Ophthalmology Grand Rounds
December 17, 2015
SUNY Downstate Medical Center

Benjamin Whigham, M.D.

Patient 1

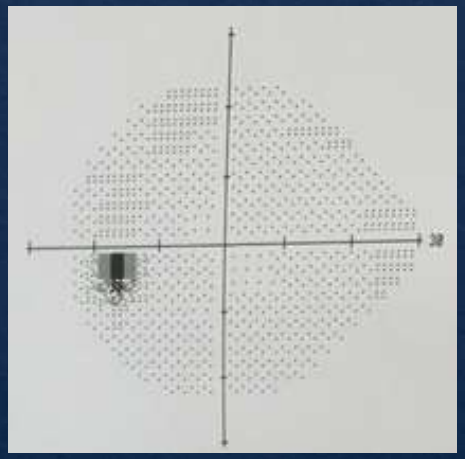
- 41yo BF with
  - Headaches x 3 weeks
  - Blurred vision OD x 1 week
  - Gaps in vision (“Like your hand is not there”)
- ROS: Otherwise negative
- POHx: Reading glasses
- Meds: Biotin (supplement)
- FH: Aunt went blind in one eye due to “migraine” in her 30’s
- SH: +Tobacco, +Recent Travel (India, Hong Kong)

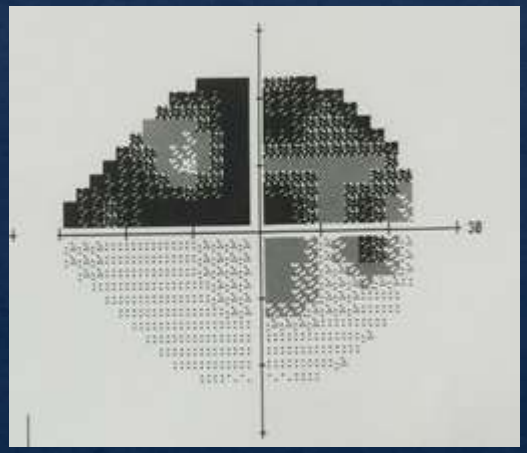
Patient 1

- DVAsc: 20/70+1 od 20/20 OS
- Pupils: 4:2 sluggish OD 4:2 brisk OS +Right RAPD
- EOMs: Pain OD with adduction, full OU
- CVF: FTCF OU (but "cannot see all fingers")
- Tpen: 11,9
- Red desaturation: 50% OD, 100% OS
- Ext: mild R periorbial tenderness
- SLE: WNL

