

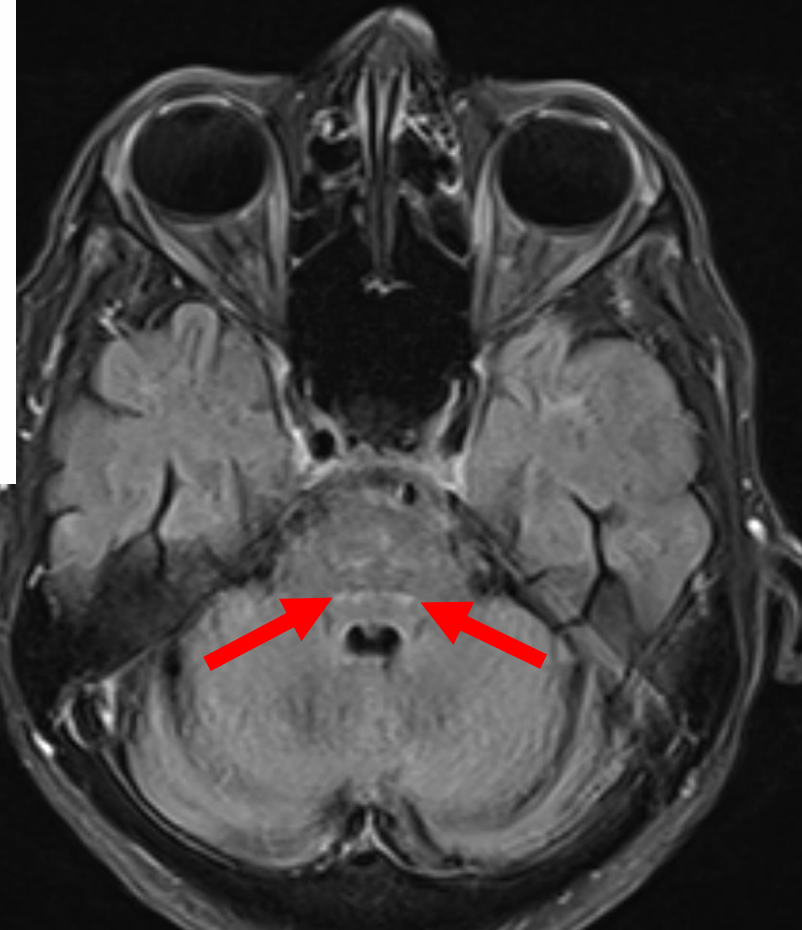
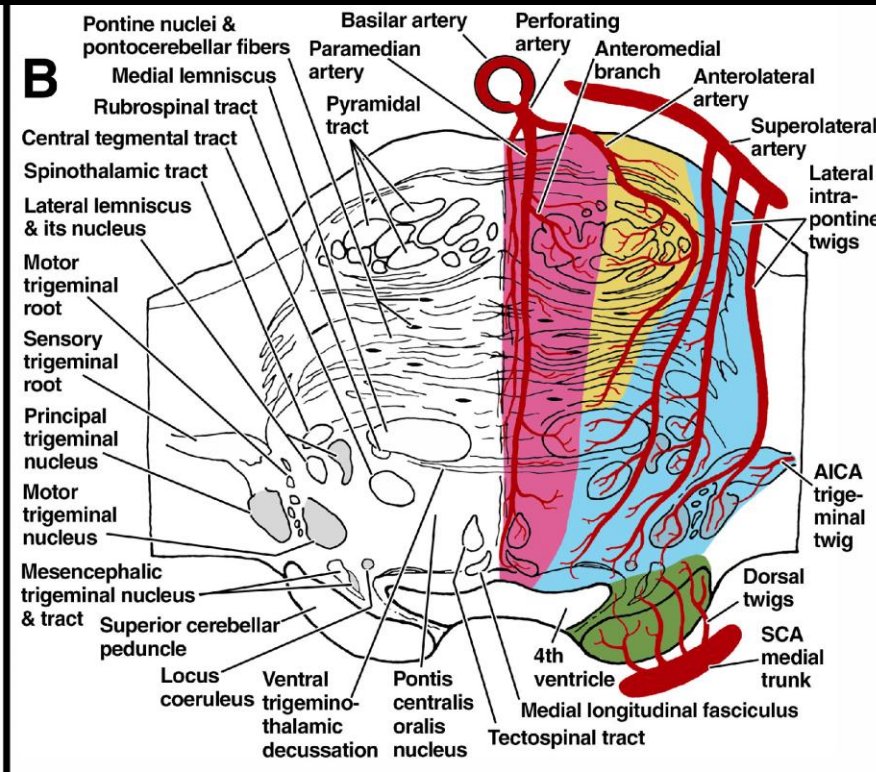
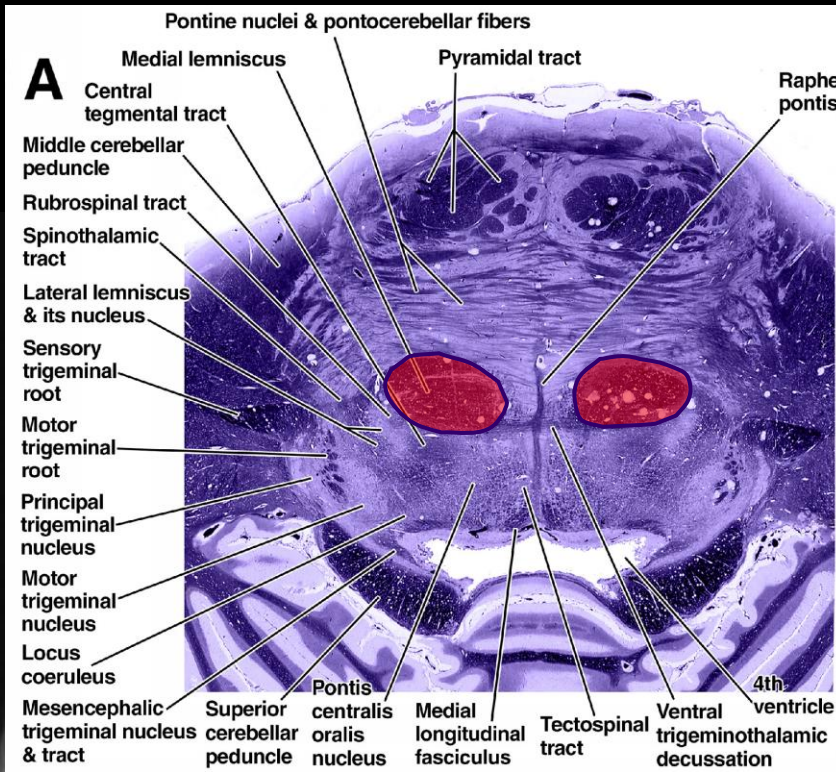
Brain White Matter Disease

Matthew Breen MD

Clinical Assistant Professor

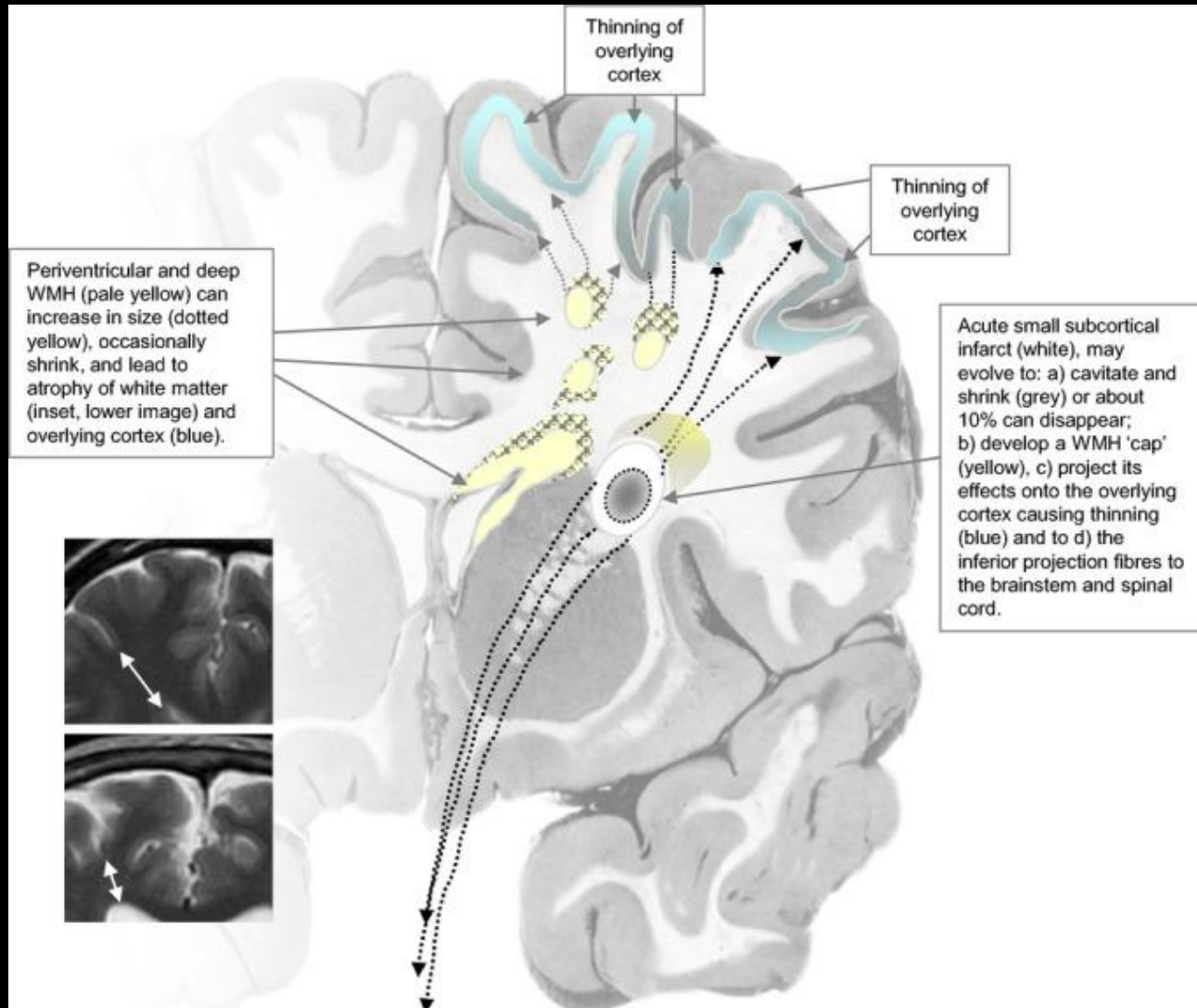
NYU Grossman School of Medicine

New York, NY



- Tatjana Vlašković, Biljana Georgievski Brkić, Zorica Stević, Marjana Vukićević, Olivera Đurović, Dejan Kostić, Nataša Stanisavljević, Ivan Marinković, Slobodan Kapor, Slobodan Marinković, Anatomic and MRI Bases for Pontine Infarctions with Patients Presentation, Journal of Stroke and Cerebrovascular Diseases, Volume 31, Issue 8, 2022
- Erbay SH, Brewer E, French R, Midle JB, Zou KH, Lee GM, Erbay KD, Bhadelia RA. T2 hyperintensity of medial lemniscus is an indicator of small-vessel disease. AJR Am J Roentgenol. 2012 Jul;199(1):163-8. doi: 10.2214/AJR.11.7444. PMID: 22733908.

Chronic small vessel ischemic disease



White matter hyperintensities (WMH)

Small vessel disease (SVD)

Microangiopathy

Leukoariosis

Binswanger disease

Correlates with cerebrovascular risk factors

- **Hypertension*****
- Age
- Diabetes
- Smoking
- Hyperlipidemia
- Other vascular disease

BASIC SCIENCE FOR CLINICIANS

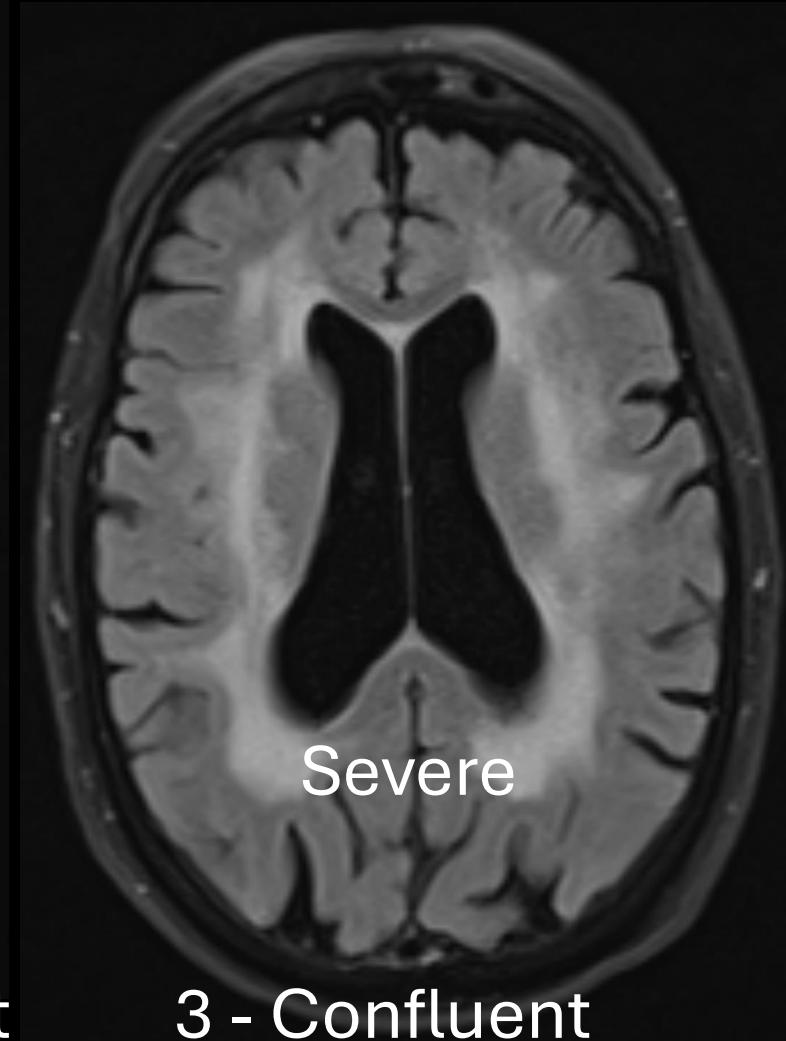
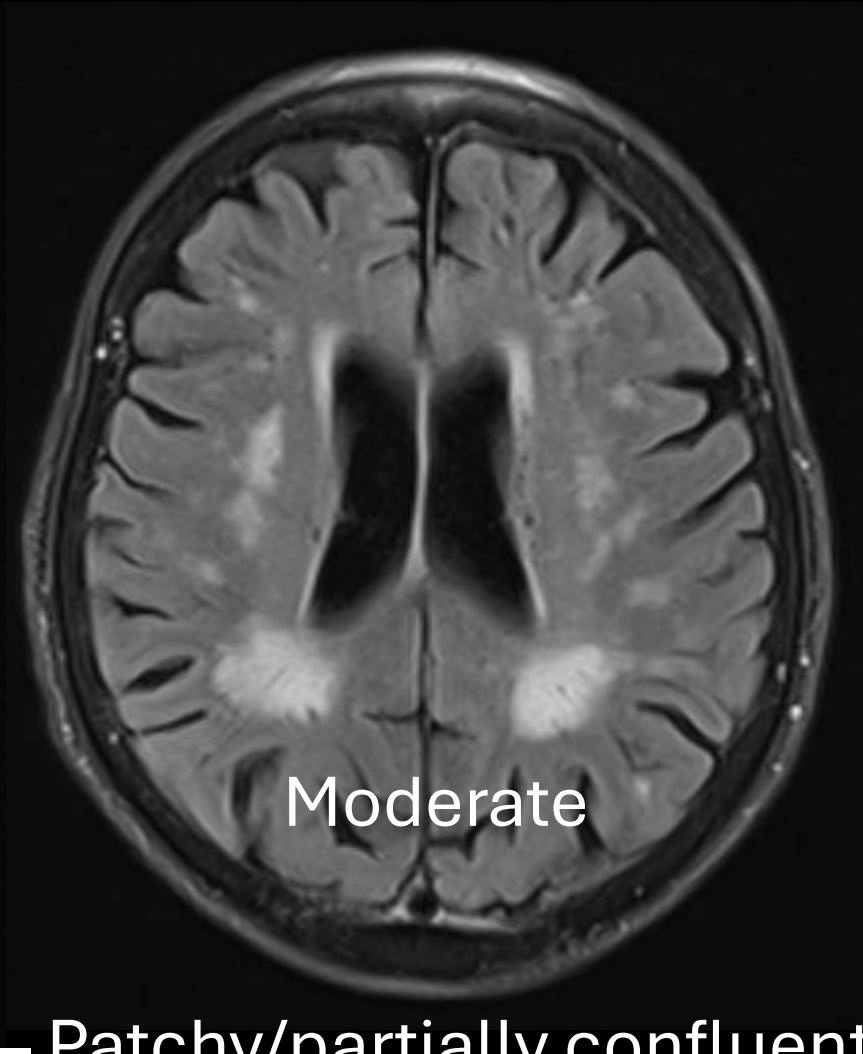
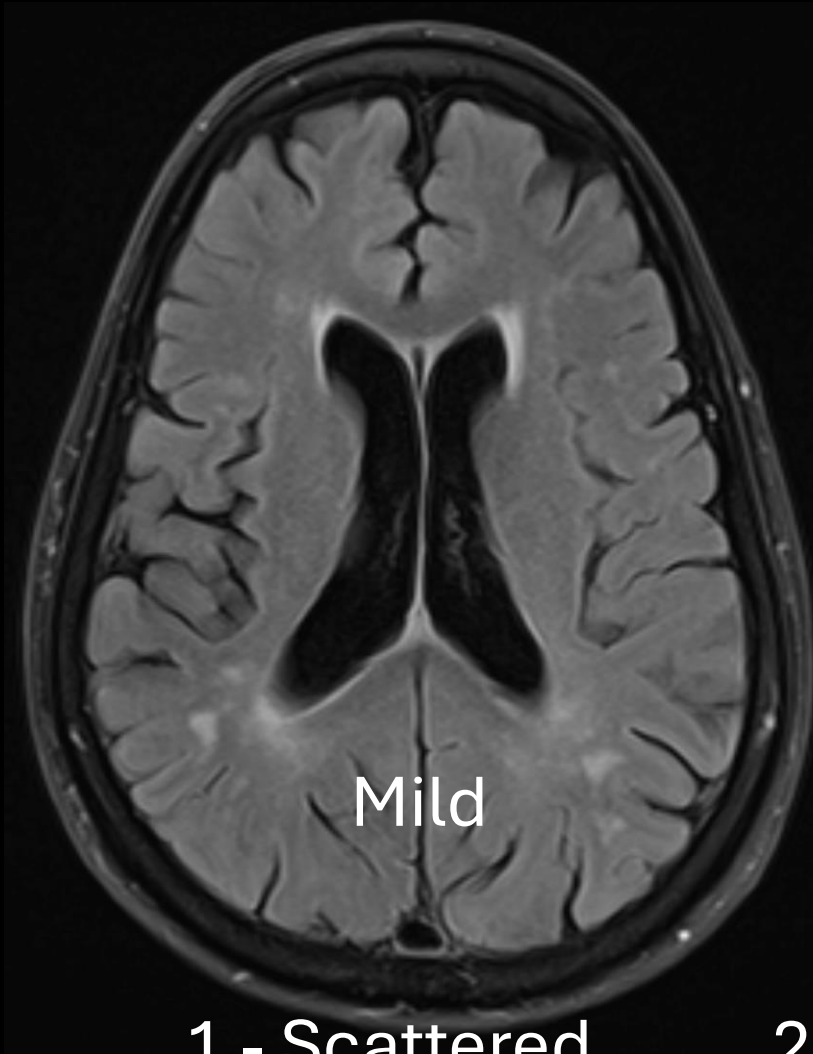


What are White Matter Hyperintensities Made of?

