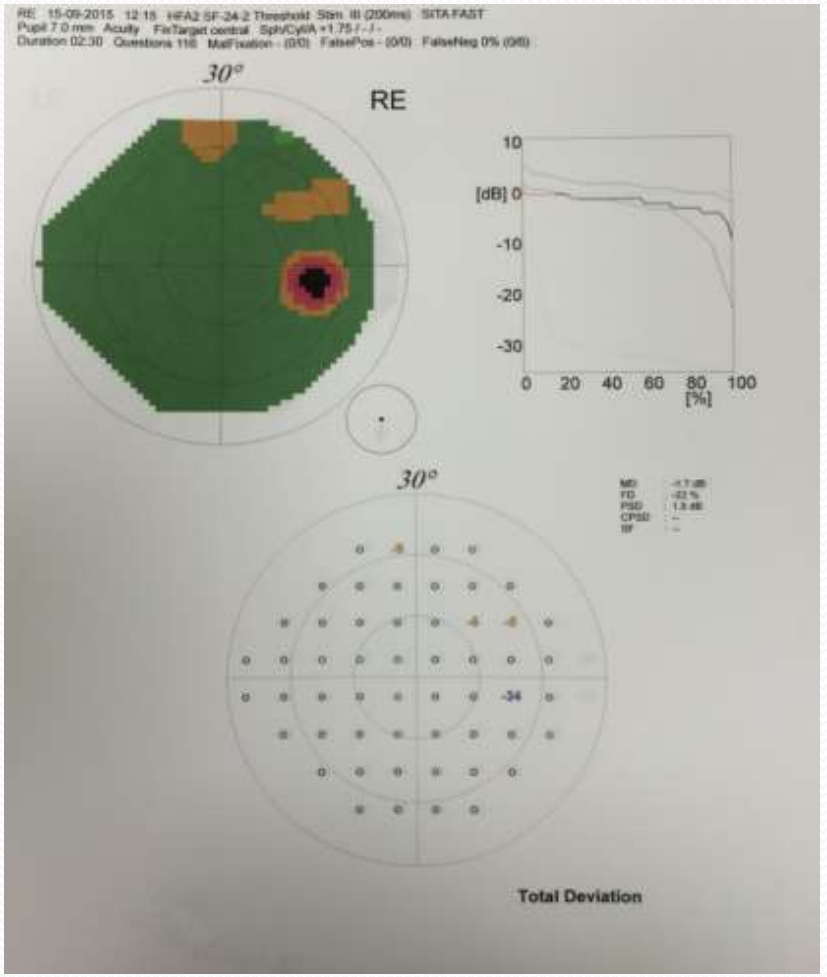
- Single dose of intravitreal PGJ2 is neuro-protective up to 5 hours after induction of primate NAION
  - PGJ2 acts towards selective post-ischemic inflammatory control
- PGJ2
  - Had no permanent systemic toxicity
  - Had no ocular toxicity

Back to Our Patient:

- 6 weeks after initial symptoms/ 2 weeks after visit to our clinic
- Patient felt her vision was getting worse, and she presented to her outside ophthalmologist
  - Progression of defects in visual field
  - VA decreased to hand motion