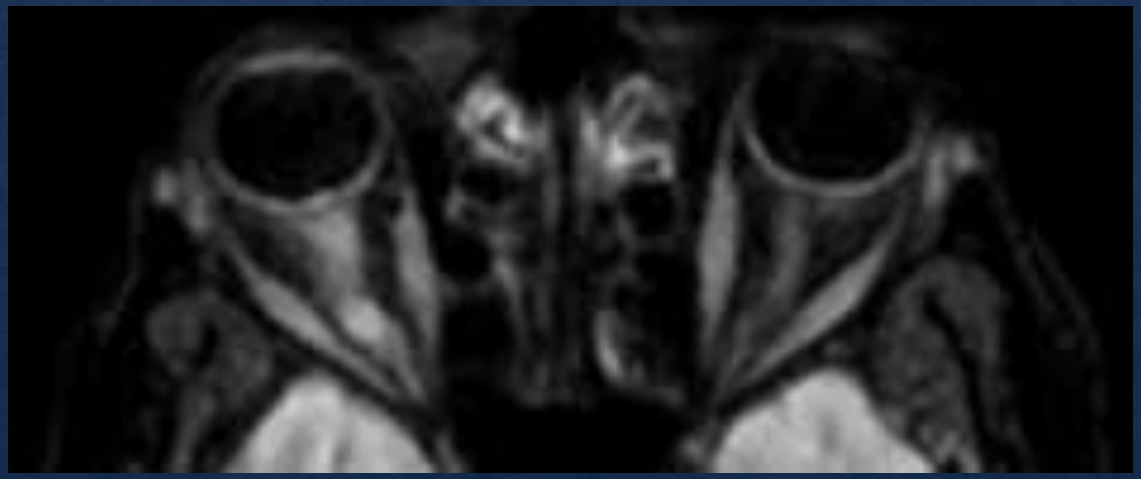
Patient 1 / DFE

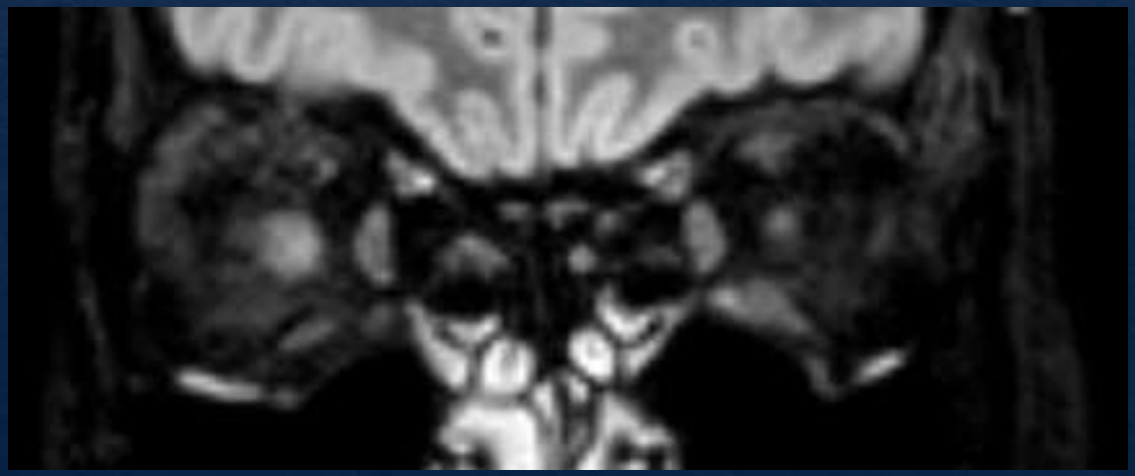
Patient 1 / HVF



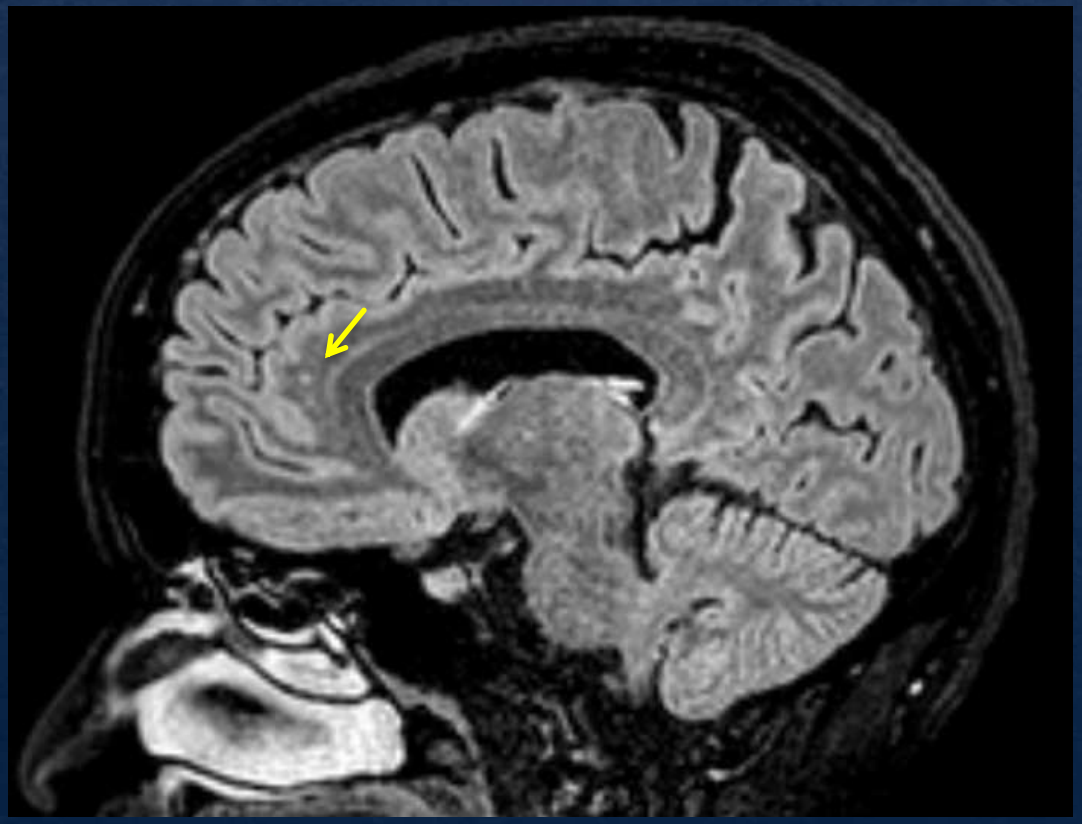


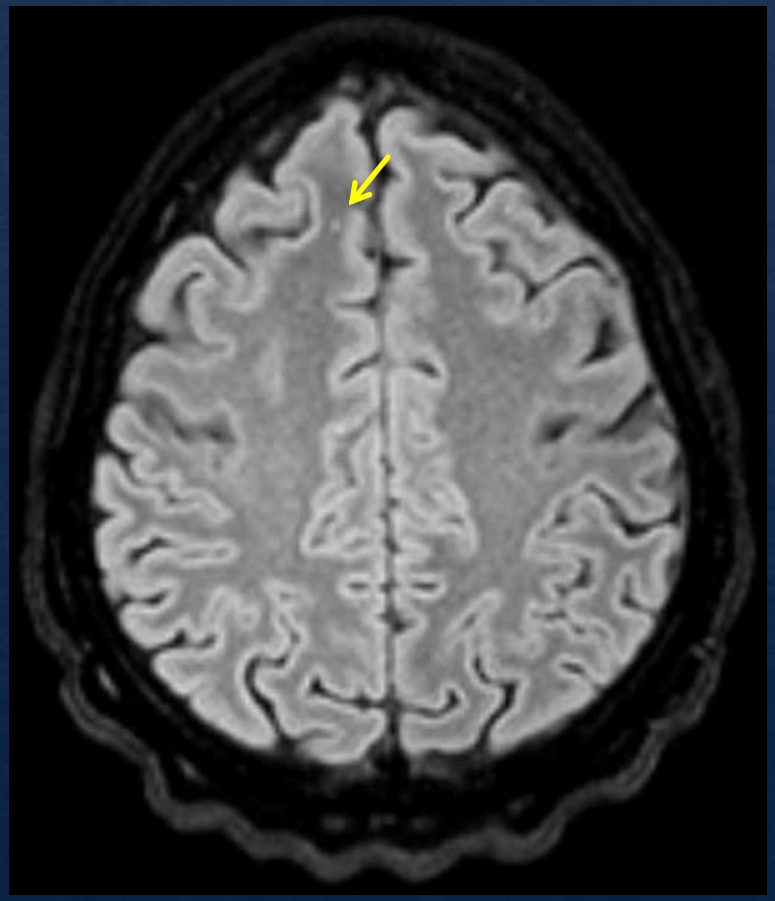
Patient 1 / MRI





Patient 1 / T2 FLAIR





Patient 1 / Ddx (Disc Edema)

- Autoimmune
  - Multiple sclerosis + Neuromyelitis optica
  - Lupus
  - Neurosarcoidosis
- Infection
  - Syphilis
  - Lyme
  - Herpes zoster

Patient 1

- ESR 52 (elevated); CRP 0.19 (low); Plt 287 (normal)
- Glucose 130
- CMP/CBC otherwise WNL

- ACE wnl; ANA negative
- Lyme, RPR, HIV negative
- NMO sent

Patient 1

- Neurology admission
- Methylprednisolone 1 gm daily x 5 days
  - Day 3:
    - DVAsc: 20/60+1 OD, 20/20 OS
    - APD OD (> 1.8 log units)
    - EOM painless
- Discharged no taper

(Optic Neuritis Study, 2008)

Patient 1 / Prognosis

- Visual recovery (ONTT) :
  - 79% improved some by 3 weeks; improvement continues up to 12 months