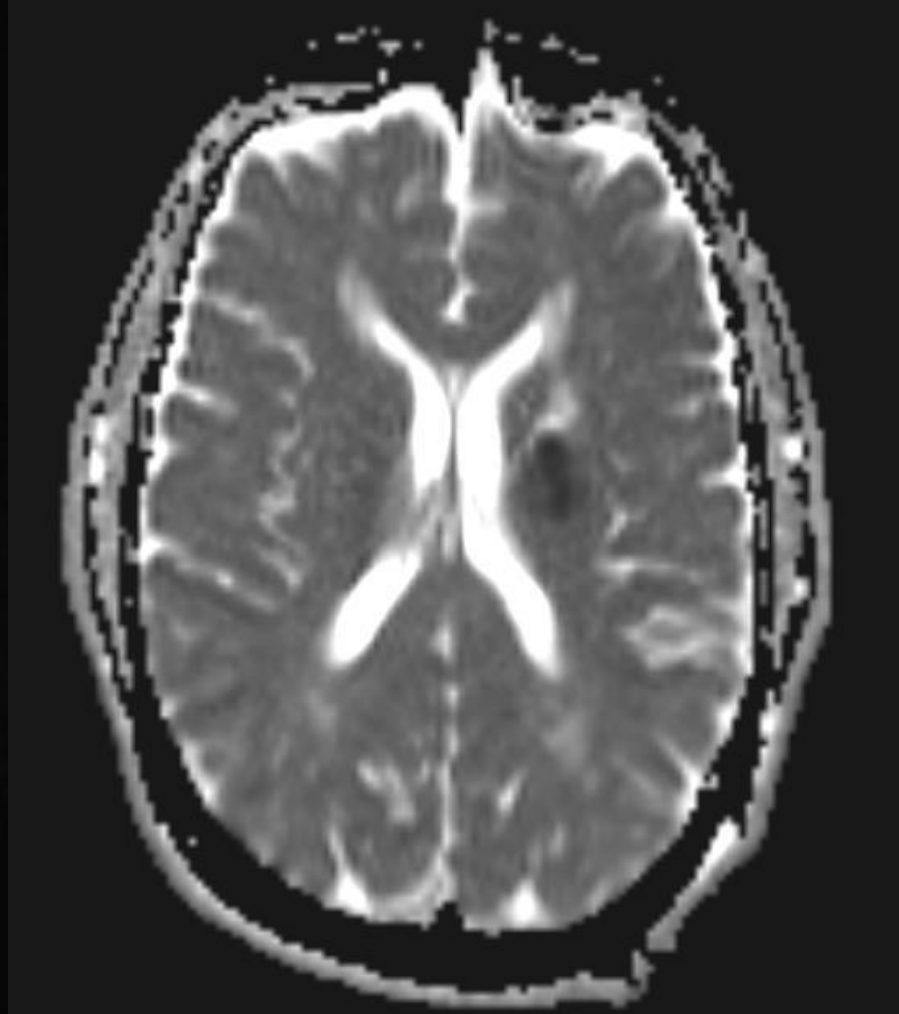
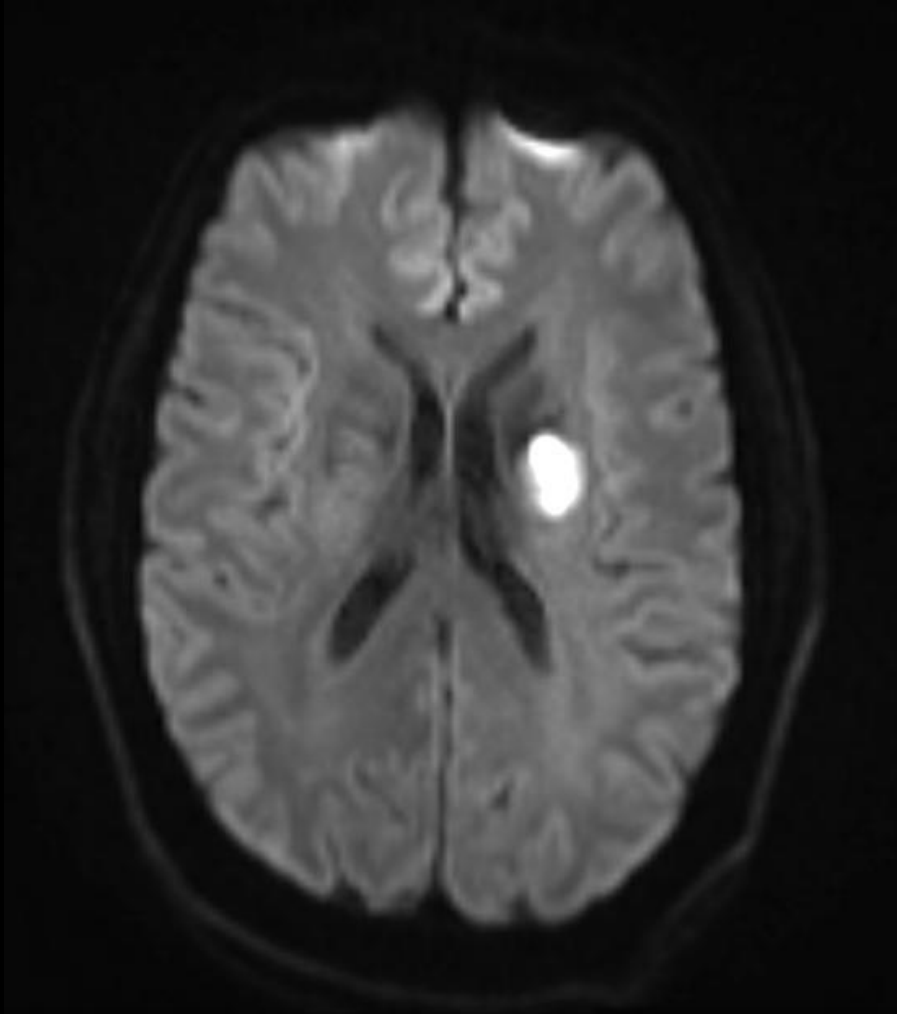
Relevance to Vascular Cognitive Impairment

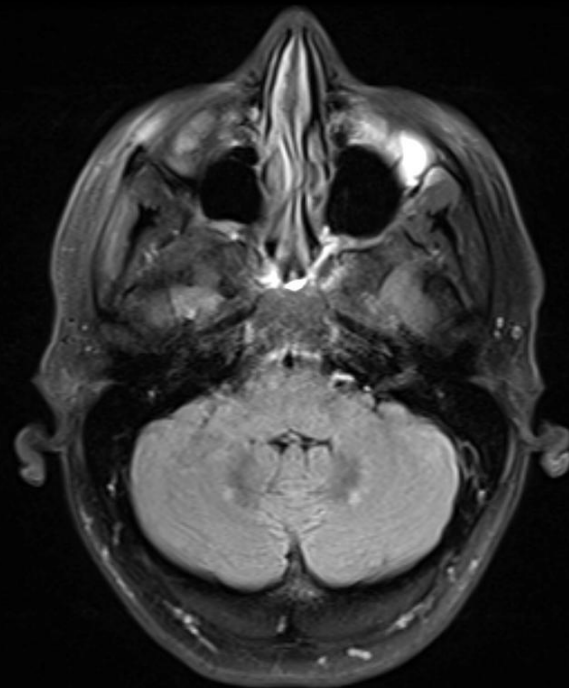
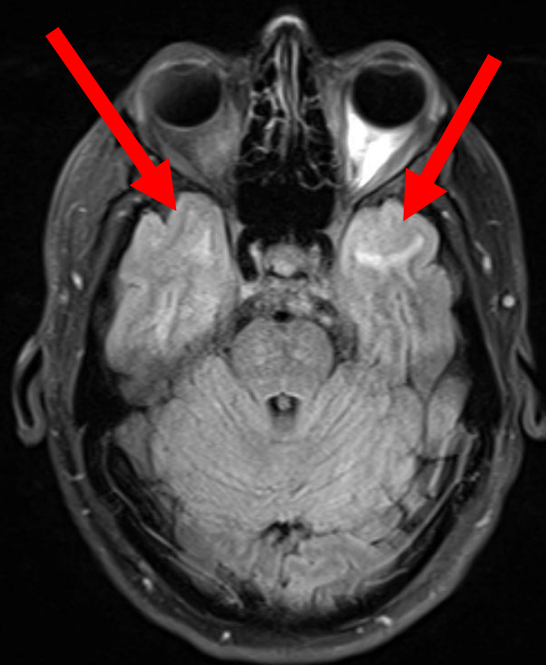
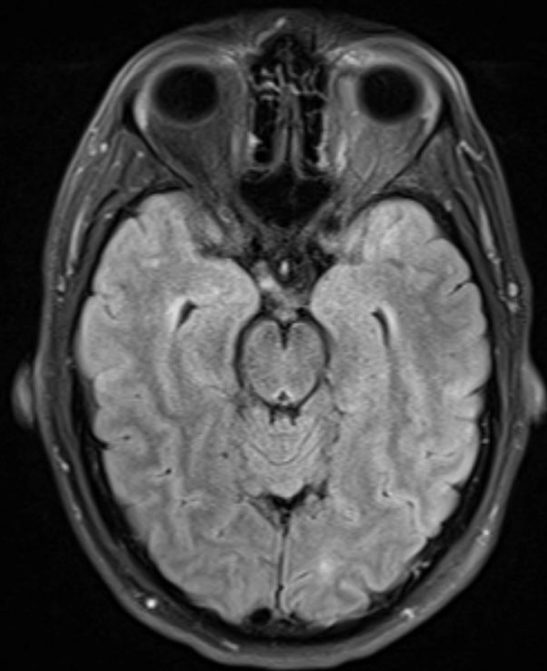
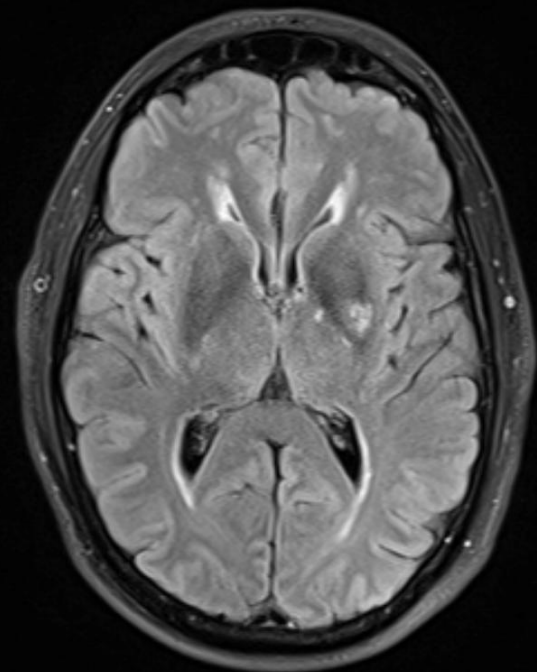
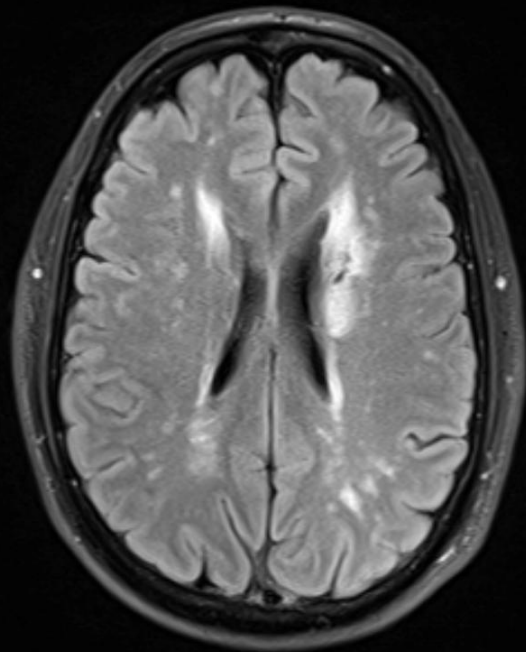
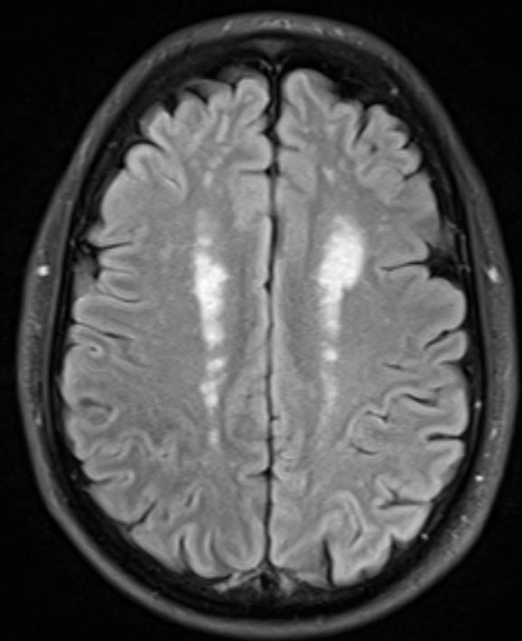
Joanna M. Wardlaw, MD, FRCP, FMedSci, FRSE; Maria C. Valdés Hernández, BSc, PhD; Susana Muñoz-Maniega, BSc, PhD

Fazekas scale



54M with history of migraines, presenting with acute onset right-sided weakness





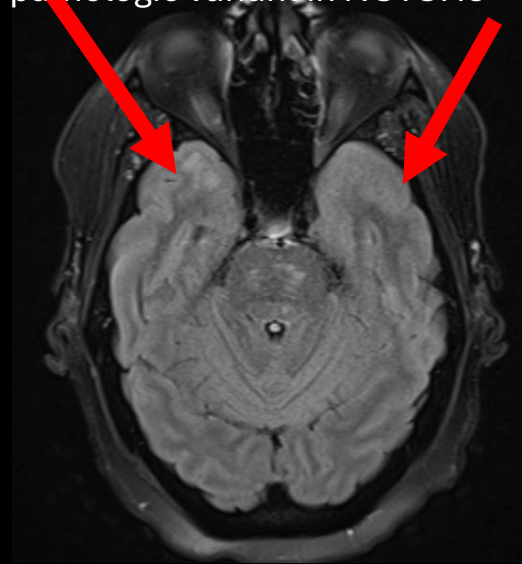
Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

- **NOTCH3** mutations
- Over 400 pathologic variants identified
- Symptoms in adulthood (age 30s-50s), migraines, infarcts, psychiatric changes, early vascular cognitive impairment
- Progressive

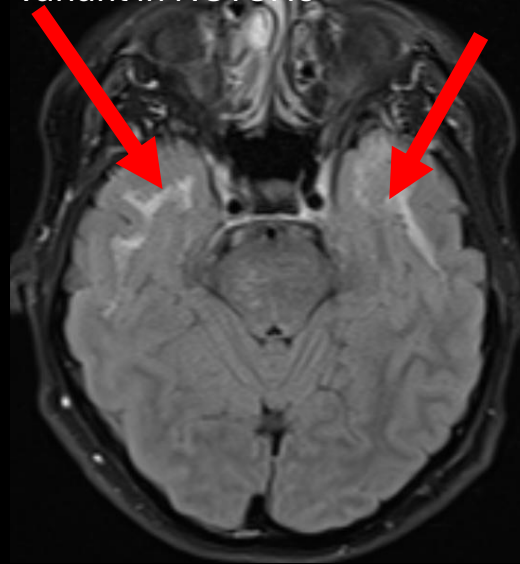
Early white matter disease for **age**, involvement of **temporal poles**, external capsules

Confirmed/highly likely CADASIL cases

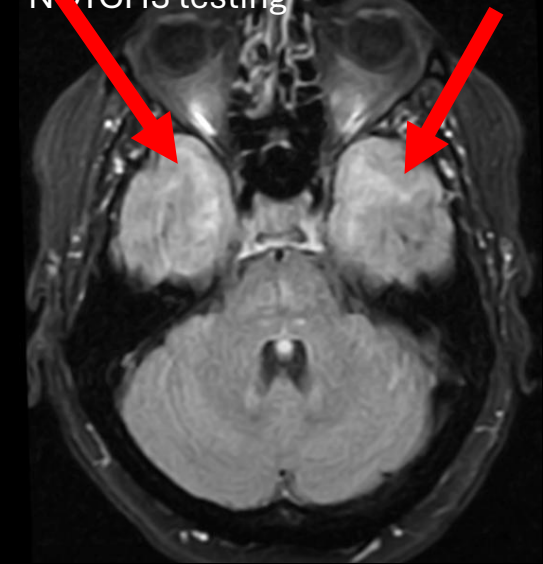
40M - heterozygous likely pathologic variant in NOTCH3



46F - heterozygous pathologic variant in NOTCH3



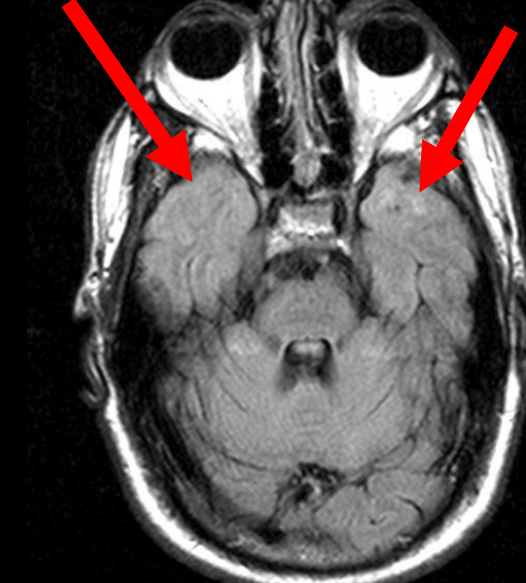
52F - reportedly abnormal NOTCH3 testing



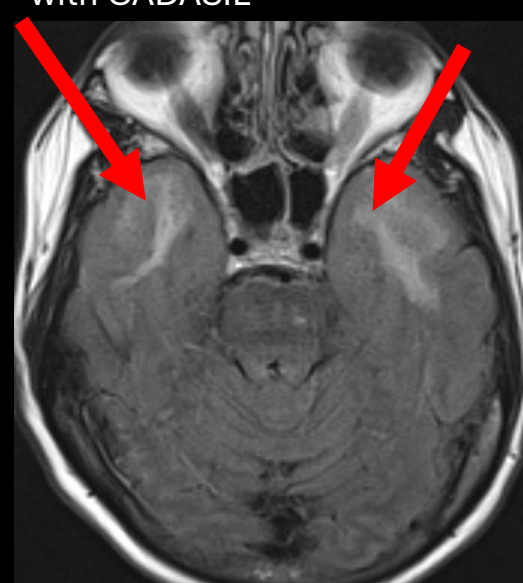
54F - heterozygous pathologic missense in NOTCH3



50M - multiple paternal family members confirmed CADASIL



62F - father and 2 daughters with CADASIL

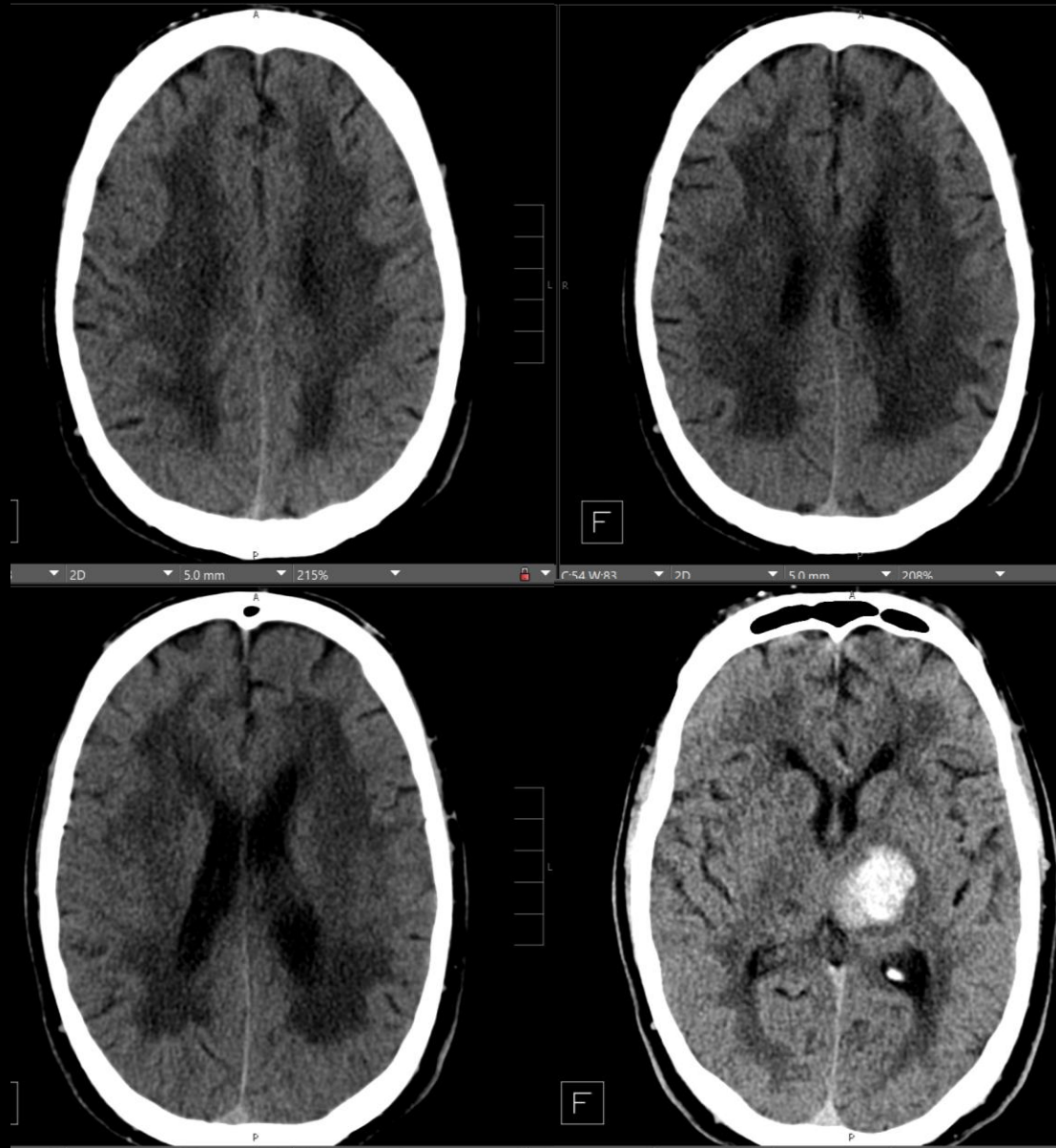


59F - heterozygous pathologic variant in NOTCH3



(missed in 2013 but then found on whole exome sequencing 2019)