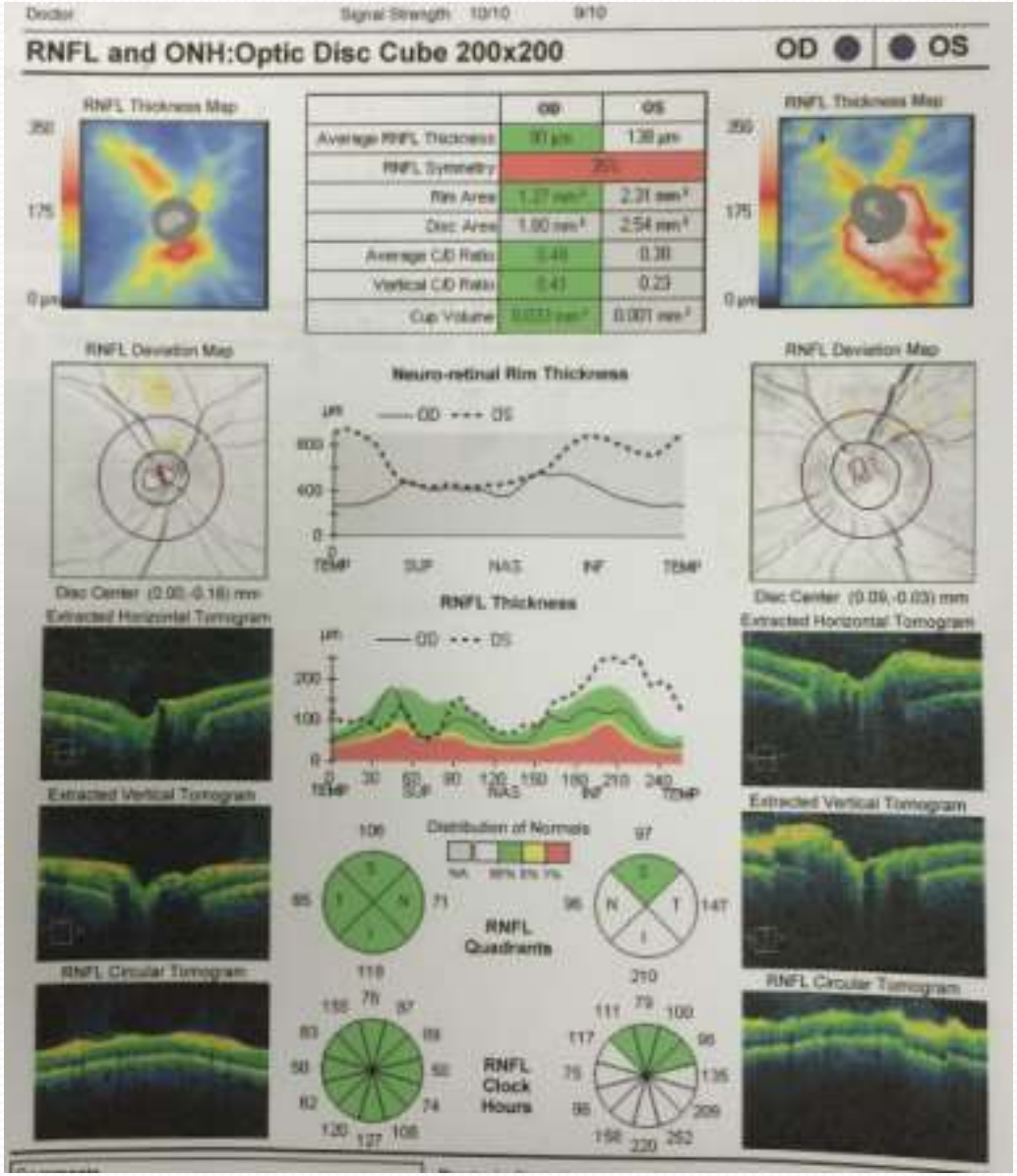
Visual Field – 9/15/15





Patient Care, Interpersonal Communication Skills, Professionalism, Practice-Based Learning and Improvement

OCT ONH – 9/15/15



Average RNFL

OD: 90

OS: 138

Patient Care, Interpersonal Communication Skills, Professionalism, Practice-Based Learning and Improvement

Additional Lab Results :

- Prothrombin gene mutation=wnl
- Protein C and S= wnl
- Antithrombin III= 77 (low); normal range= 80-120
- Homocysteine= 16.1 (elevated); normal< 10.4
- CRP= wnl (1.62)
- ESR = wnl (6)
- PTT= wnl
- PT/INR= wnl
- Lupus anticoagulant= negative

Back to Our Patient (cont.)

- Recommended:
  - Increasing ASA 81 mg PO once a day to ASA 325 mg PO once a day
  - Folic acid supplementation
  - Another course of steroids
    - IV steroids x 3-5 days
    - Recommended PO prednisone taper but patient declined (history of osteoporosis)
  - Vision continues to be poor, but no second eye involvement

Reflective Practice

- This case provided the opportunity to take a good history, perform an ophthalmic exam, and consider a differential diagnosis.
- Moreover, I was able to evaluate the scientific literature for risk factors, models of disease and treatment options related to the condition of non-arteritic anterior ischemic optic neuropathy.
- The patient received information on the condition and was given a plan for proper treatment.

Core Competencies

- Patient care – The patient was appropriately treated in a timely matter with the patient's best interest in mind. The patient was made aware of what plans were made in order to treat the condition.
- Medical knowledge – The case provided the opportunity to learn more about the presentation, differential diagnosis and treatments of NAION.
- Practice Based Learning – The scientific literature was reviewed and the information was applied to improve patient care and physician knowledge.
- Systems Based Practice– The patient was treated appropriately after discussion with colleagues and ancillary staff.
- Professionalism–The patient was treated in a kind and respectful manner at all times.
- Interpersonal Skills and Communication – A thorough history and review of systems was obtained from the patient. The treatment plan was shared with the patient in language free of medical jargon that the patient could understand.

References

- Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of Nonarteritic Anterior Ischemic Optic Neuropathy. *Survey of Ophthalmology* 2010; 55: 47-63
- Berstein SL, Miller NR. Ischemic optic neuropathies and their models: disease comparisons, model strengths and weaknesses. *Jpn J Ophthalmol* 2015; 59: 135-147
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- Hayreh SS, Podhajsky PA, Zimmerman B. Ipsilateral recurrence of nonarteritic anterior ischemic optic neuropathy. *Am J Ophthalmol* 2001; 132: 734–742.
- Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. *Eye* 2015; 29: 65-79
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- Newman NJ, Scherer R, Langenberg P, Kelman S, Feldon S, Kaufman D et al. The fellow Eye in NAIONL report from the Ischemic Optic Neuropahty Decompression Trial follow-up study. *Am J Ophthalmol* 2002; 134: 317-328.
- Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. *JAMA* 1995; 273: 625–632
- Salomon O, Huna-Baron R, Steinberg DM, Kurtz S, Seligsohn U. Role of aspirin in reducing the frequency of second eye involvement in patients with non-arteritic anterior ischaemic optic neuropathy. *Eye* 1999; 13: 357–359

Thank you

- Dr. Elmalem (facilitator)
- Our patient

Medical Knowledge, Systems Based Practice, Patient Care, Professionalism, Interpersonal Communication