  - Baseline vision is prognostic indicator
  - 97% will gain ≥ 3 lines of vision (if ≤ 20/50)
  - Visual field recovery: 85% average threshold
- 15-year risk of MS:
  - Uncertain MRI → 50%
  - ≥ 1 lesion → 72%
  - 0 lesions (25%) + disc edema (32%) → 14% chance

(Beck, Cleary, & Backlund, 1994)
(Fang, Lin, & Donahue, 1999)
(Optic Neuritis Study, 2008)

Patient 2 / Presentation

- 35yo BF presents with
  - Pain OD x 3 days (non-specific; worse with movement/rubbing)
  - Blurring OD x 1 day
  - “dust spread across vison”
- ROS negative
- PMHx: Gastritis (Nexium)
- POHx: Refractive error (glasses)
- Family: Negative
- Social: Negative x 3

Patient 2

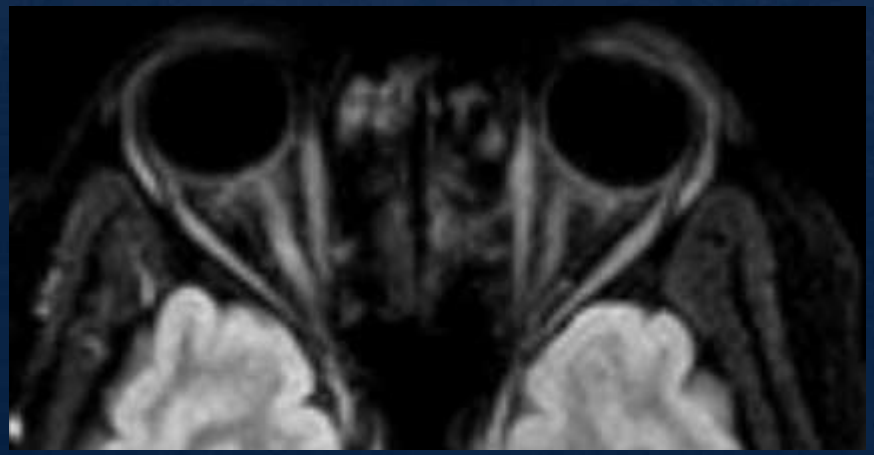
- DVAcc: 20/25 OD, 20/20 OS
- P: 7:3 sluggish OD + right RAPD 7:3 brisk OS
- EOM: Full OU (pain with abduction OD)
- CVF: FTFC OU
- Tapp: 13 OD 16 OS
- Color: 11/16 OD 16/16 OS