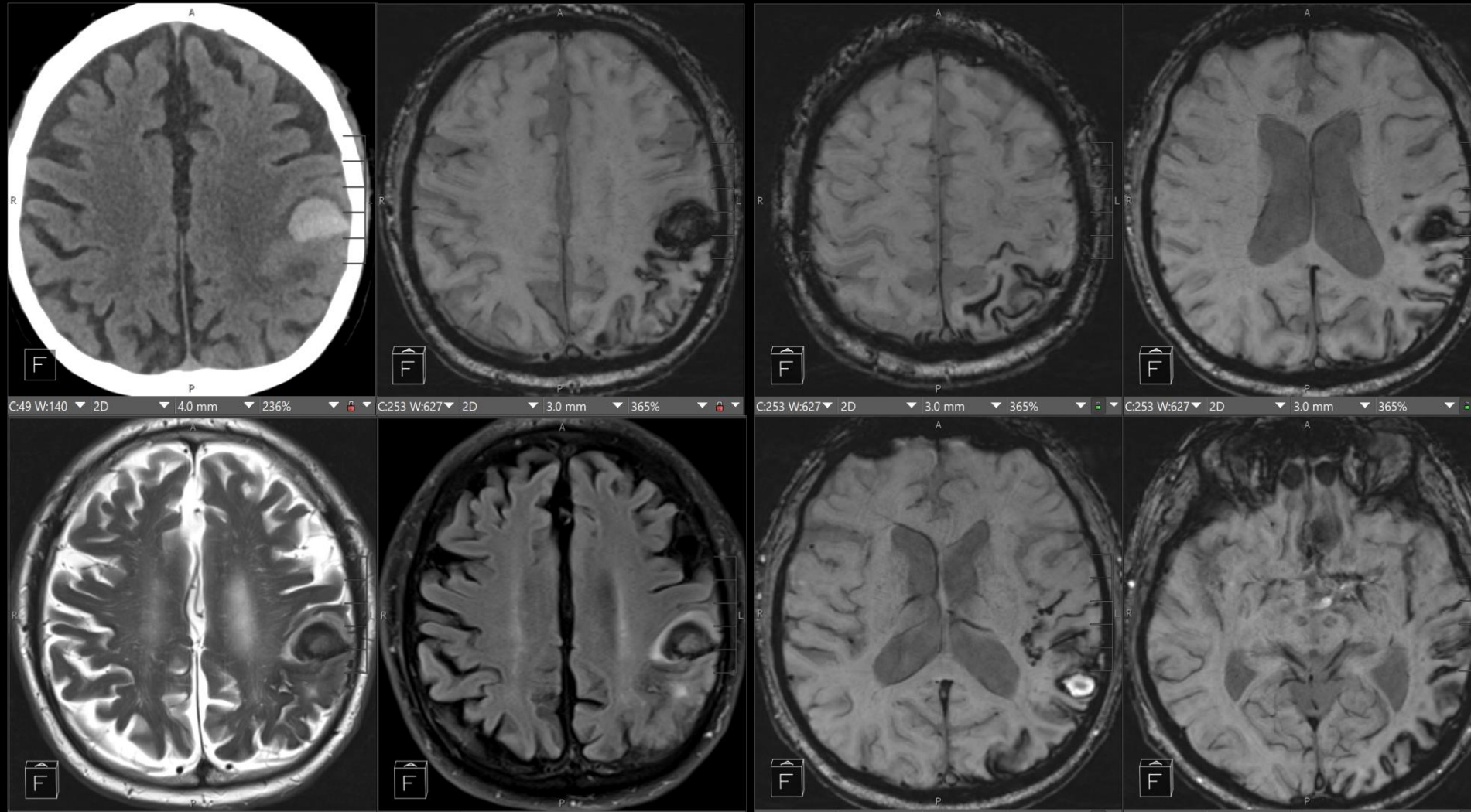
54 F, uncontrolled hypertension



Hypertensive Angiopathy

Courtesy of
Rajan Jain, MD

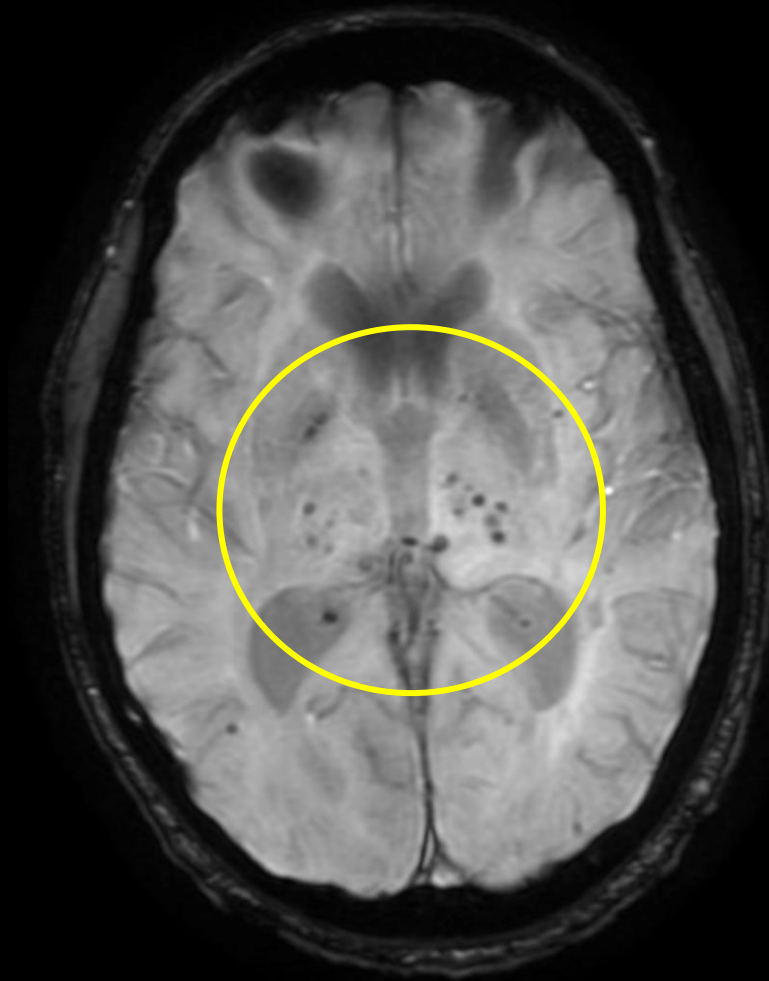
77 M



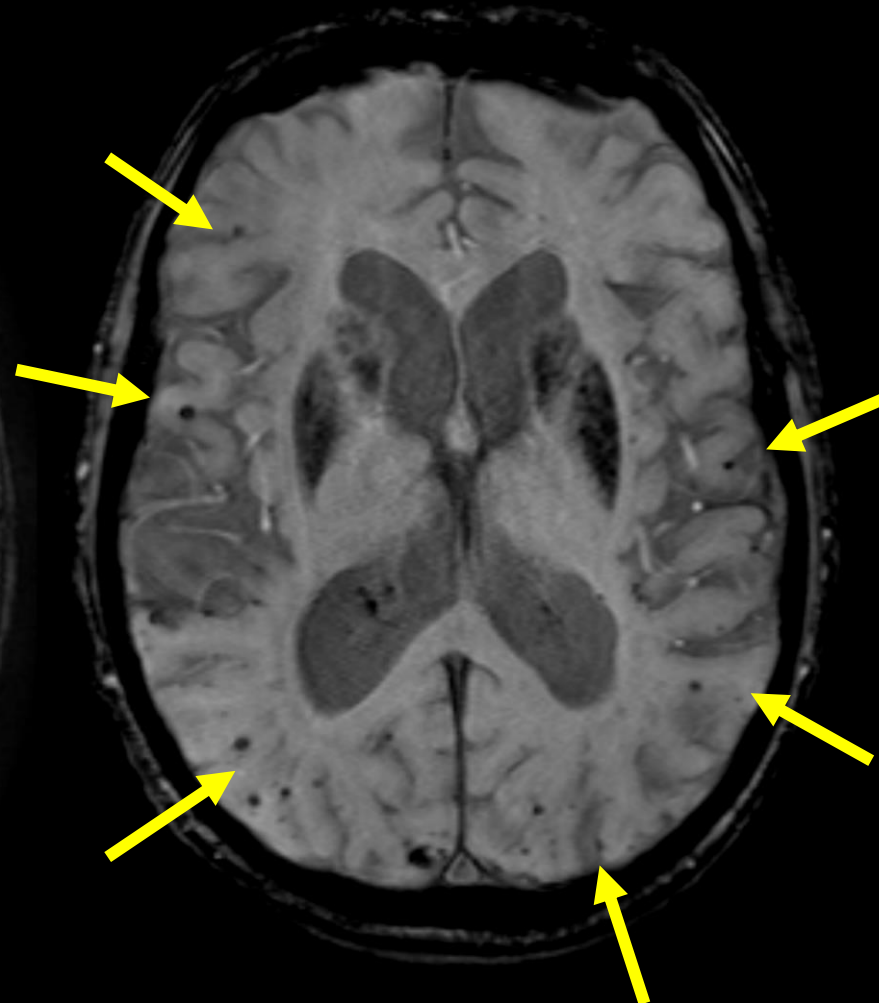
Cerebral Amyloid Angiopathy

Courtesy of
Rajan Jain, MD

Hemorrhage distribution

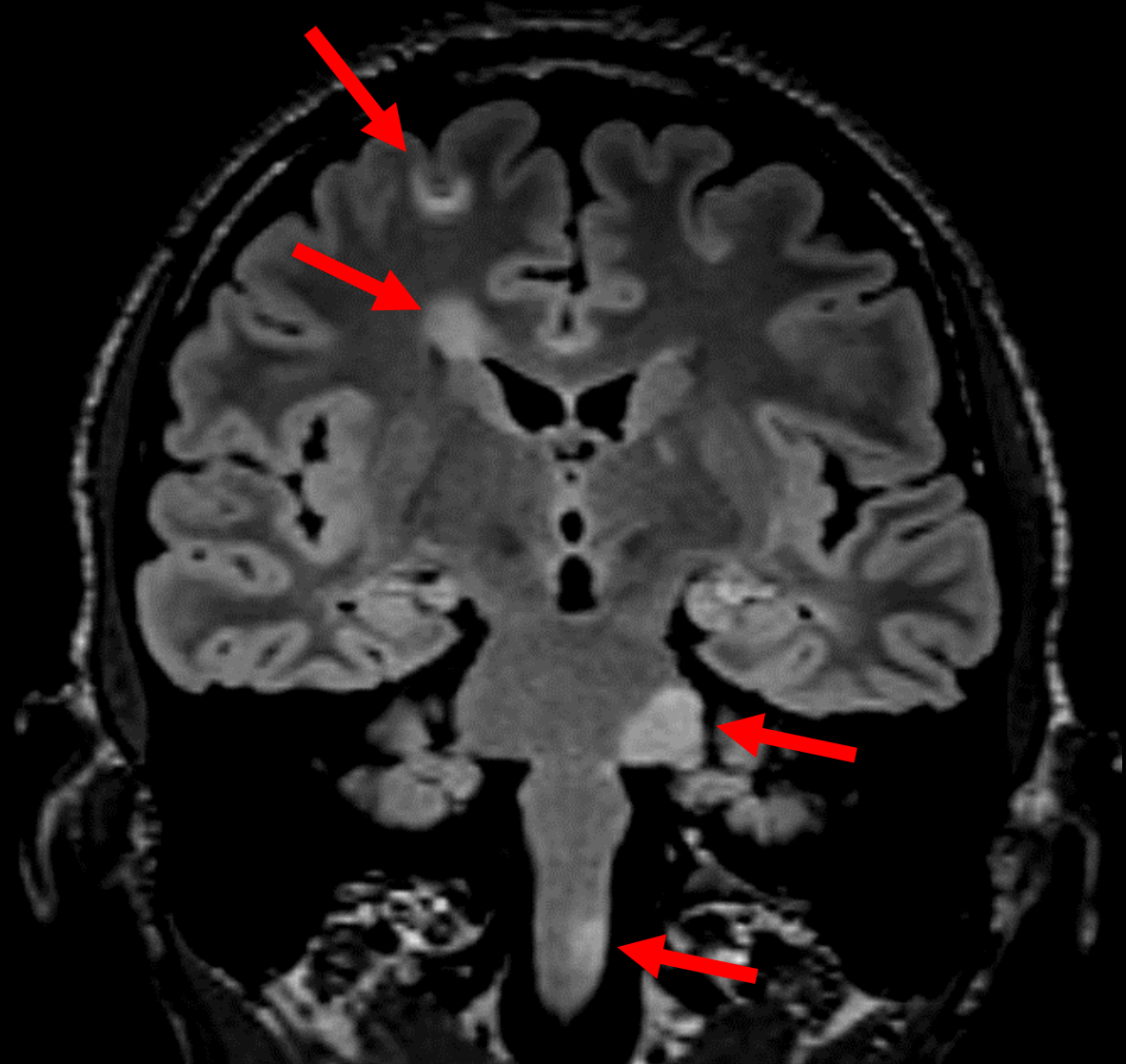
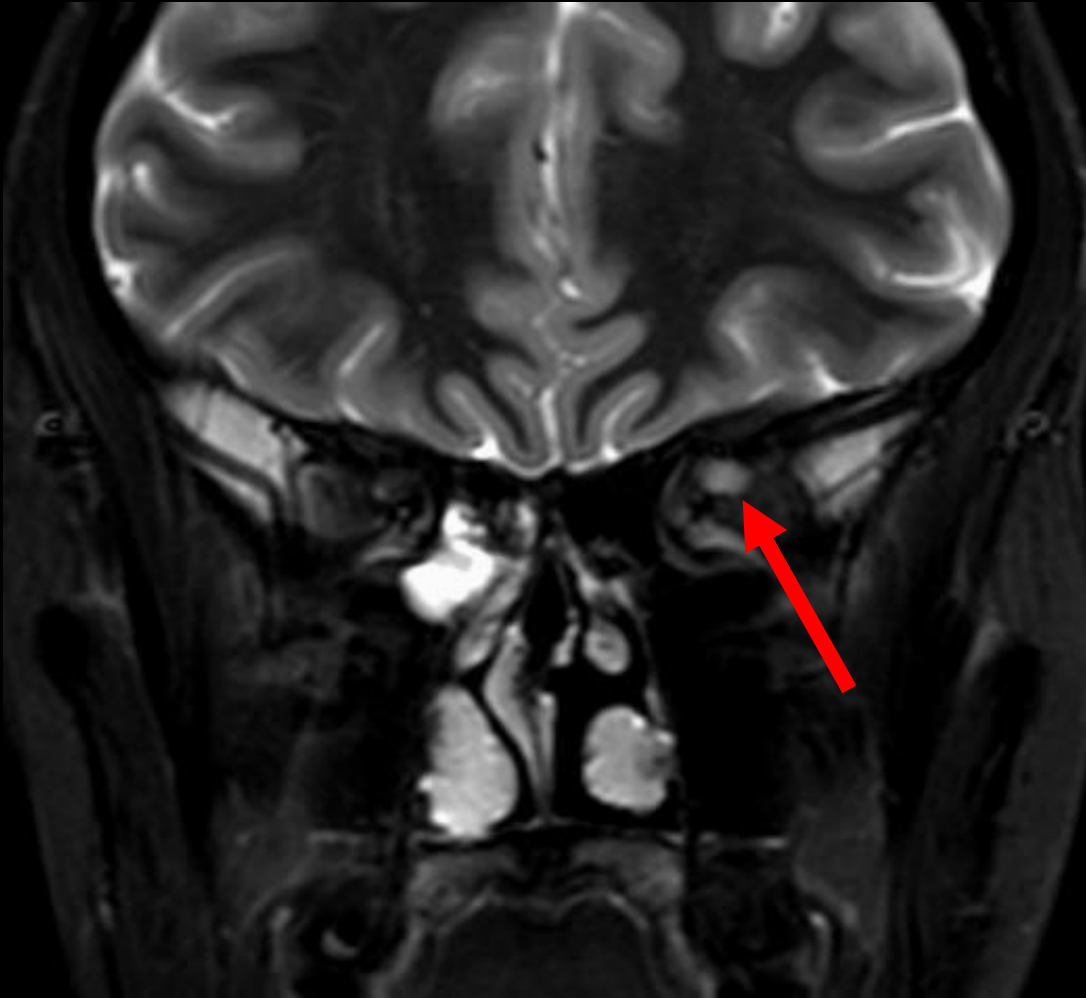


Hypertensive angiopathy



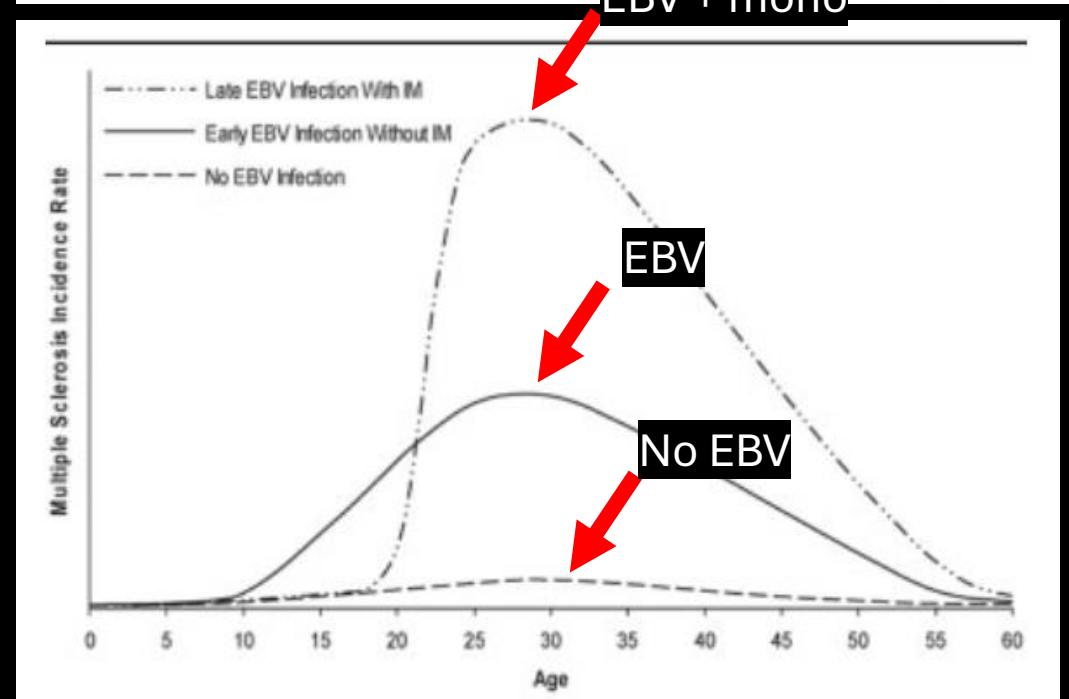
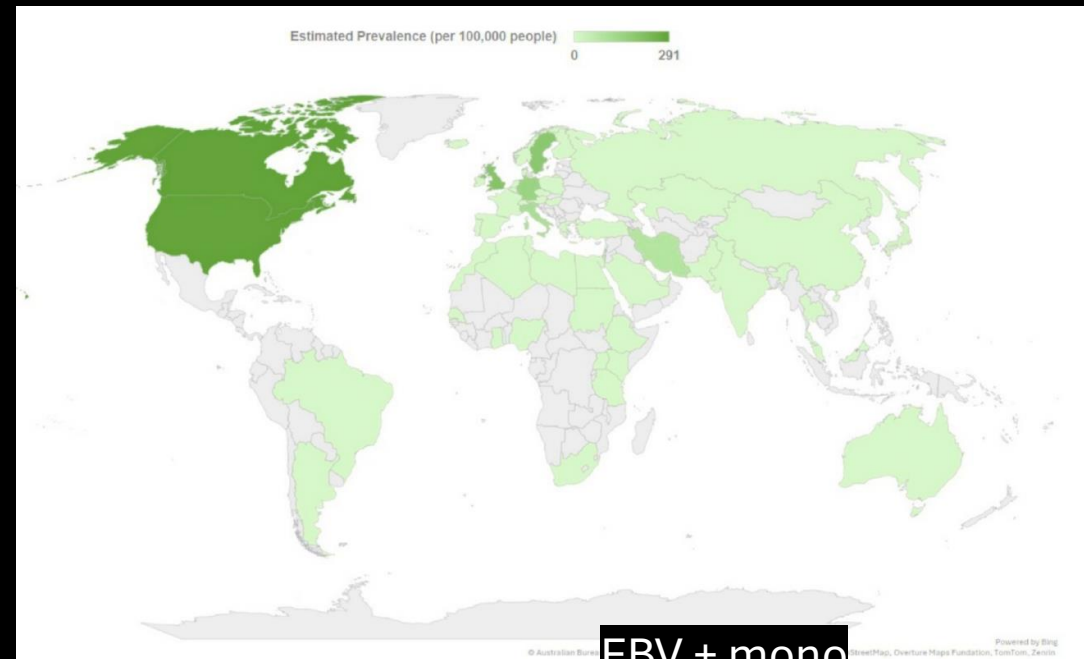
Cerebral amyloid angiopathy