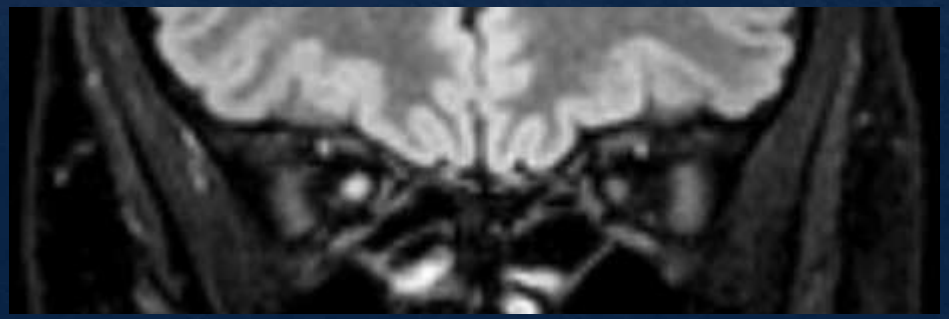
Patient 2

- External: TTP right eye/periorbital area
- SLE: mild PSC OU
- DFE: WNL
  - C/D: 0.4 s/p OU, mild temporal ppa OD, mild temporal tilt to discs OU
  - Macula: flat OU
  - V/P: vessels wnl; no heme/holes/tears

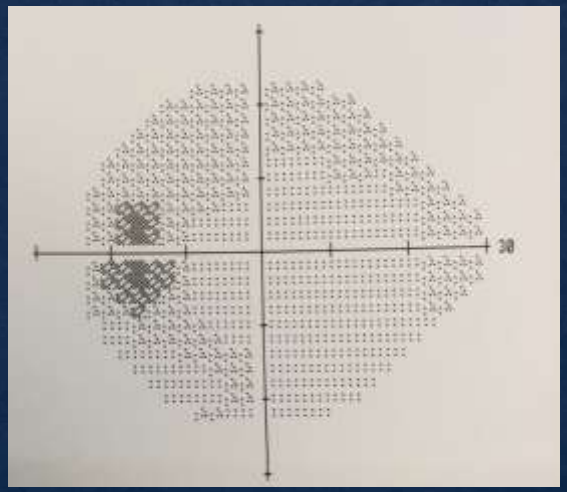
Patient 2

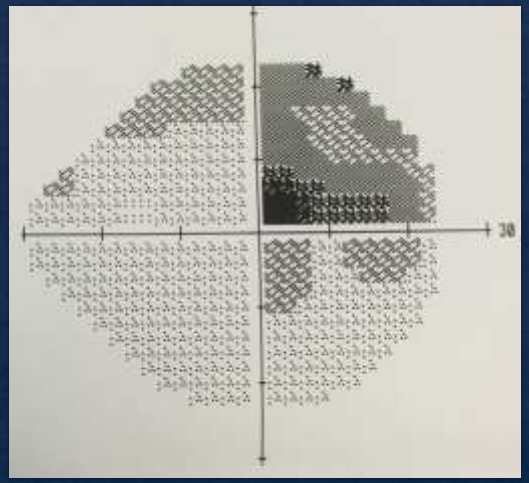
- Neurology admission
- Begin methylprednisolone 1 gm x 3 days
- ESR, CRP, ACE, ANA, Lyme, RPR, NMO
- MRI, HVF





Patient 2 / Day 3





Patient 2 / Day 3

- s/p IVMP (1 gm x 2 days)
- Pain improved
- DVAcc: 20/80+1 OD 20/20 OS
- Pupils: 7:3 sluggish OD 7:3 brisk OS
  +right RAPD (1.5 – 1.8 log units)
- EOM: Full OU (no pain)
- Color: 10.5/12 OD 12/12 OS (stable)
- Nerves: WNL OU

Patient 2 / Day 4

- Completed 3-day course methylprednisolone
- Home off steroids (no PO prednisone taper)

- Presented ED 1 week later (Day 12)
- Reported mild improvement in vision but increasing pain
  - Right-sided
  - Worse with light + palpation to temple
  - Improves with administration of cycloplegic

Patient 2 / Day 12 (ED)

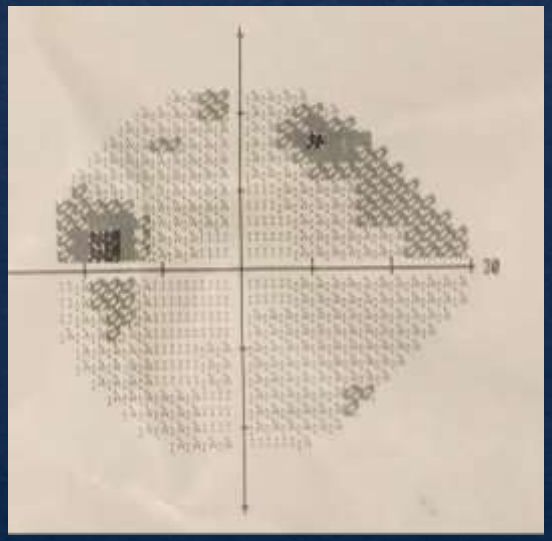
- DVAcc: **20/50 OD** 20/20 OS
- Pupils: 7:3 sluggish OD 7:3 brisk OS
  + right RAPD
- EOM: Full OU, Pain with adduction OD
- Color: 15/15 OD, 15/15 OS
- Red desat: 50% OD, 100% OS
- Penlight: 5% OD, 100% OS

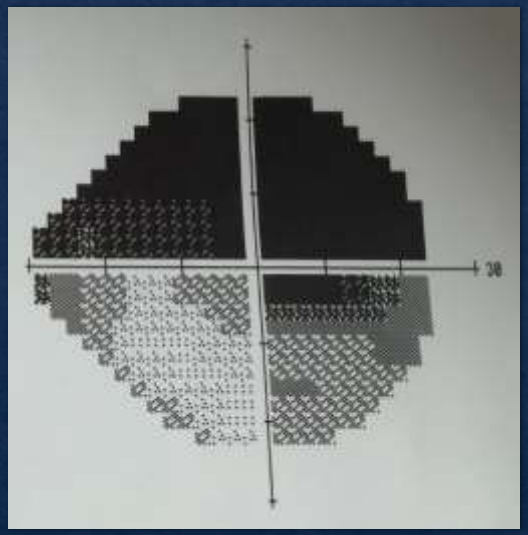
- External: mild tenderness to deep palpation at temples
- SLE/DFE: unchanged

Patient 2 / Day 12

- ACE 55 (ULN 52);
  - CXR negative x 2
- ESR, CRP, ANA, Lyme, RPR all normal/negative
- NMO pending
- Differential/plan?

Patient 2 / Day 13





Patient 2 / Day 13

- Recommended IV steroids **with taper**
- ONTT: 1gm/day (Q6H) IVMP x 3 days → PO Pred 1 mg/kg/day x 11 days → Taper

- Vision remains 20/50 - 20/100 x 3 days in hospital
- Recommend
  - PPD post steroids
  - RTC 5 days

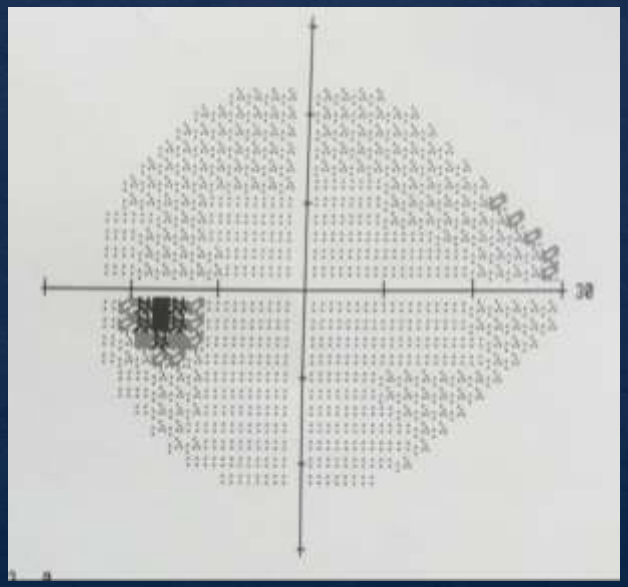
(Optic Neuritis Study, 2008)

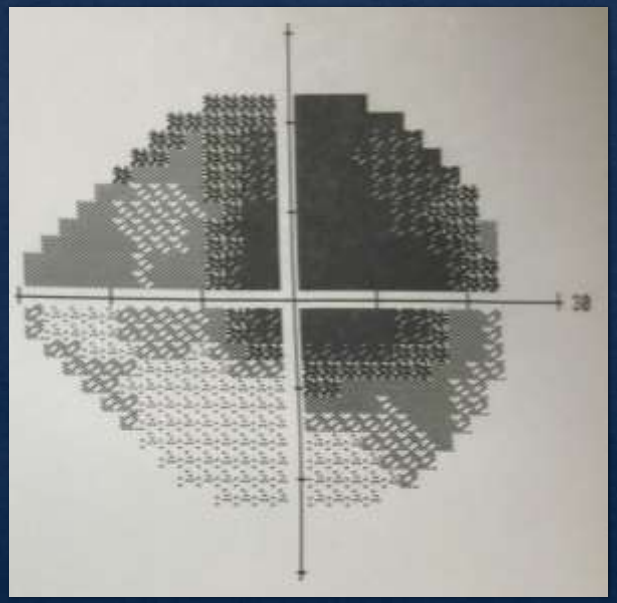
Patient 2 / Day 21

- DVAcc: **CF at 3 feet OD** 20/20 OS
- P: 7:3 sluggish OD + Right RAPD 7:3 brisk OS
- EOM: Full OU