32F, left vision loss and episodes of weakness



Multiple sclerosis

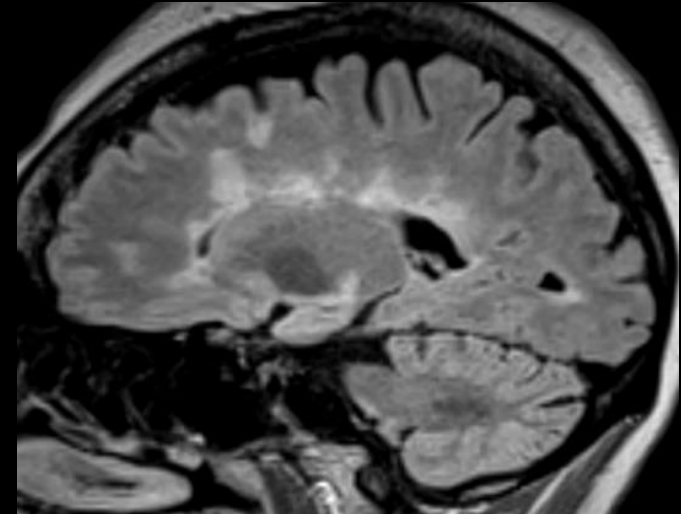
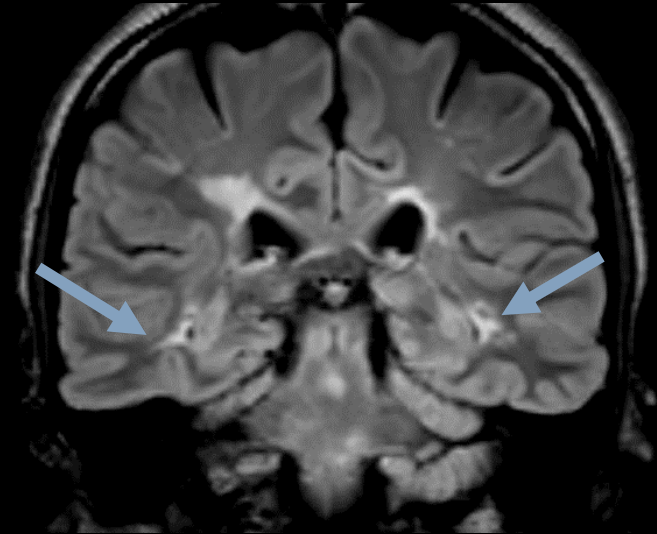
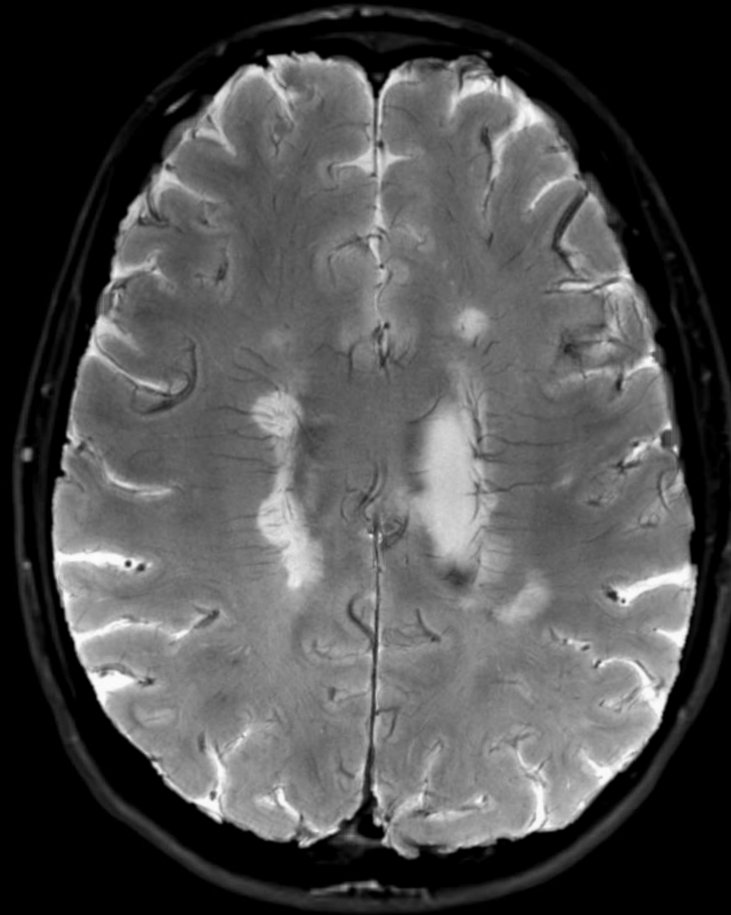
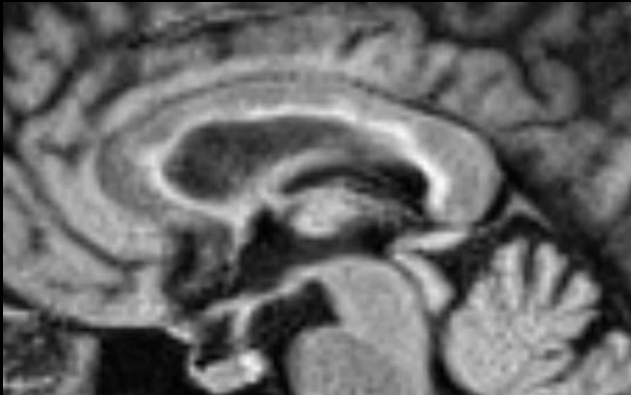
- Autoimmune demyelinating disease almost exclusive to **northern hemisphere** (vitamin D deficiency?)
- More common in women
- MS patients have near-universal seropositivity for **EBV**, associated with infectious **mononucleosis**
 - General population: 95%
 - MS population: >99%



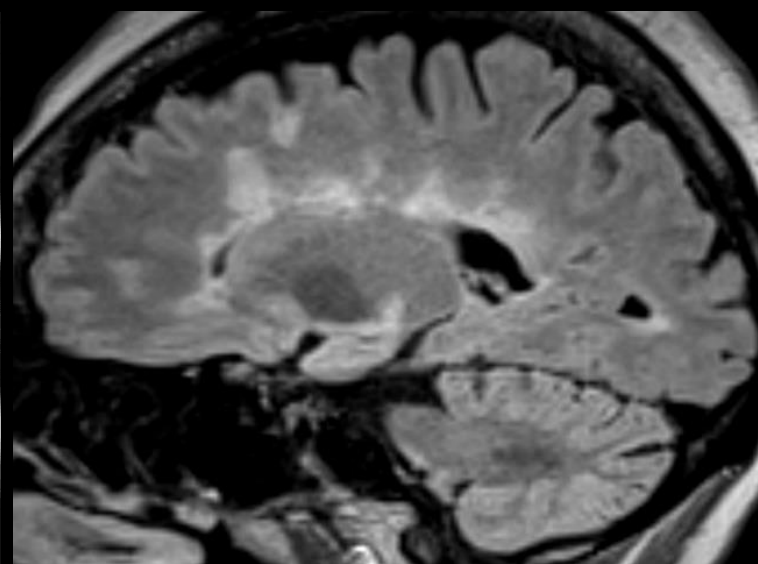
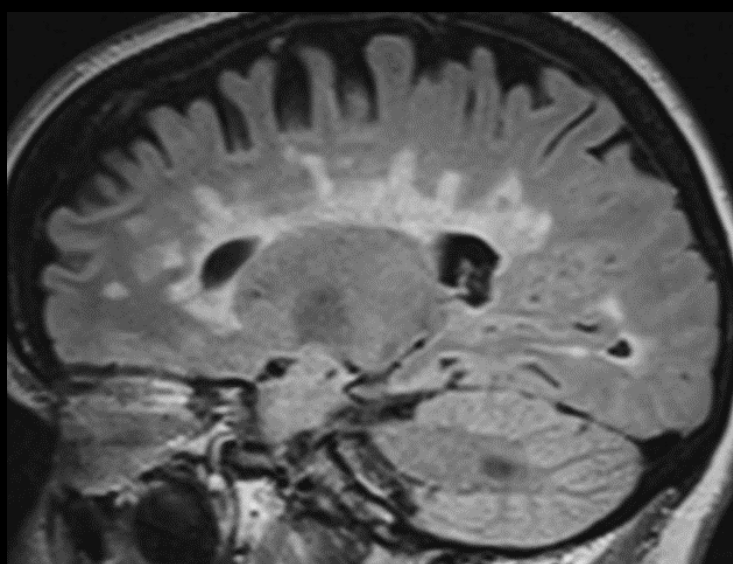
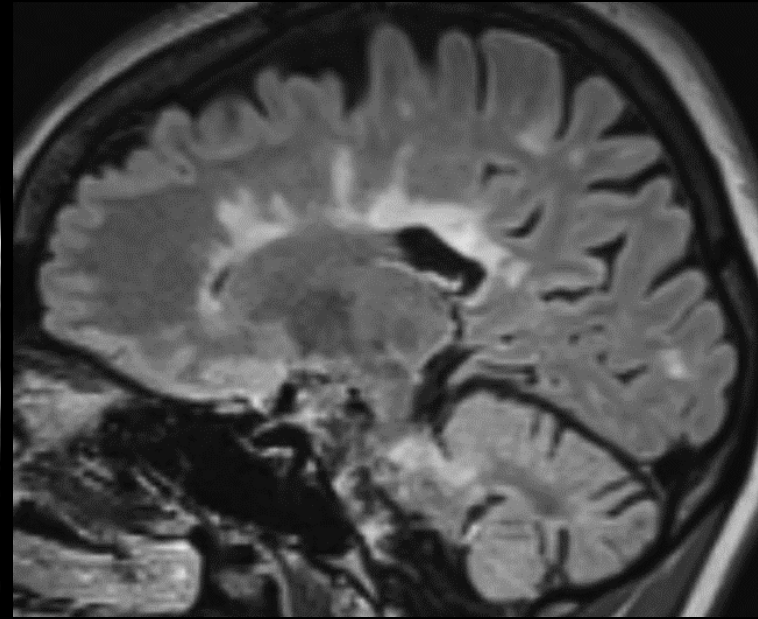
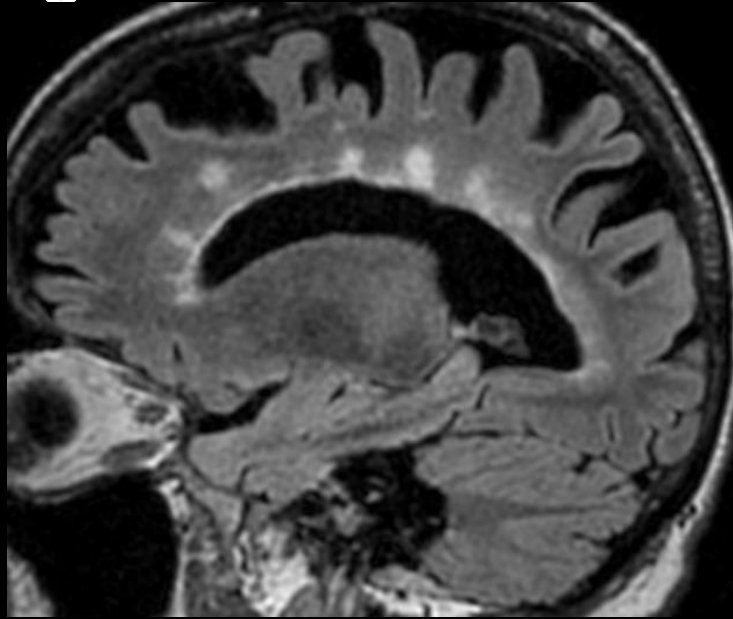
- Gupta NS, Shrivastav SK, Singh IK, Kumari S, Jha NK, Gupta R. Decoding the molecular and cellular aspects of multiple sclerosis: From diagnosis to therapeutic strategies. Brain Res. 2025 Sep 15;1863:149844. doi: 10.1016/j.brainres.2025.149844. Epub 2025 Jul 19. PMID: 40691929.
- Ascherio A, Munger KL. Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007 Apr;61(4):288-99. doi: 10.1002/ana.21117. PMID: 17444504.

Periventricular

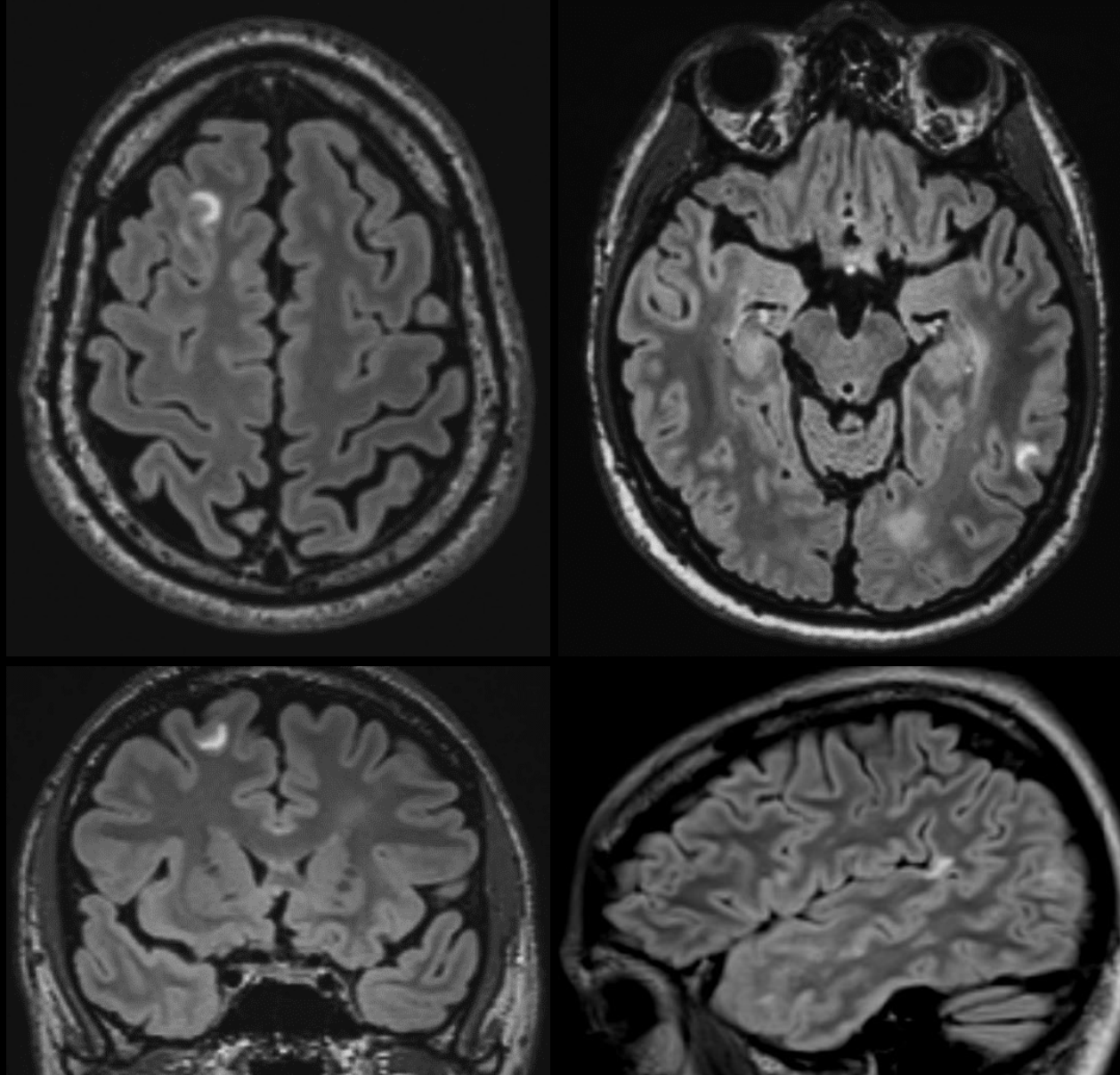
Ovoid
Perivenular
Temporal lobes not spared
Callosal interface



Dawson's fingers



Juxtacortical / Cortical



Infratentorial

Most common cranial nerve affected?

CN3 <1%

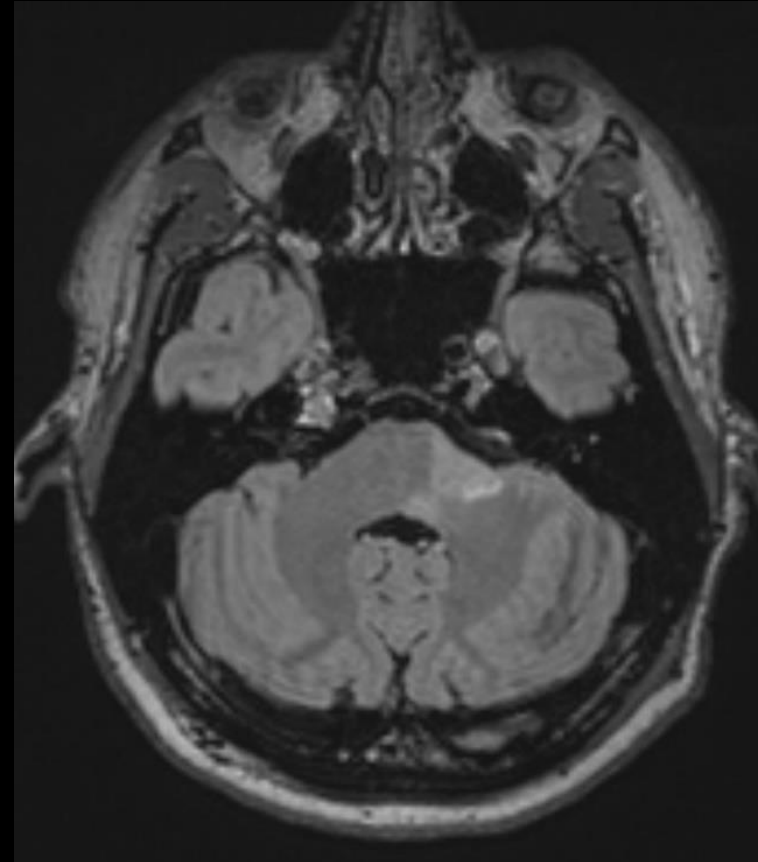
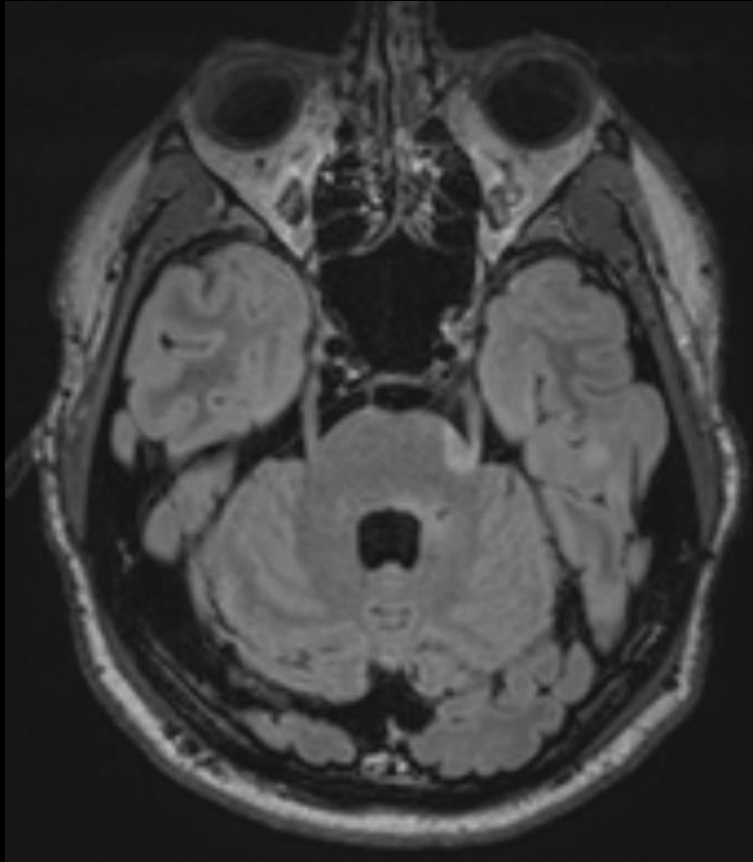
CN4 <<1%