- **NMO Antibody Positive**
- Repeat MRI Brain/Spine: Negative

Patient 2 / Day 21





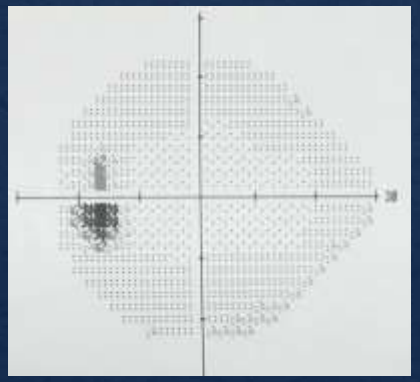
Patient 2 / Days 22 - 34

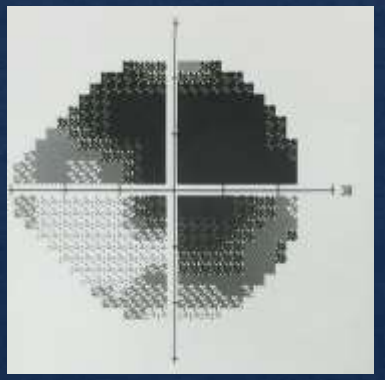
	Day 22	Day 24	Day 26	Day 28	Day 30	Day 32	Day 34
NVAcc:	20/400	20/400	20/200	20/200	20/200+1	20/50+1	20/20-2
Color:	<50%	50%	50%	50%	80%	12/15 CP	14/16 CP
EOM:	Full	Full	Full	-	-	-	-
Plasmapheresis session*:	1	2	3	4	-	-	-
Prednisone:	60mg	60mg	60mg	60mg	60mg	60mg	60mg

*5th session cancelled (low fibrinogen/bleeding)

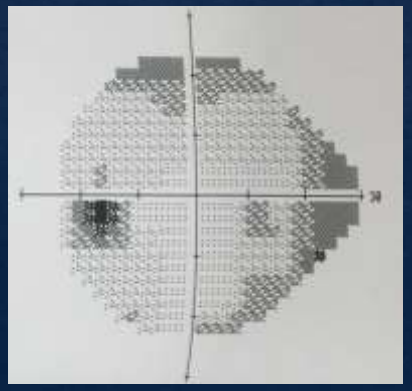
Patient 2 / Plasmapheresis

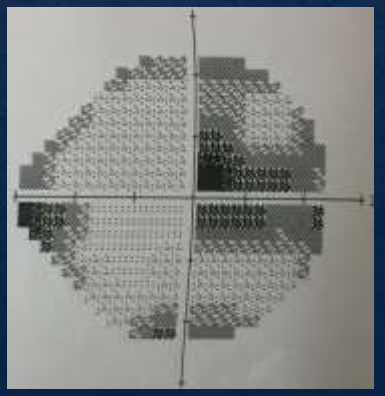
- Day 28 (final plasma tx)
  - NVAcc: 20/200 OD,
  - 20/20 OS
  - CP: 0/12 OD, 12/12 OS





- Day 35 (1-week post)
  - DVAcc: 20/30 OD,
  - 20/20 OS
  - CP: 10/12 OD, 12/12 OS





Patient 2 / Plan

- Prednisone 60mg daily x 2 weeks, then taper
- Planned Azathioprine 2-3 weeks post DC
- Follow in Ophthalmology / Neurology clinics

NMO – What is it?

Inflammatory Demyelinating Diseases of CNS

- Relapsing-Onset multiple sclerosis
- Primary progressive MS
- Optic-spinal MS
- **Neuromyelitis optica (NMO), and its associated "spectrum of disorders" (NMOSD)** –
  - AQP4 autoimmune channelopathy
  - Anti-MOG associated encephalomyelitis
  - An idiopathic underlying condition
- CRION (Chronic relapsing inflammatory optic neuritis)…

(Weinshenker & Wingerchuk, 2014)
(Spadaro et al., 2015)

Inflammatory Demyelinating Diseases of CNS

- Acute disseminated encephalomyelitis
- Acute hemorrhagic leukoencephalitis
- Balo concentric sclerosis
- Schilder disease or diffuse myelinoclastic sclerosis
- Marburg multiple sclerosis
- Tumefactive multiple sclerosis
- Solitary sclerosis

Neuromyelitis Optica: History

- Discovered 19th century ("Devic disease")
- For 20th century was distinguished from MS based on unique and specific clinical characteristics.
- Early 2000's: Anti-AQP4-IgG discovered → Testing
- 2006 → New guidelines for NMO
- In 2007 NMO spectrum disorders (NMSOD)
- 2015 → New guidelines NMSOD (again):
  - "It allows for NMOSD diagnosis in AQP4-IgG-seropositive patients with involvement of almost any CNS region as well as in those with restricted involvement of a single region"

(Wingerchuk et al., 2015)

NMO: Traditional Definition

- Clinically defined

- Severe CNS demyelinating syndrome
  - Simultaneous bilateral optic neuritis (ON) and acute myelitis
  - No other CNS symptoms outside this region
  - Monophasic event

NMO: 2007 Definition

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

- Optic neuritis
- Acute myelitis
- At least two of three supportive criteria
  1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
  2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
  3. NMO-IgG seropositive status

(Wingerchuk, Lennon, Pittock, Lucchinetti, & Weinshenker, 2006)

Table 1 NMOSD diagnostic criteria for adult patients

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

NMO vs NMOSD:

- (1) there are no established biological differences between patients diagnosed with NMO compared with NMOSD (using 2006 and 2007 definitions, respectively) in AQP4-IgG-seropositive patients
- (2) limited NMOSD syndromes affecting CNS regions other than the optic nerve and spinal cord often herald subsequent clinical attacks consistent with conventional NMO in AQP4-IgG-positive patients
- (3) current immunotherapeutic strategies are the same for relapsing NMO and NMOSD, regardless of AQP4-IgG serologic status.

(Wingerchuk et al., 2015)

NMO Spectrum Disorders

Anti-AQP4 Assays
- 60-80% sensitive
- >= 97% specific

Generally worse than MS
- 50% will be blind in ≥ 1 eye at 5 years

(Wingerchuk et al., 2015)

(Waters et al., 2012)

NMO Prevalence

- NMO Incidence: 0.053 to 0.40, / 100,000
- NMO Prevalence: 0.52 to 4.4. / 100,000
- MS Prevalence US: 90 / 100,000

- Italian study: NMOSD accounted for 1.5% of MS clinic attendees (56% of which NMO)
  - Might be higher in other groups
  - Africans/Asians > Caucasians
  - Temperate > Cold

(Bizzoco et al., 2009)
(Marrie & Gryba, 2013)

NMO Treatment

- General lack of randomized control trials
- Acute: Prevent irreversible CNS damage
  - IVMP 1gm/d x3- 5 days + 2-6 month pred taper
  - If IV steroids fail: Plasma Exchange (RCT evidence)
  - If Plasma Exchange fails → Cyclophosphamide (or consider IVIG)
- Chronic: Prevent relapse
  - Prednisone (tapered after 2 months; 10-20 mg/d), Azathioprine (test for *TMPT*, goal: 2 mg/kg/day)
  - Mycophenolate mofetil, Rituximab, Methotrexate, Mitoxatrone

(Kimbrough et al., 2012)

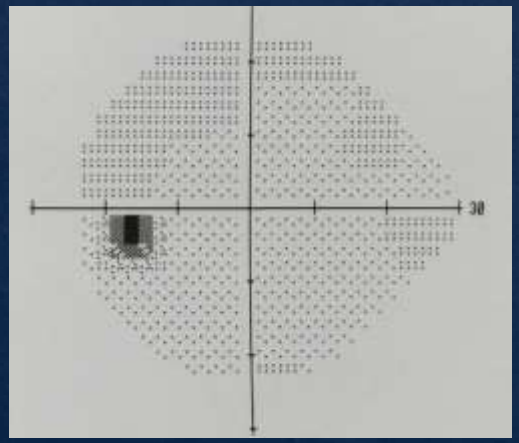
NMO Treatment

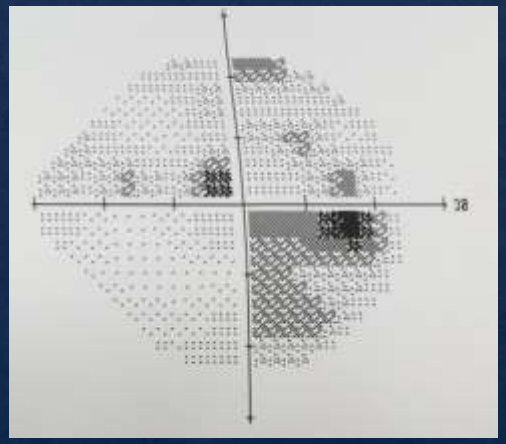
- Uncertain NMO versus MS: Treat as NMO
  - IFN-beta may aggravate NMO
  - Worsening also reported with Natalizumab / Fingolimod