CN5 5%

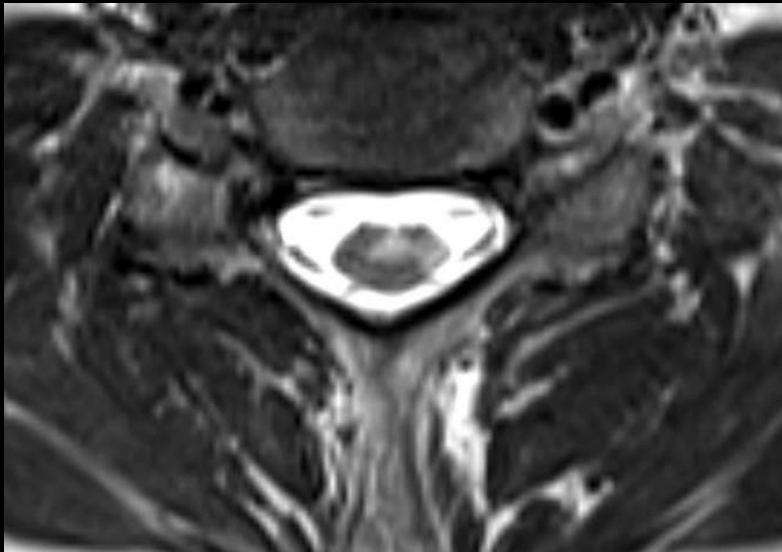
CN6 1%

CN7 4%

CN8 <1%

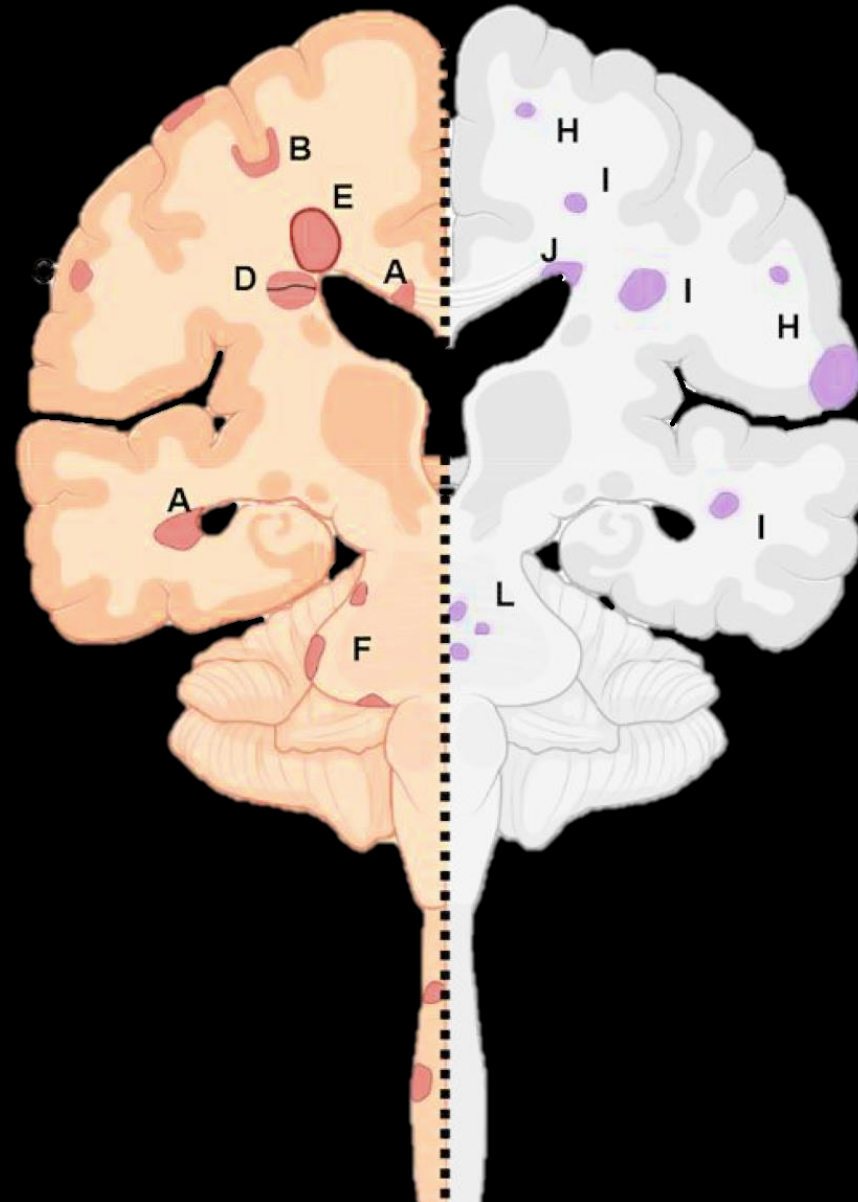


Spinal cord



Multiple sclerosis

Microangiopathy



Central vein sign

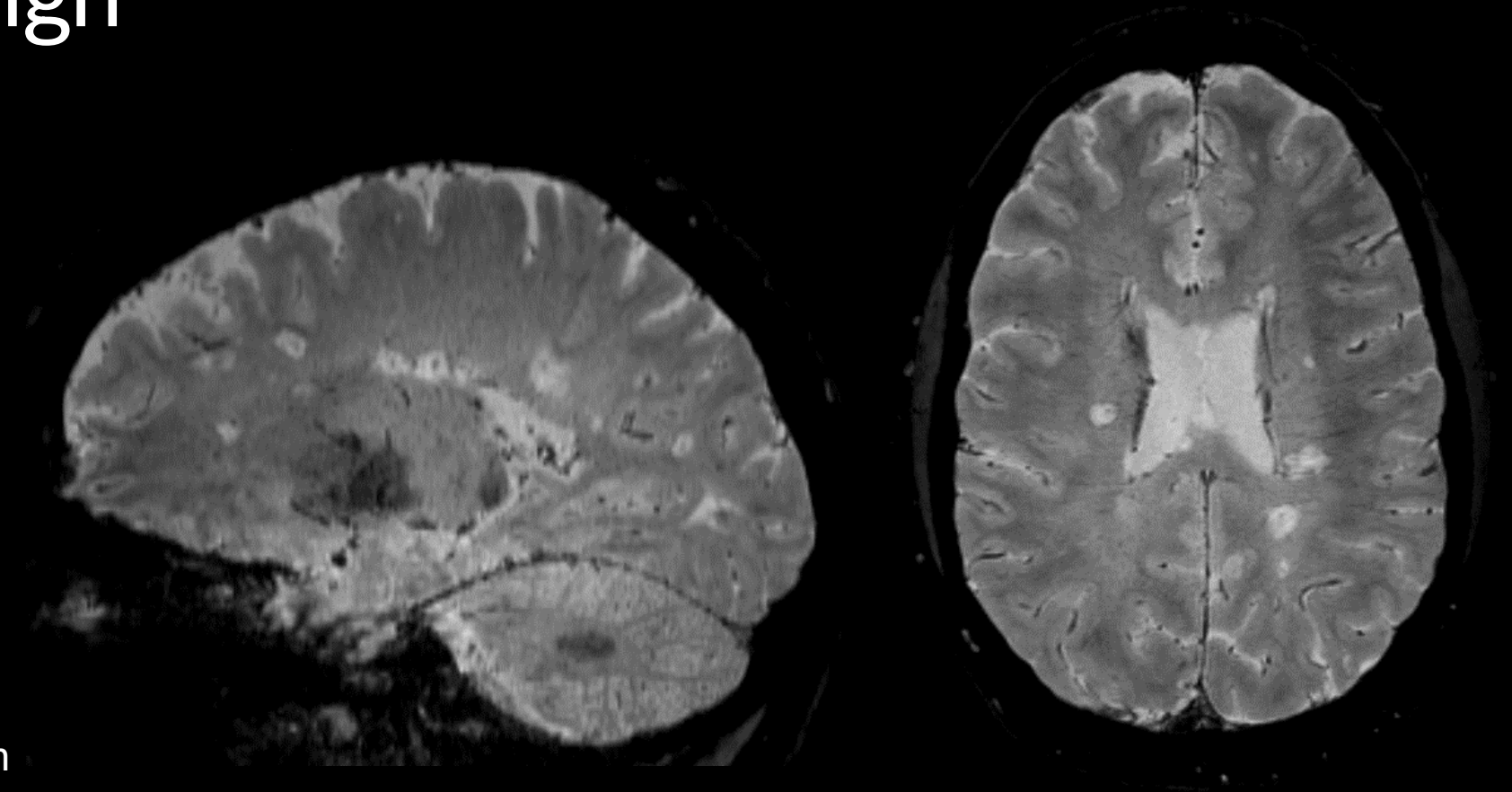
Detection

- 58% on 1.5T
- 74% on 3T
- 82% on 7T

Prevalence

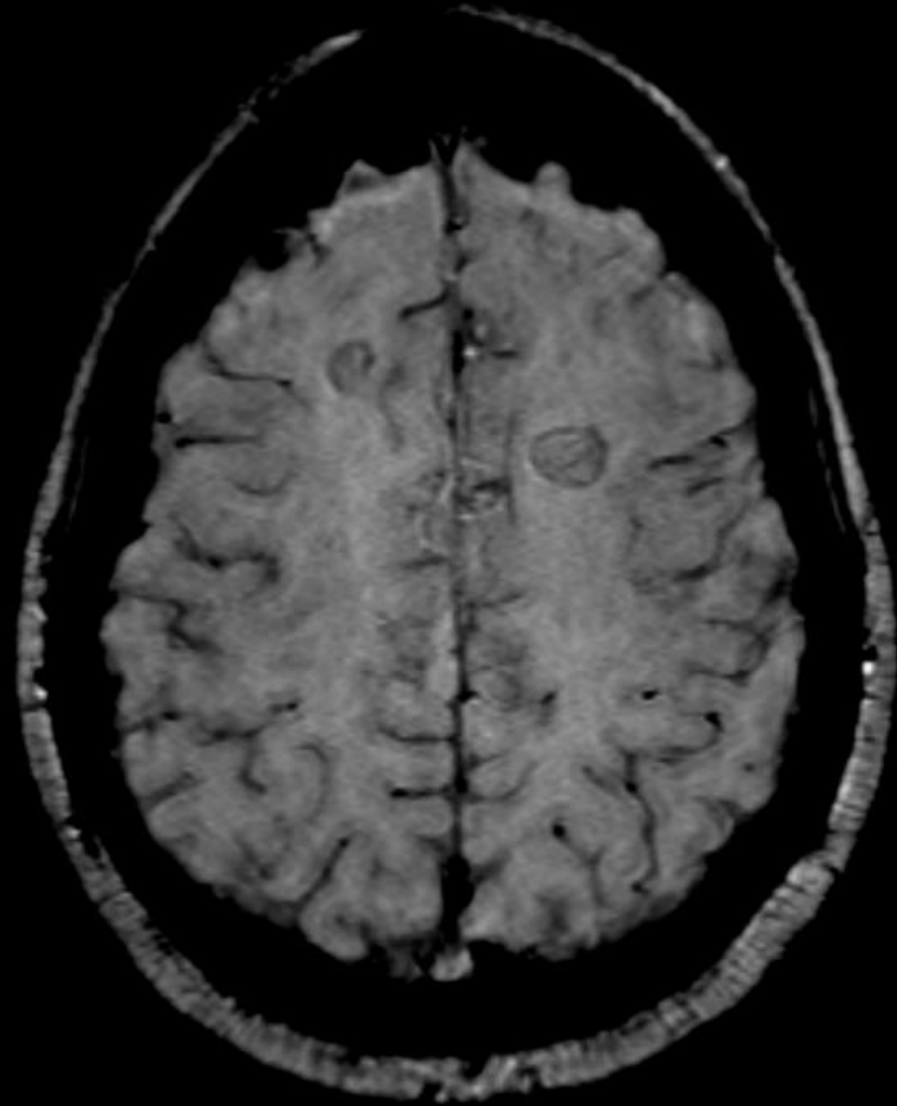
- MS patients: ~80%
- Non-MS patients: ~20%

~90% specific when present in
>30% of lesions



Paramagnetic rim sign

Correlates with histiocytes seen in chronic active lesions



2017 McDonald Criteria

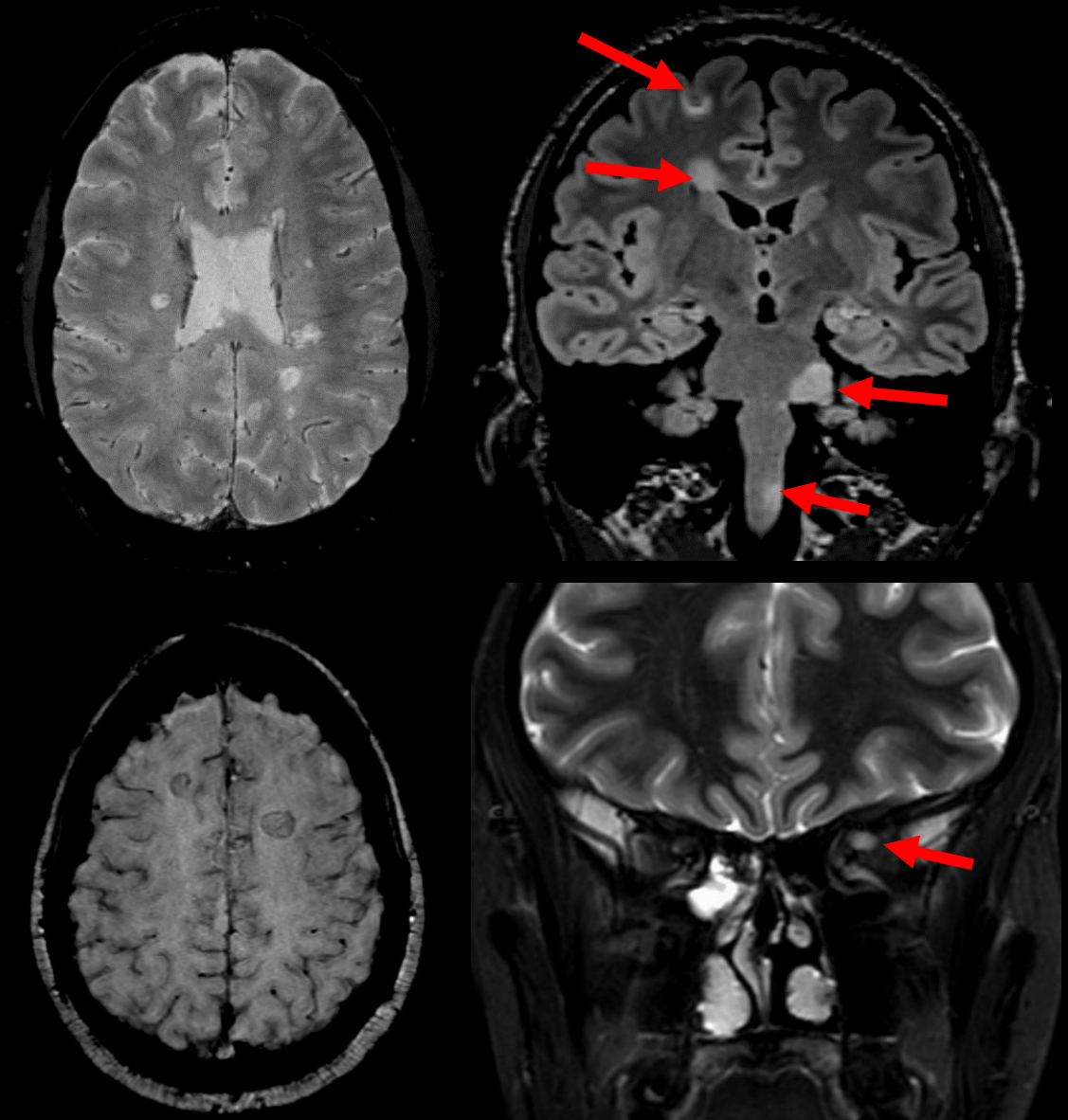
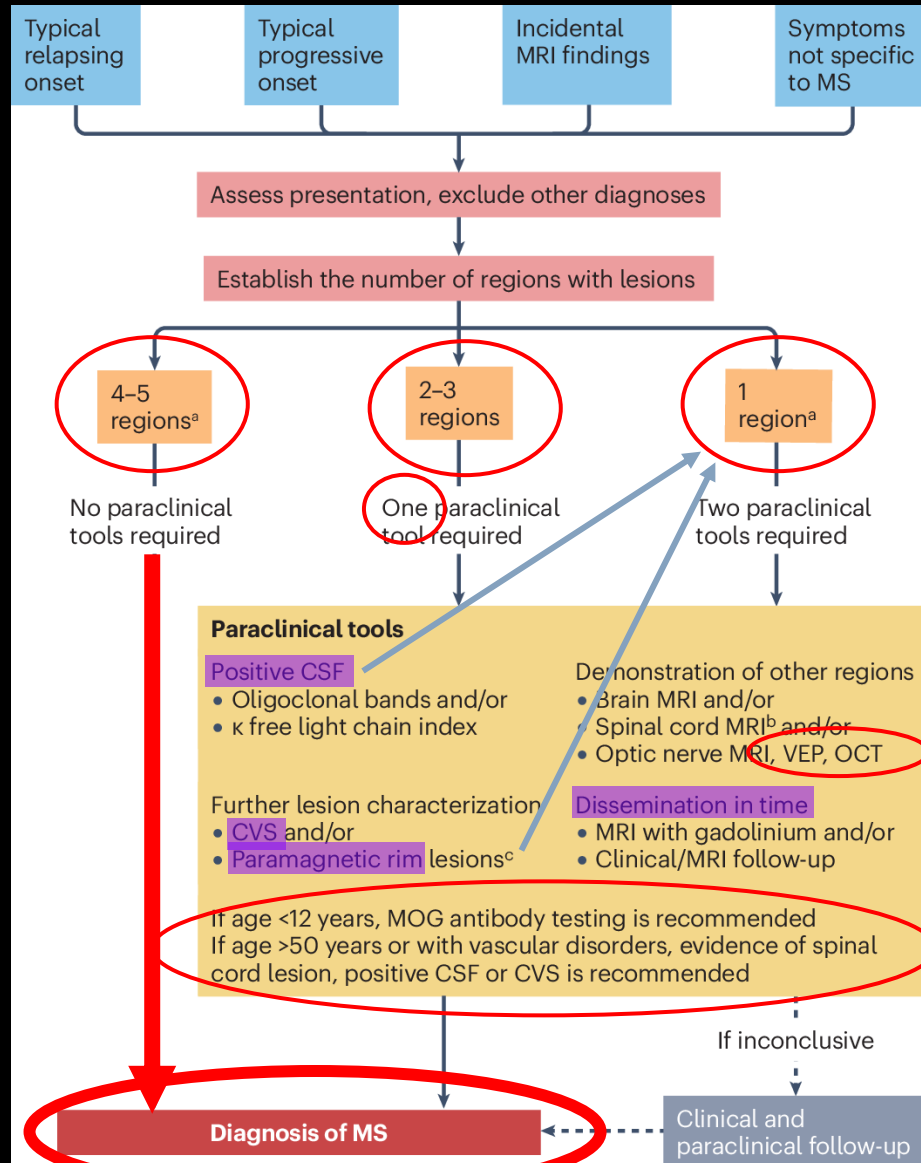
Dissemination in space

- 2 or more brain regions affected

Dissemination in time

- Two separate time points or lesion ages

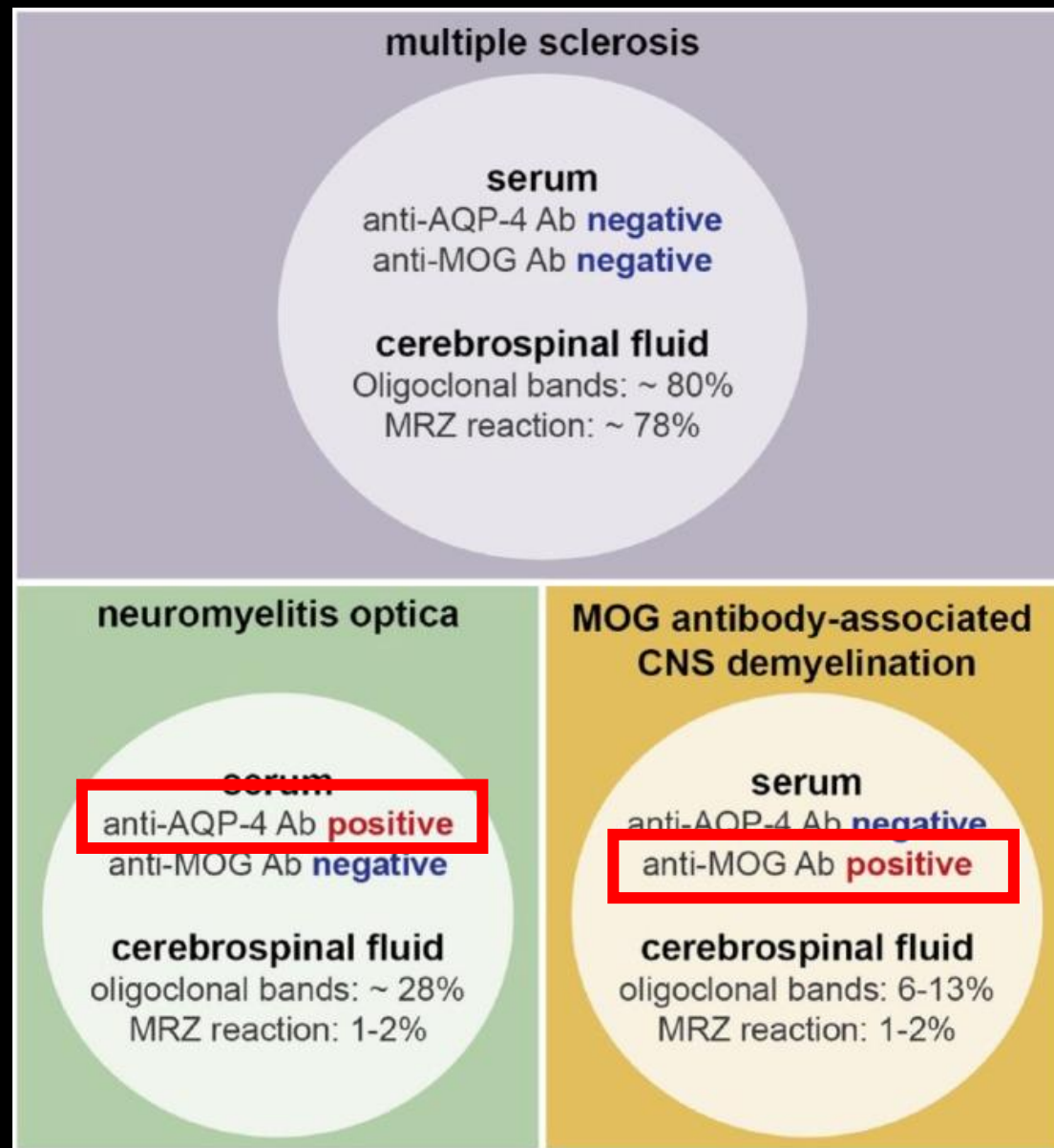
2024 McDonald Criteria



Moccia, M., Ciccarelli, O. & Thompson, A. Implementation of the 2024 revision of the McDonald criteria for multiple sclerosis. *Nat Rev Neurol* **21**, 664–666 (2025). <https://doi.org/10.1038/s41582-025-01141-3>

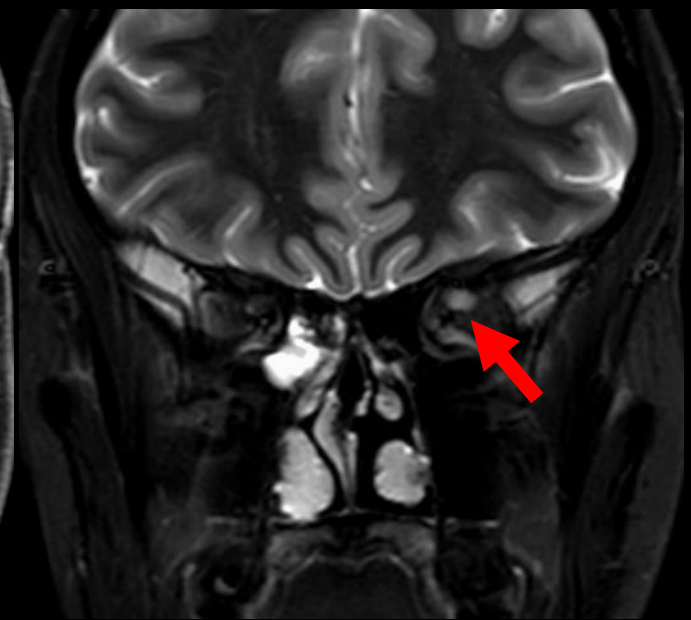
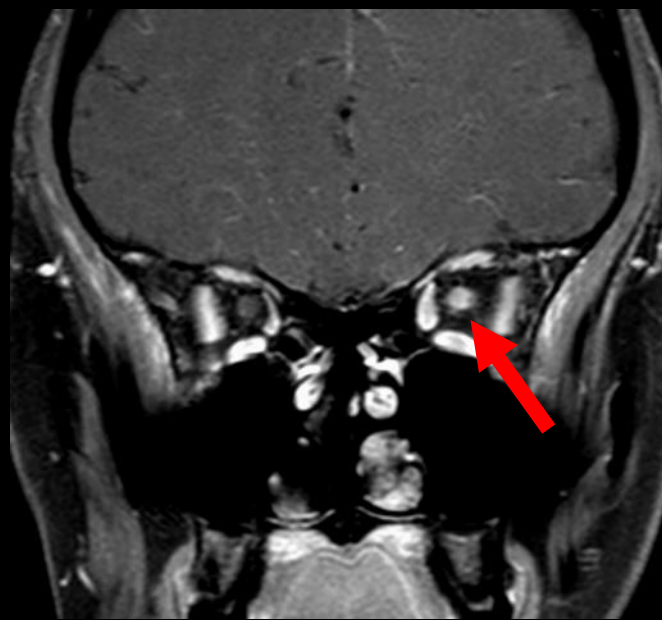
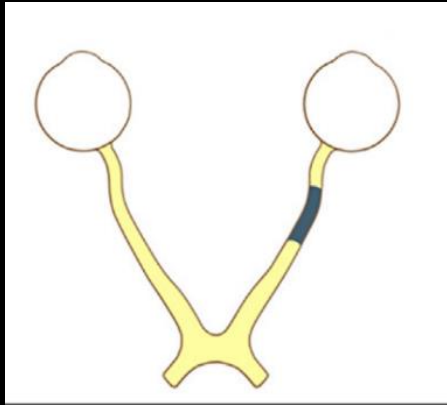
Aquaporin-4 is on **astrocytes**

Myelin damage is secondary

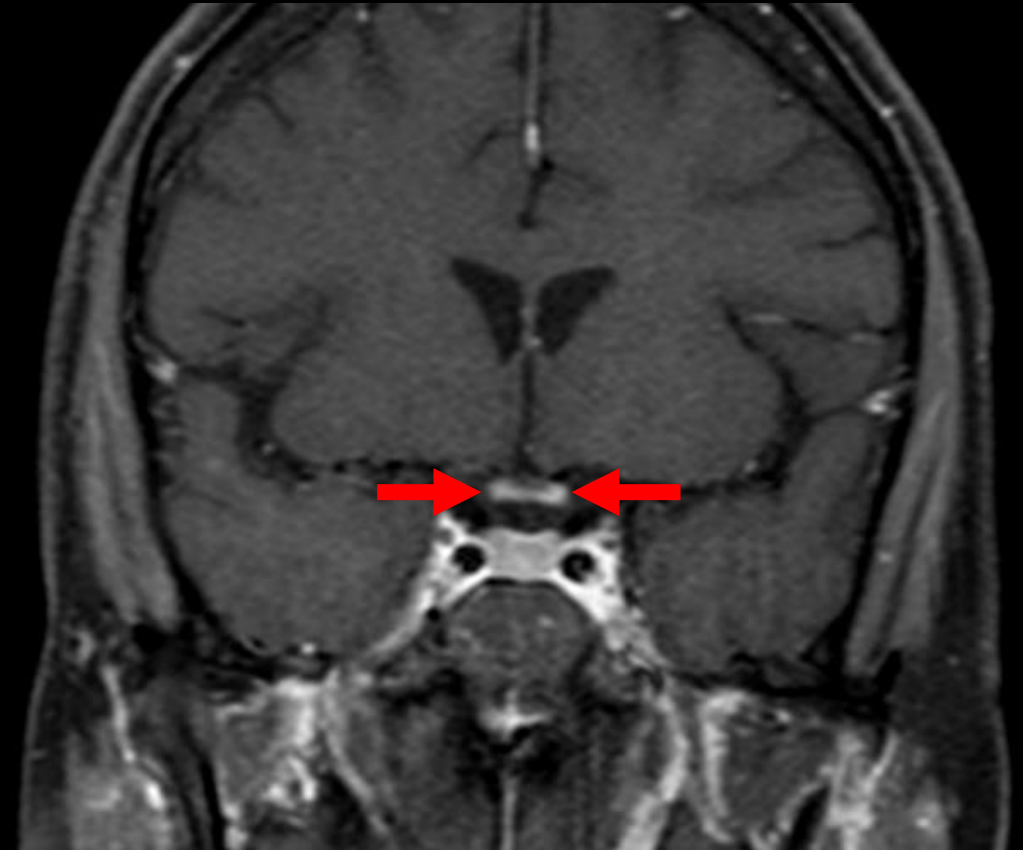
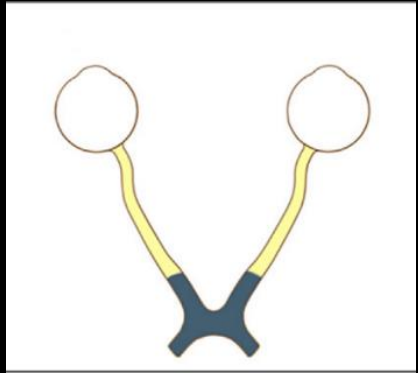


MOG is on **oligodendrocytes**

MS optic neuritis

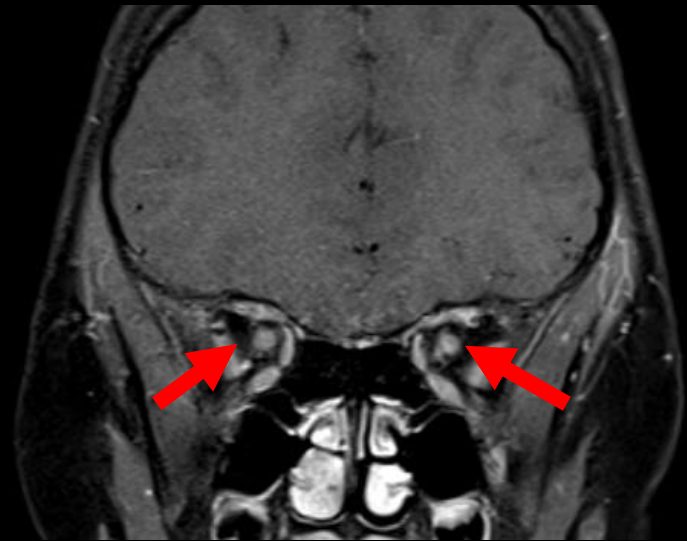
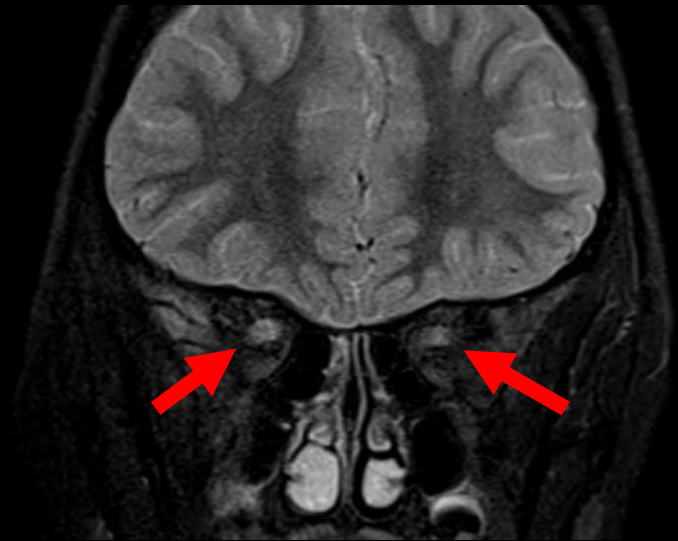
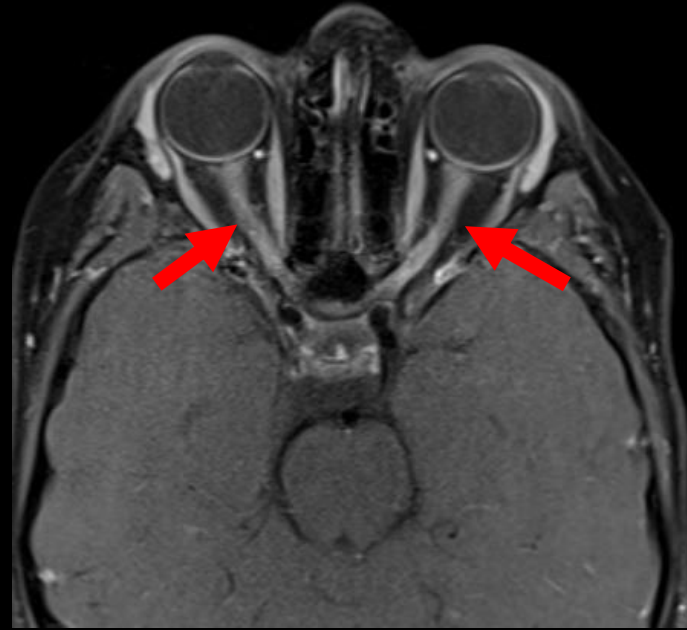
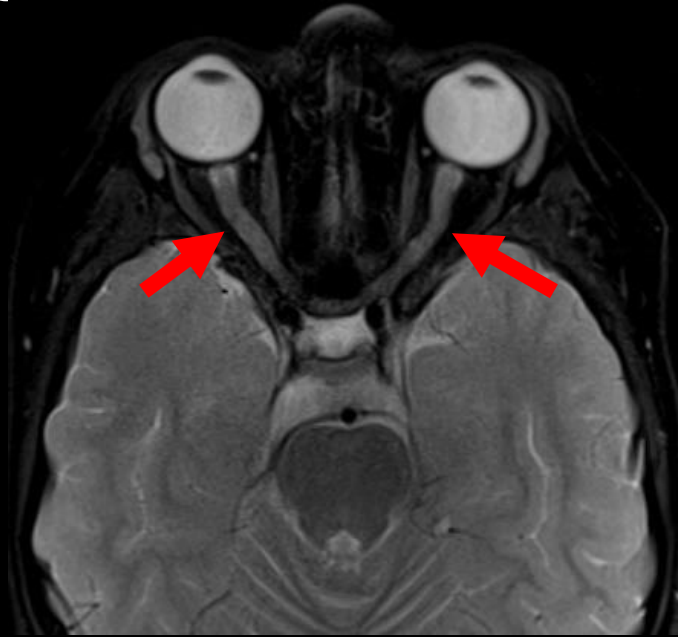
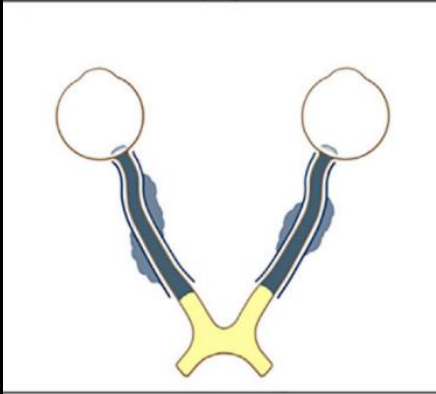


NMO optic neuritis



Neuromyelitis opti-CHIASM

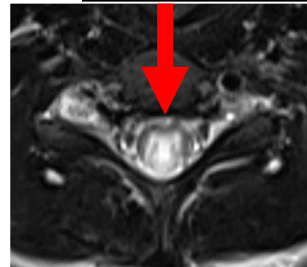
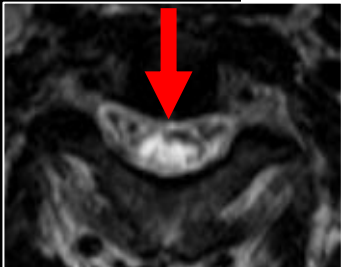
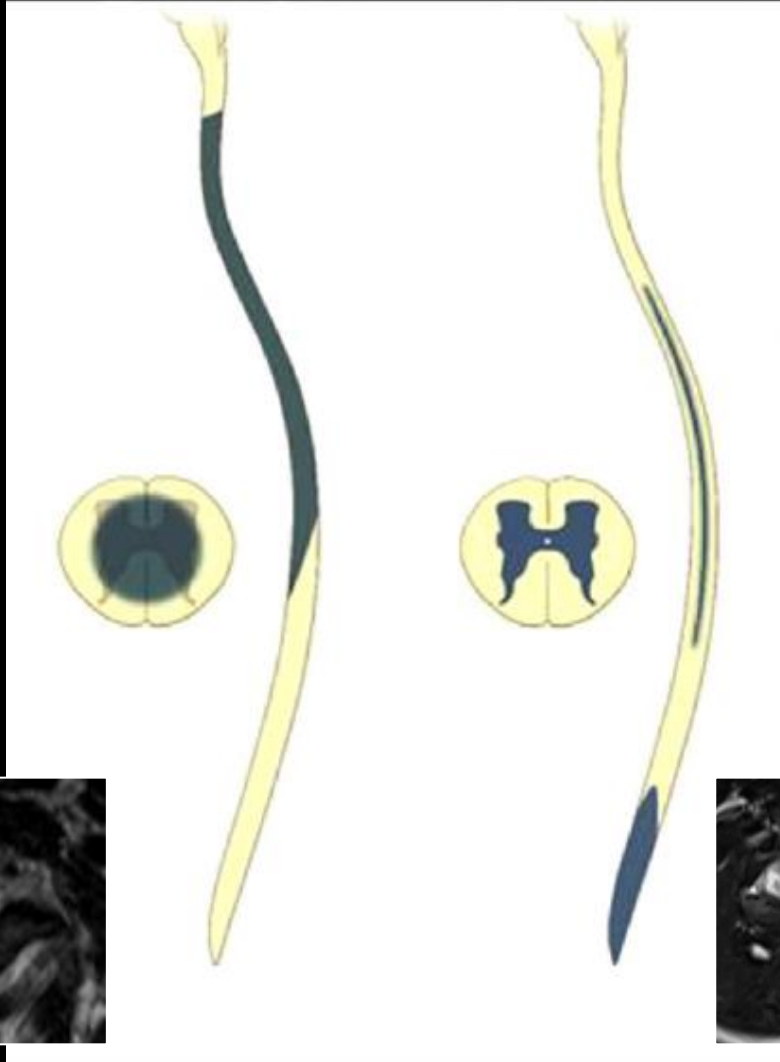
MOG optic neuritis



LETM - Longitudinally extensive transverse myelitis

NMOSD

MOGAD

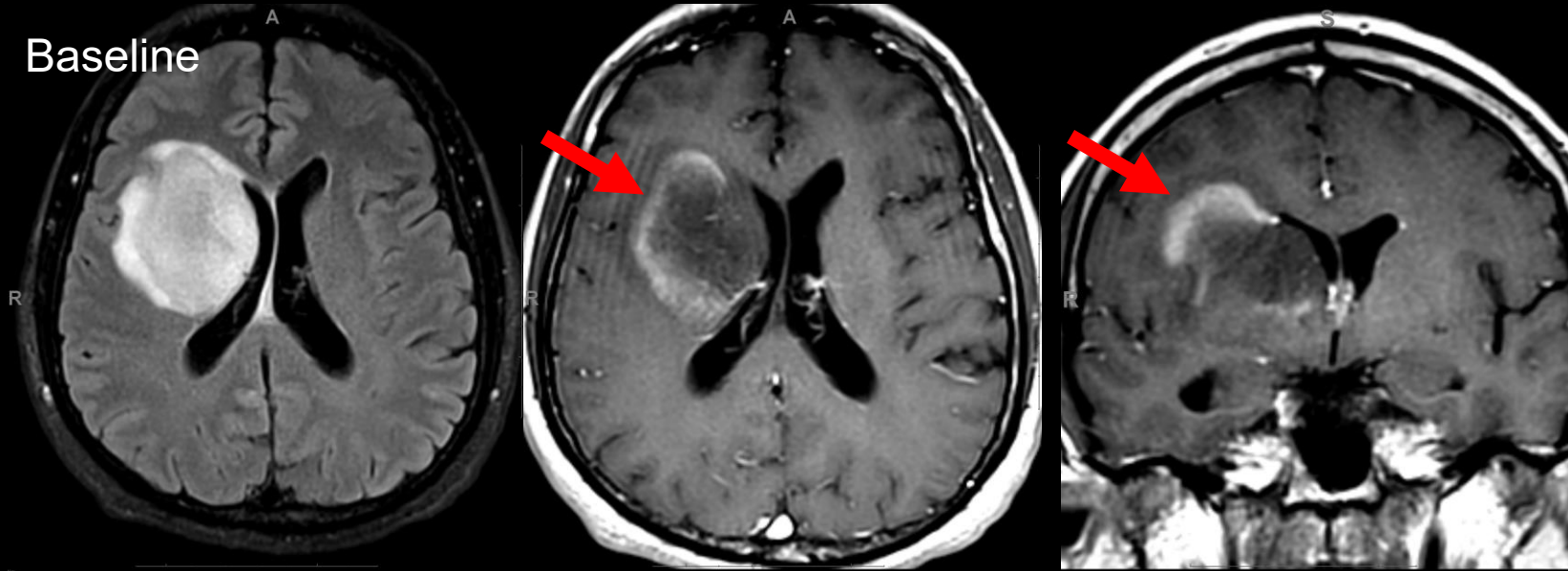


Some things to remember

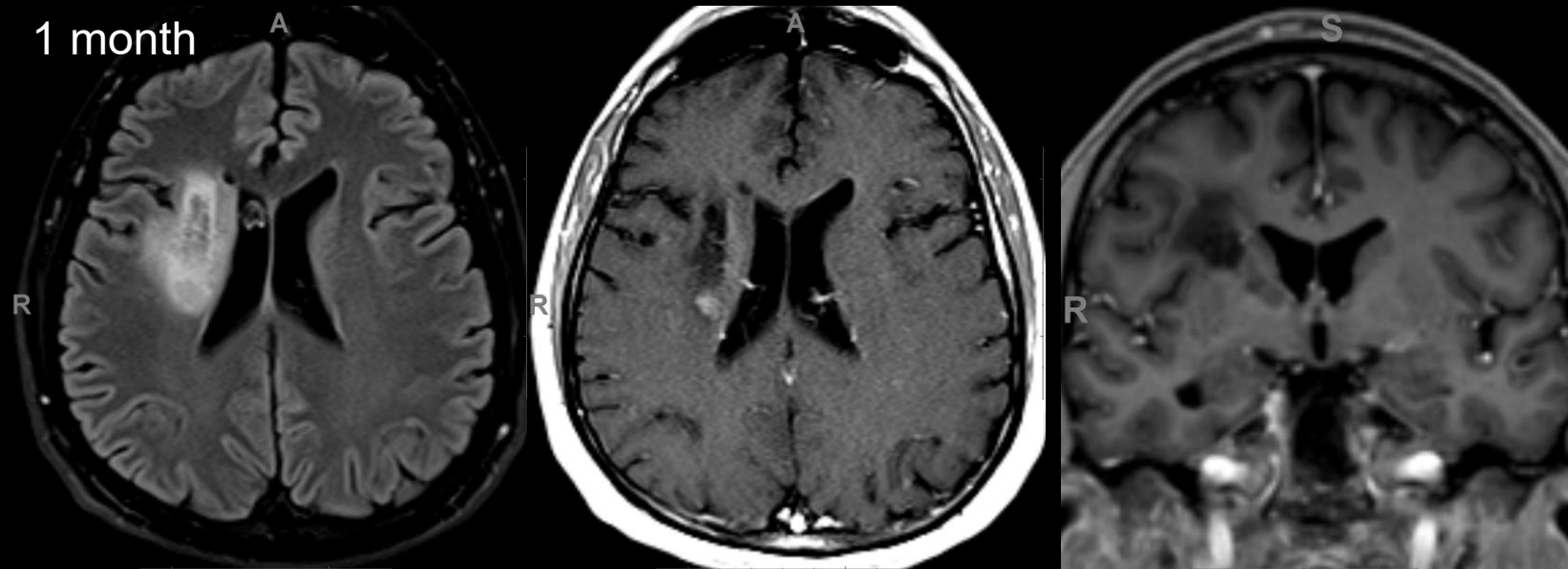
- NMOSD
 - 40 year olds
 - Black/Asian patients
 - Frequent relapses
 - Severe disability
 - Neuromyelitis opti-CHIASM
 - Upper cord
- MOGAD
 - Children get ADEM
 - Adults get optic neuritis
 - Usually monophasic (MOnophasic MOGAD)
 - Can cause encephalitis/seizures (FLAMES)
 - More likely to involve lower cord