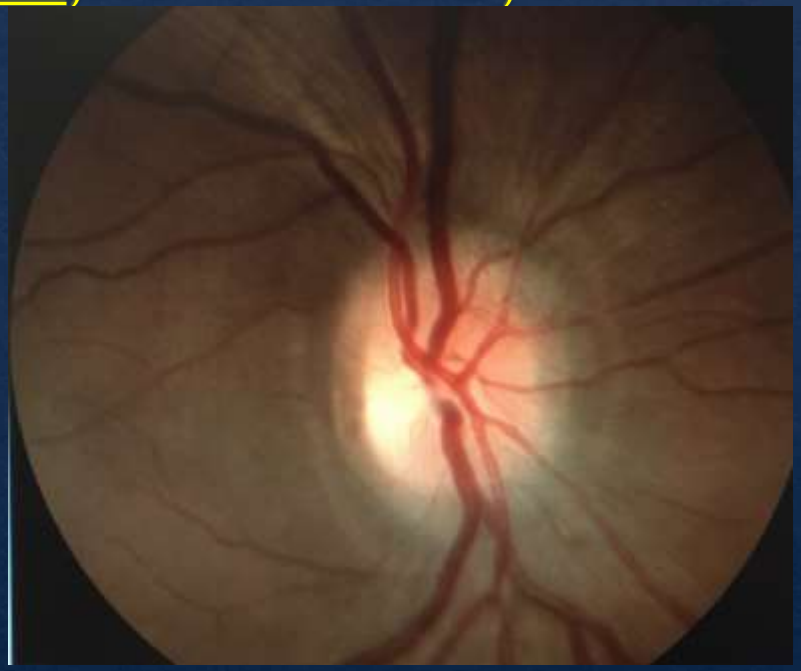
(Kimbrough et al., 2012)

Patient 1 / Day 30

- Pain resolved / Vision improved
- 20/40-2 (previously 20/60+1) OD, CP 4.5/12 OD, 24-2 Unreliable but with defects:







- Improved disc edema (Grade 1-2+)
- **NMO positive**
- Started Prednisone 80 mg/day (Taper 10 mg / week)
- To establish with provider in home state for monitoring

References

- Beck, R. W., Cleary, P. A., & Backlund, J. C. (1994). The course of visual recovery after optic neuritis. Experience of the Optic Neuritis Treatment Trial. *Ophthalmology, 101*(11), 1771-1778. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/7800355
- Bizzoco, E., Lolli, F., Repice, A. M., Hakiki, B., Falcini, M., Barilaro, A., . . . Mata, S. (2009). Prevalence of neuromyelitis optica spectrum disorder and phenotype distribution. *J Neurol, 256*(11), 1891-1898. doi:10.1007/s00415-009-5171-x
- Fang, J. P., Lin, R. H., & Donahue, S. P. (1999). Recovery of visual field function in the optic neuritis treatment trial. *Am J Ophthalmol, 128*(5), 566-572. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10577523
- Kimbrough, D. J., Fujihara, K., Jacob, A., Lana-Peixoto, M. A., Leite, M. I., Levy, M., . . . Br. (2012). Treatment of Neuromyelitis Optica: Review and Recommendations. *Mult Scler Relat Disord, 1*(4), 180-187. doi:10.1016/j.msard.2012.06.002
- Marrie, R. A., & Gryba, C. (2013). The incidence and prevalence of neuromyelitis optica: a systematic review. *Int J MS Care, 15*(3), 113-118. doi:10.7224/1537-2073.2012-048
- Optic Neuritis Study, G. (2008). Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol, 65*(6), 727-732. doi:10.1001/archneur.65.6.727
- Spadaro, M., Gerdes, L. A., Mayer, M. C., Ertl-Wagner, B., Laurent, S., Krumbholz, M., . . . Kumpfel, T. (2015). Histopathology and clinical course of MOG-antibody-associated encephalomyelitis. *Ann Clin Transl Neurol, 2*(3), 295-301. doi:10.1002/acn3.164
- Waters, P. J., McKeon, A., Leite, M. I., Rajasekharan, S., Lennon, V. A., Villalobos, A., . . . Pittock, S. J. (2012). Serologic diagnosis of NMO: a multicenter comparison of aquaporin-4-IgG assays. *Neurology, 78*(9), 665-671; discussion 669. doi:10.1212/WNL.0b013e318248dec1
- Weinshenker, B. G., & Wingerchuk, D. M. (2014). The two faces of neuromyelitis optica. *Neurology, 82*(6), 466-467. doi:10.1212/WNL.0000000000000114
- Wingerchuk, D. M., Banwell, B., Bennett, J. L., Cabre, P., Carroll, W., Chitnis, T., . . . International Panel for, N. M. O. D. (2015). International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology, 85*(2), 177-189. doi:10.1212/WNL.0000000000001729
- Wingerchuk, D. M., Lennon, V. A., Pittock, S. J., Lucchinetti, C. F., & Weinshenker, B. G. (2006). Revised diagnostic criteria for neuromyelitis optica. *Neurology, 66*(10), 1485-1489. doi:10.1212/01.wnl.0000216139.44259.74