56 M with progressive left side weakness

Baseline



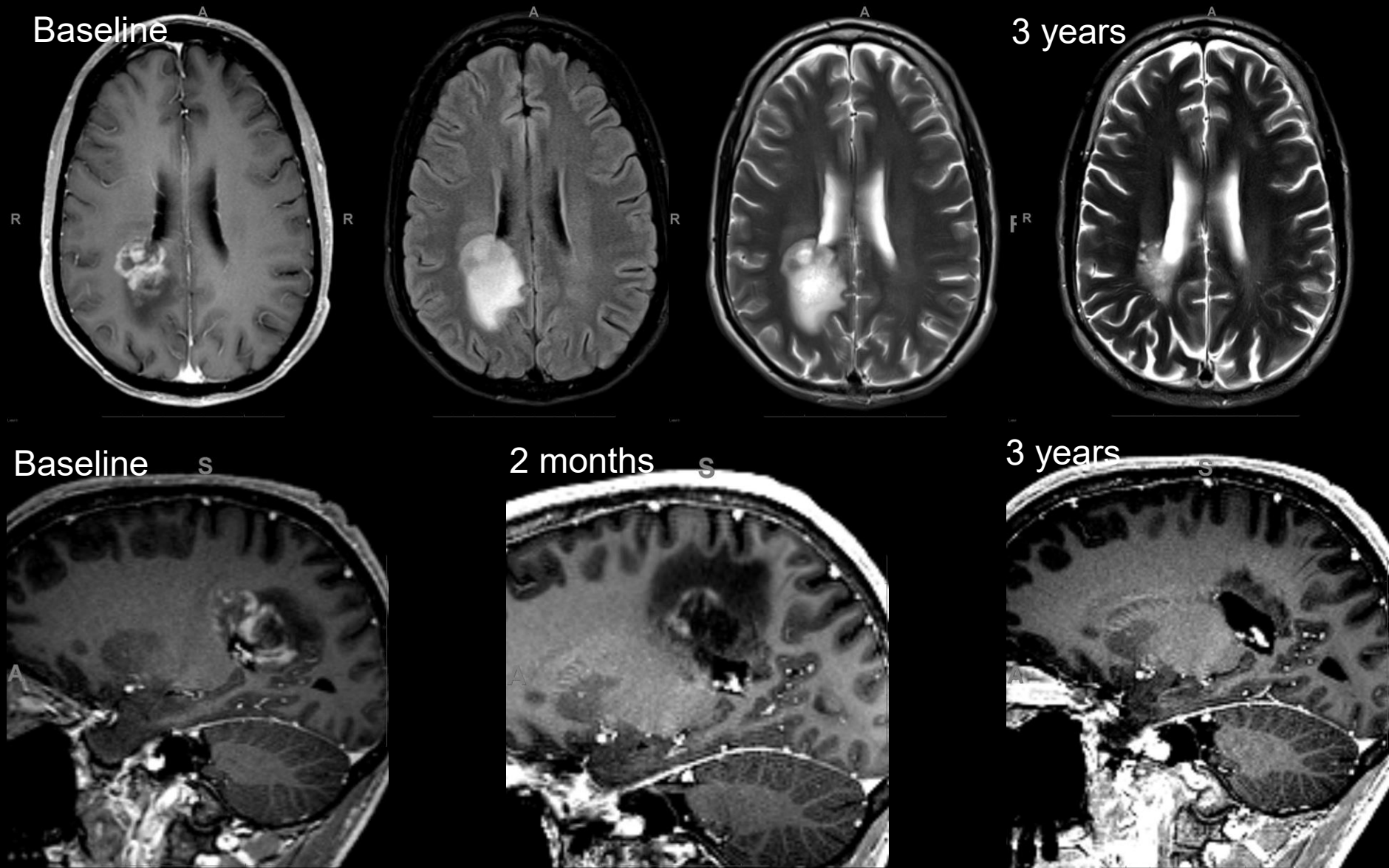
1 month



Tumefactive Demyelinating Lesion

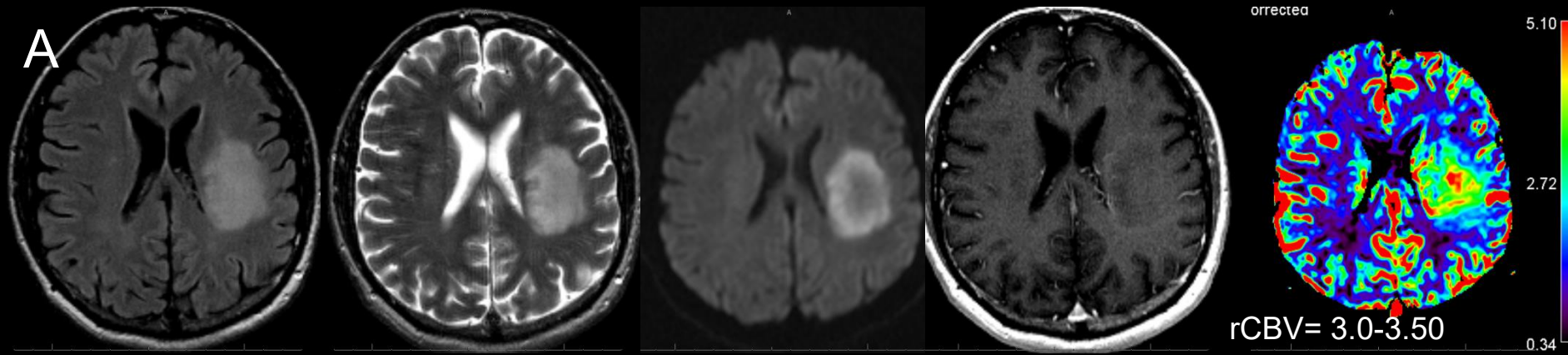
Courtesy of
Rajan Jain, MD

35 M, Headache, foot drop. Numbness and tingling in hand, left leg not moving properly.

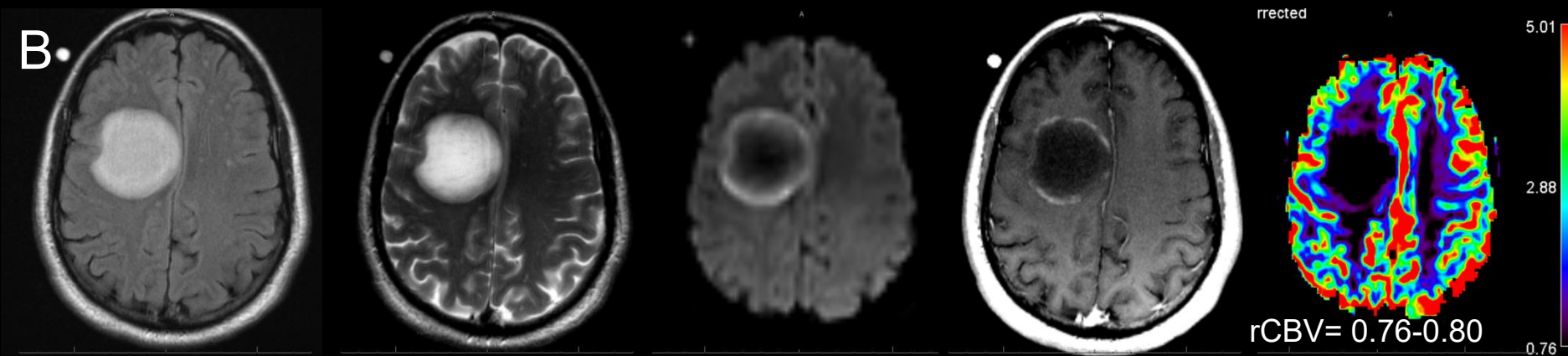


Tumefactive Demyelinating Lesion

Courtesy of
Rajan Jain, MD



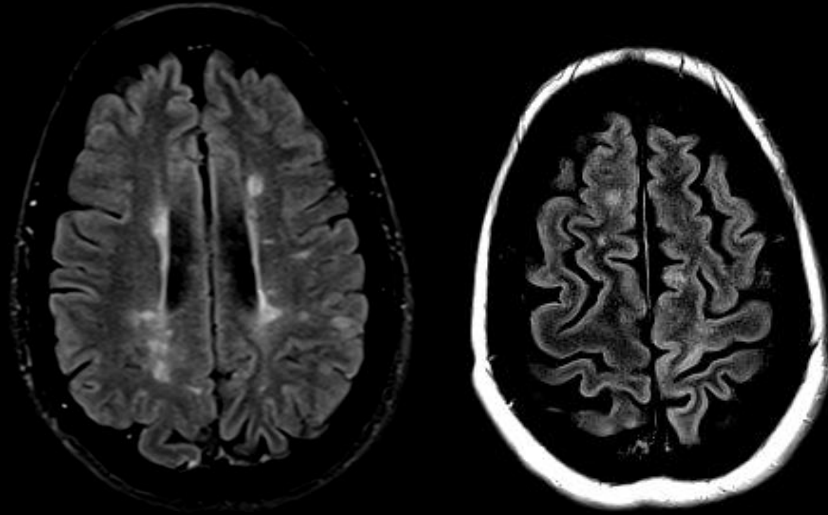
Grade III Glioma



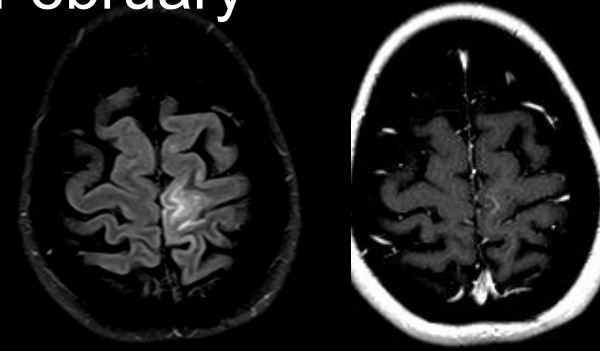
Tumefactive Demyelinating Lesion

50 years old female, MS, on Tysabri
(natalizumab)

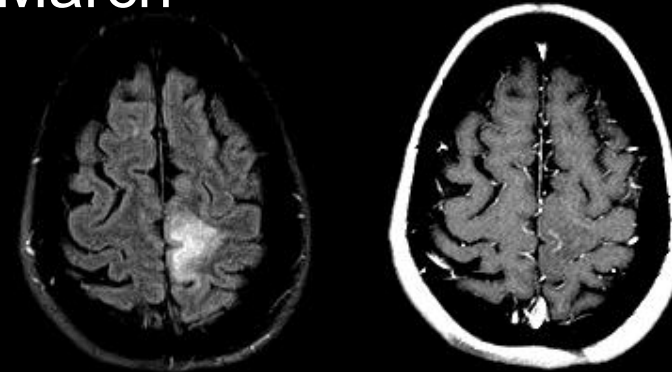
Right foot numbness, weakness



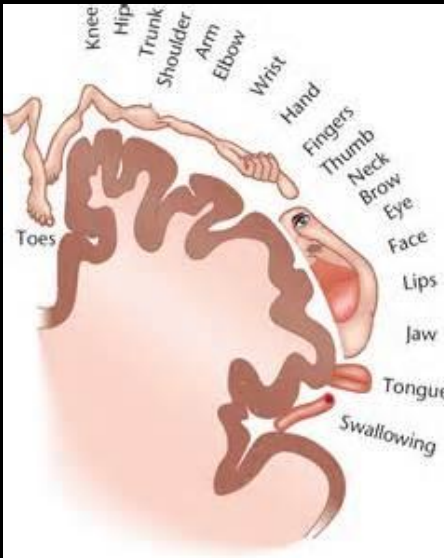
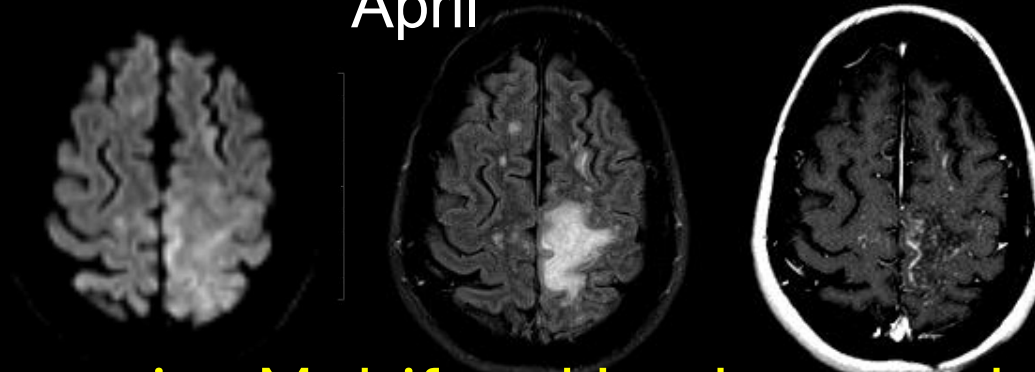
February



March

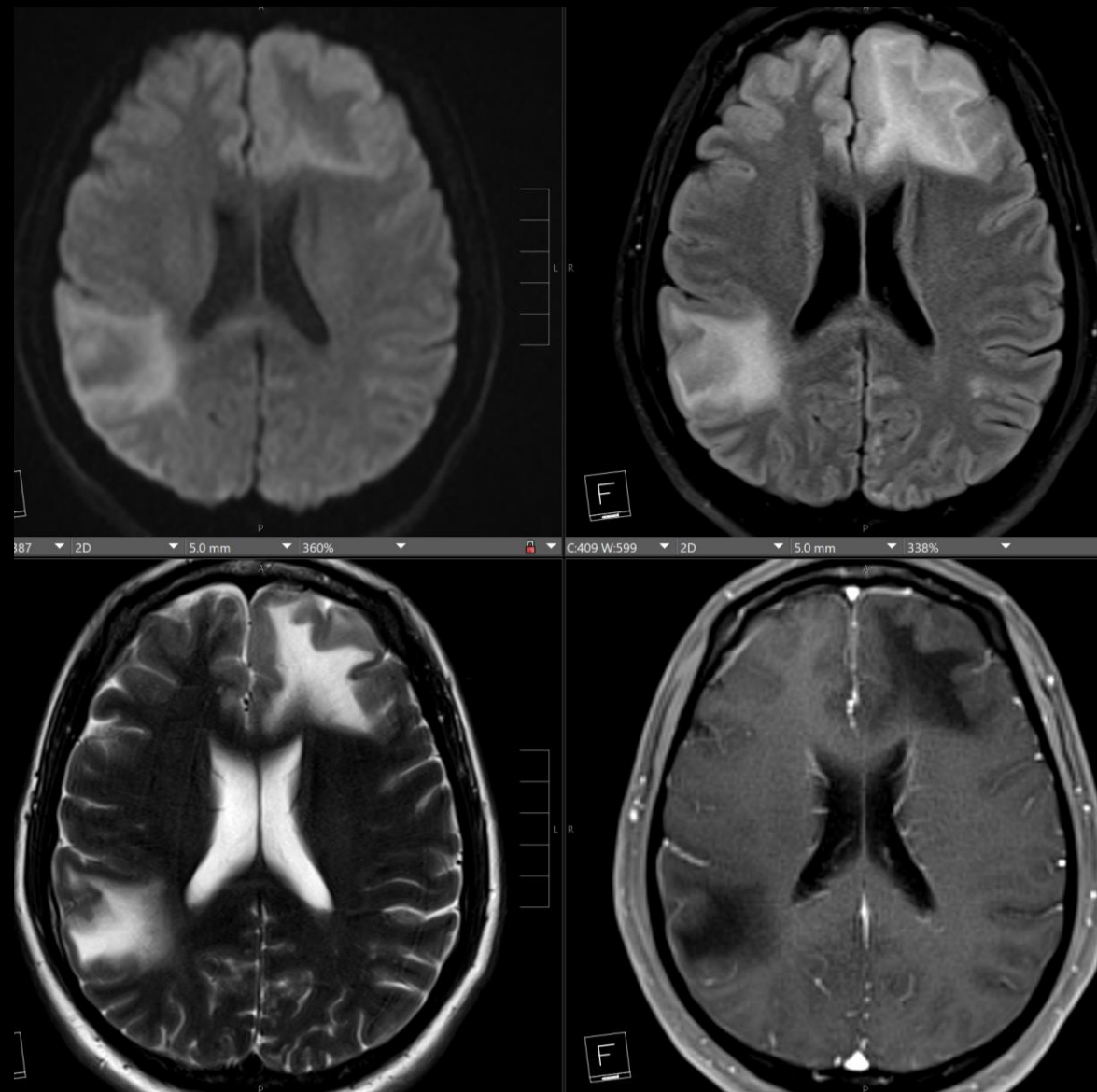


April



Progressive Multifocal Leukoencephalopathy (PML)

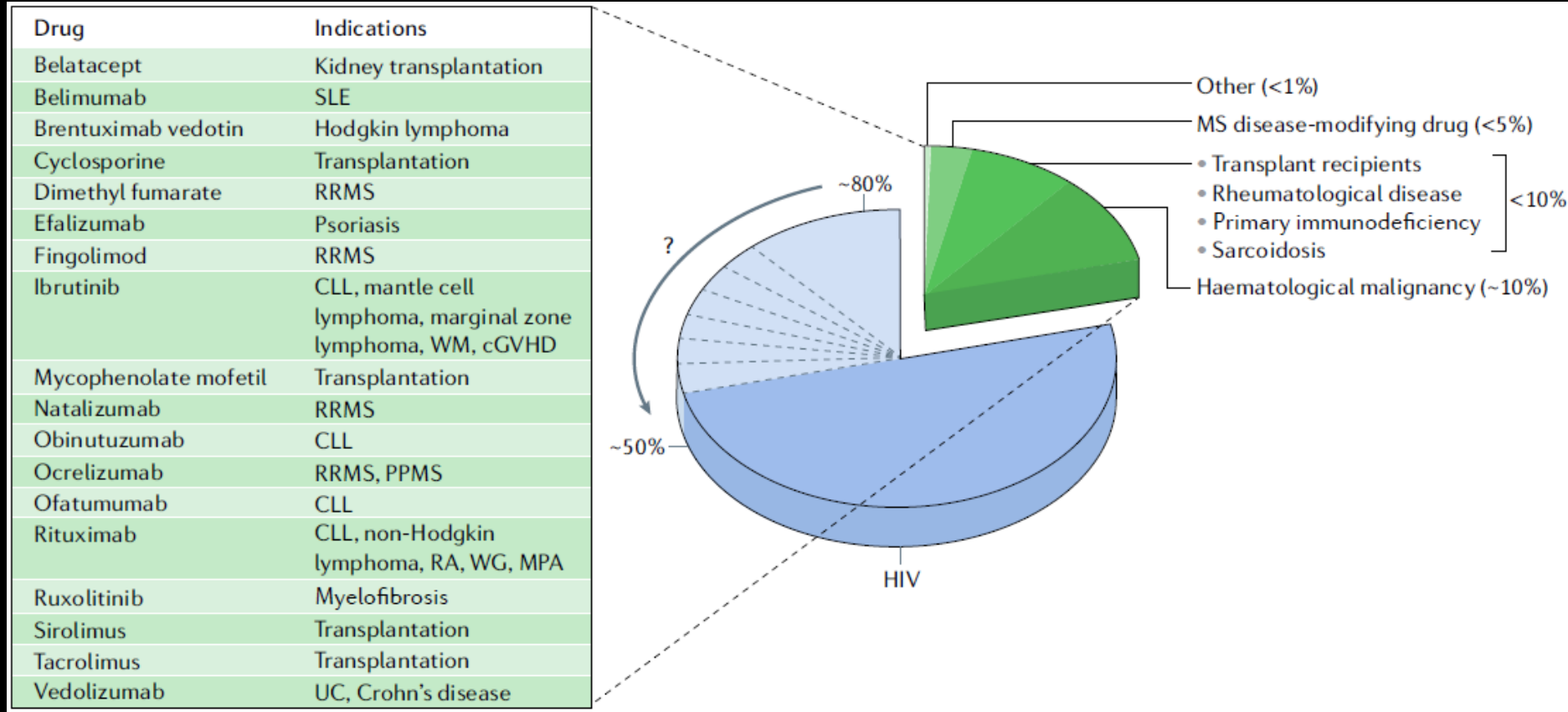
32 M, HIV/AIDS, noncompliance with medications, 1 week of abnormal behavior



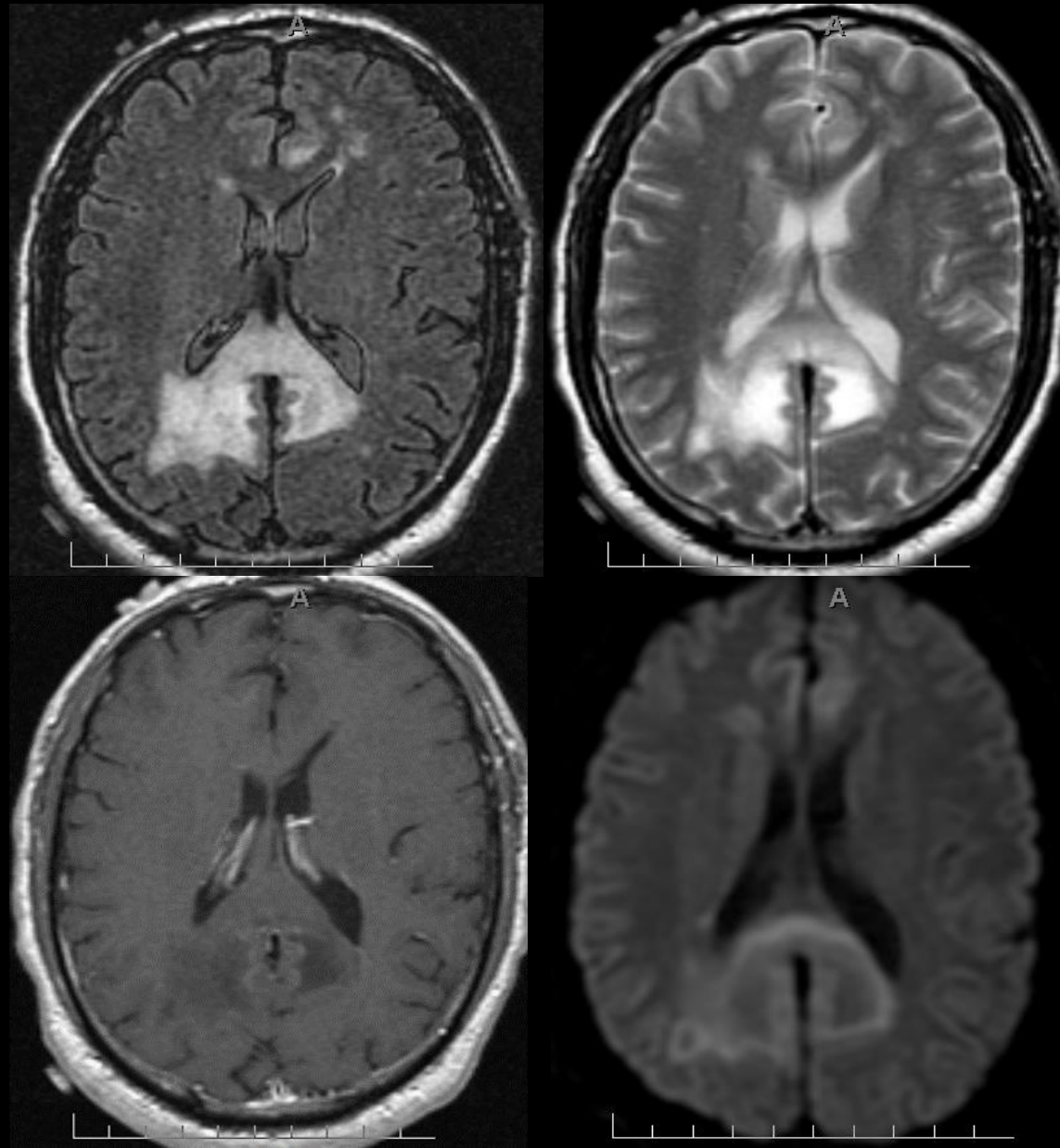
Progressive Multifocal Leukoencephalopathy (PML)

Courtesy of
Rajan Jain, MD

PML



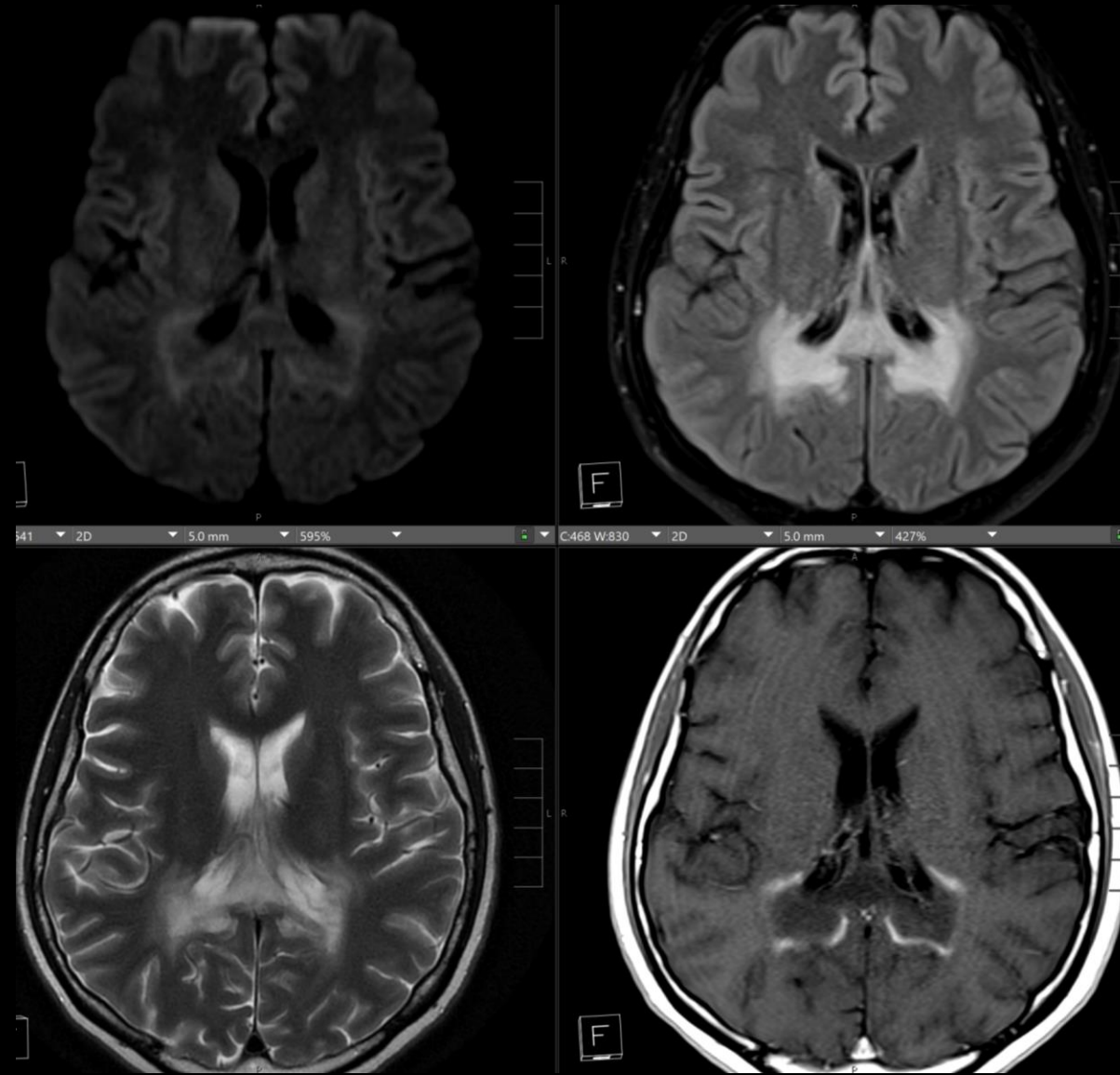
- Natalizumab (3 in 1000) >> Fingolimod and other S1P modulators > Dimethyl fumarate



Progressive Multifocal Leukoencephalopathy (PML)

Courtesy of
Rajan Jain, MD

41 M, Growth hormone deficiency, **primary adrenal insufficiency**



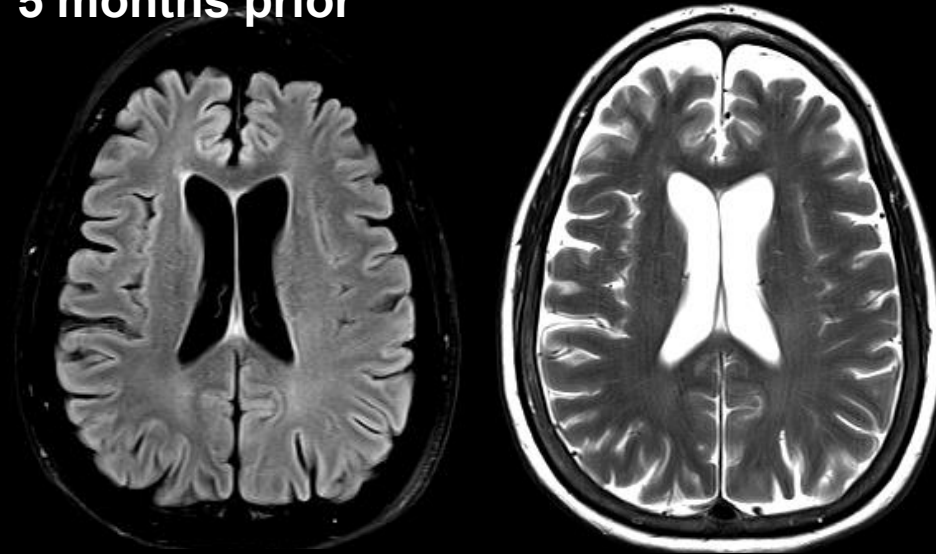
X-linked adrenoleukodystrophy (Adult onset)

Courtesy of
Rajan Jain, MD

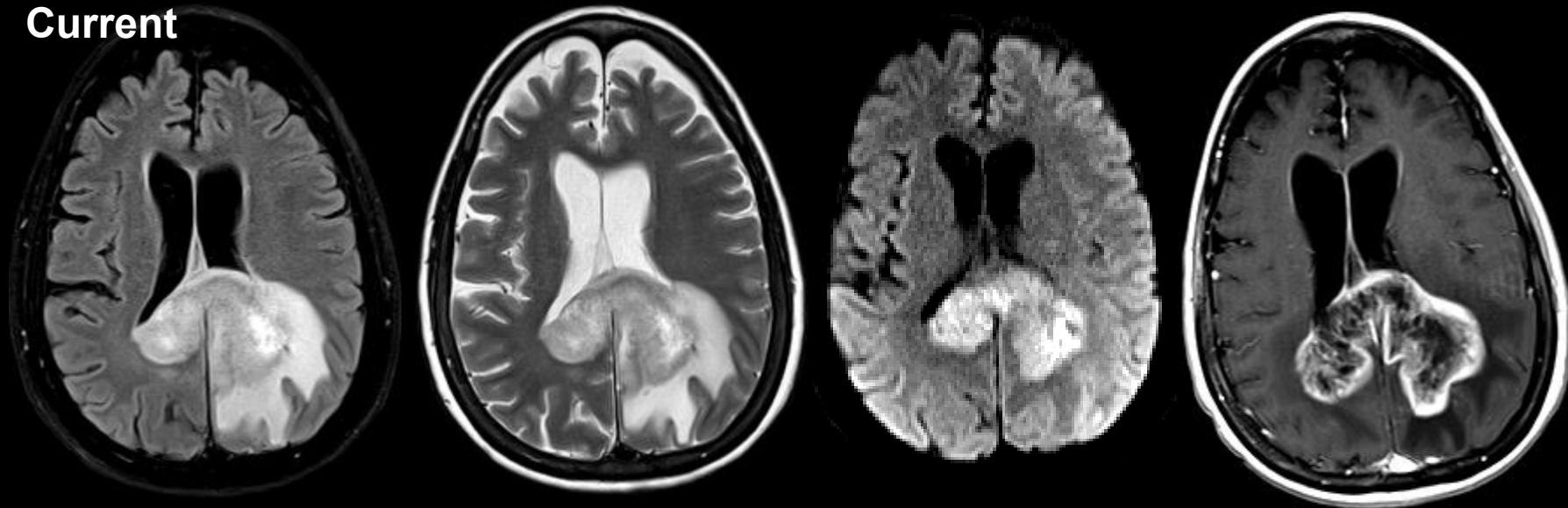
57 F, headaches

GBM

5 months prior

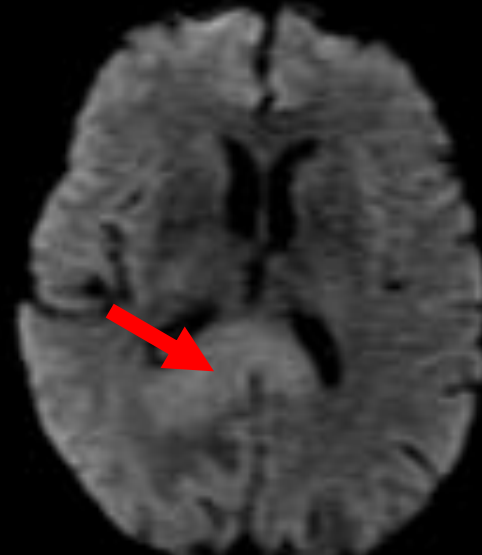
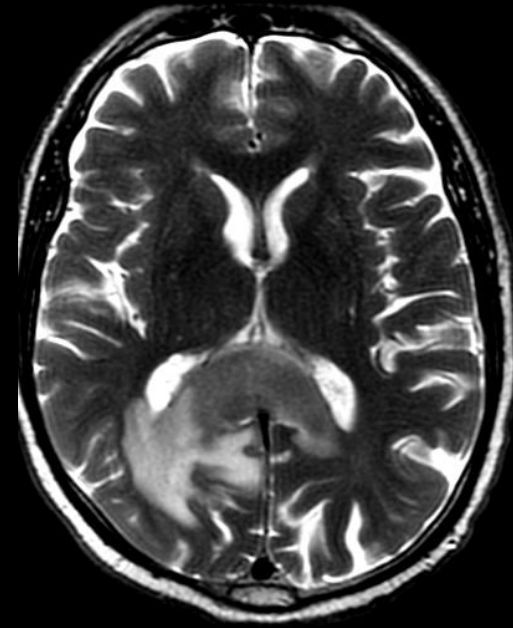
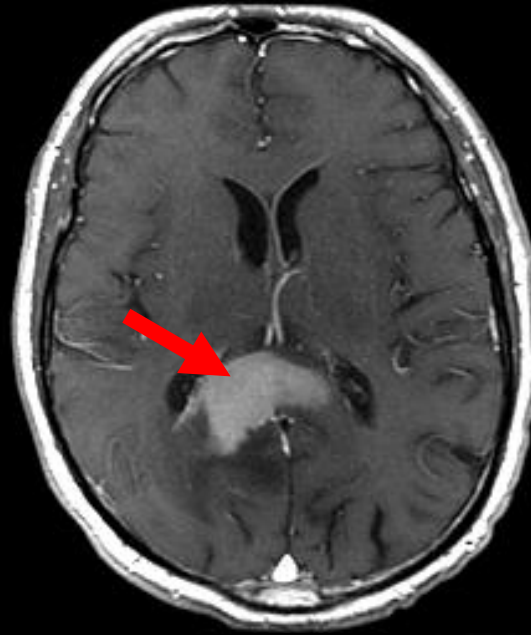


Current



Courtesy of
Rajan Jain, MD

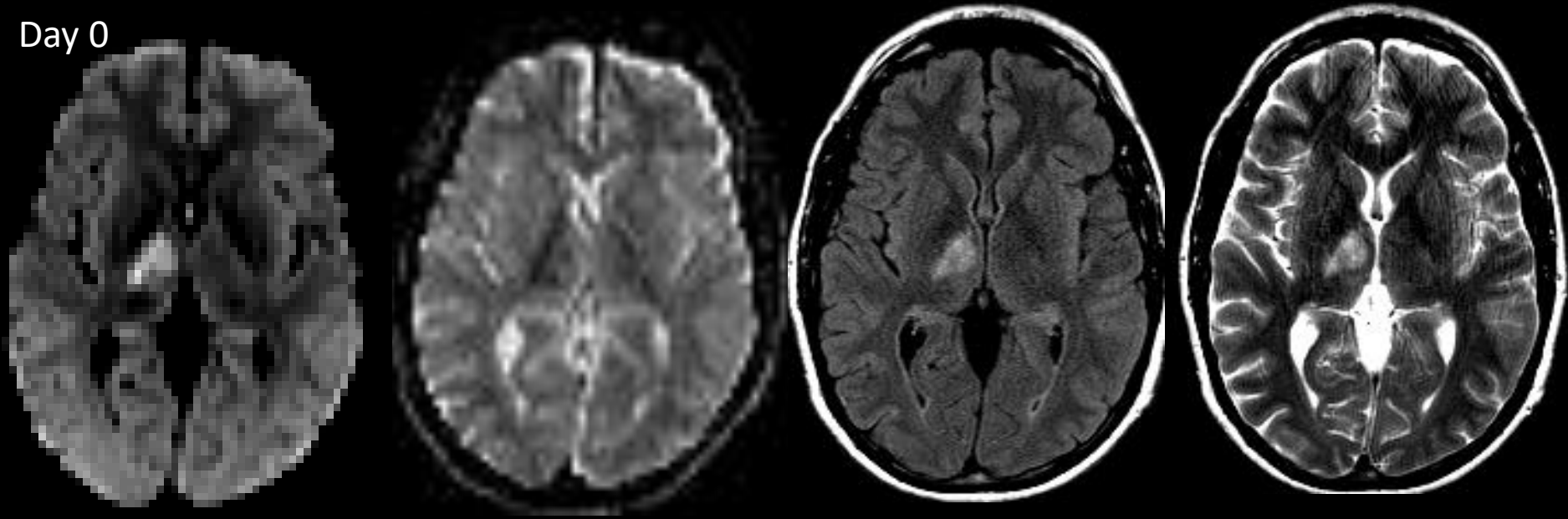
Lymphoma



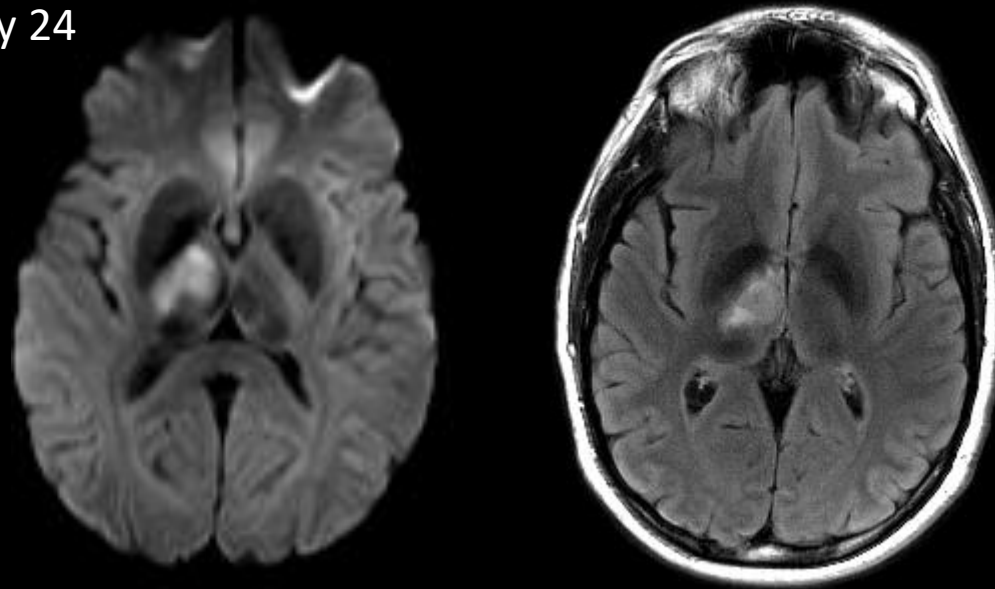
Courtesy of
Rajan Jain, MD

47M, Left facial and hand numbness with unsteady left lower extremity, **called infarct**

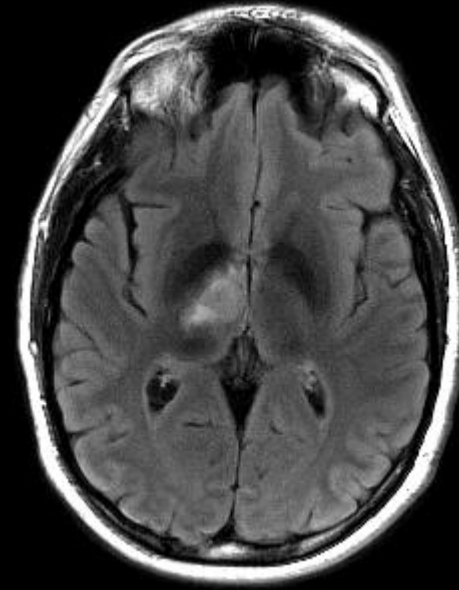
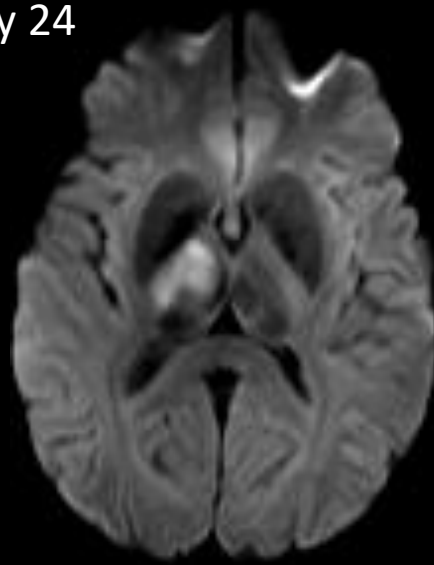
Day 0



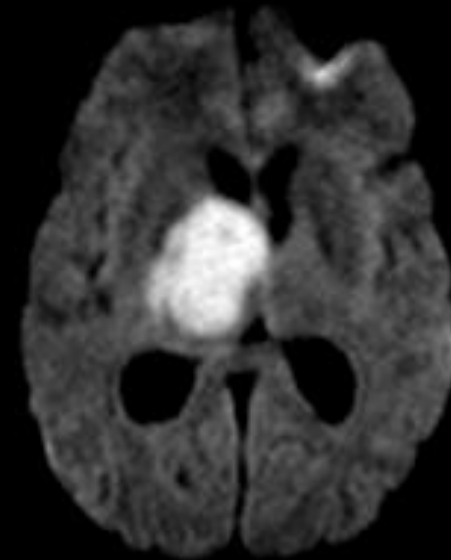
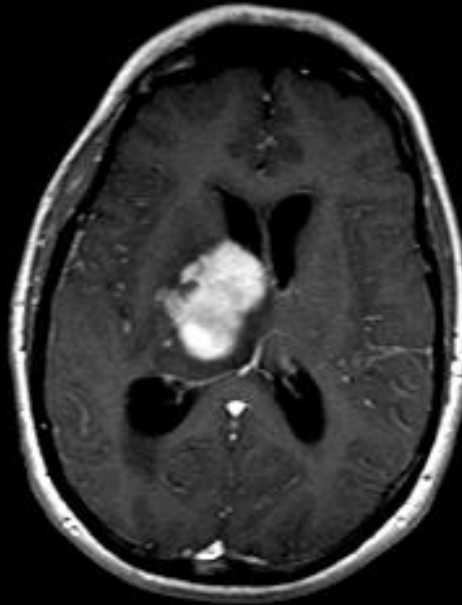
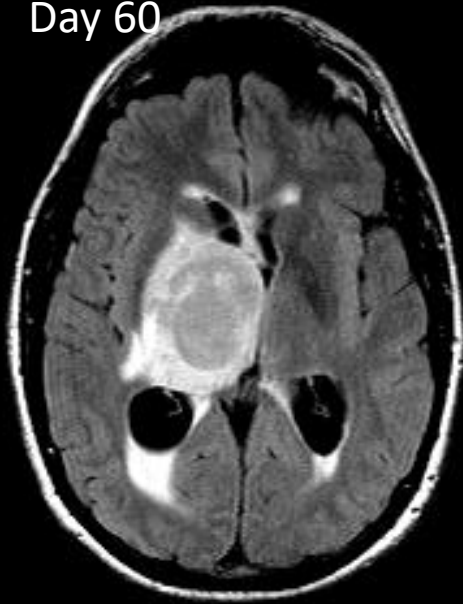
Day 24



Day 24



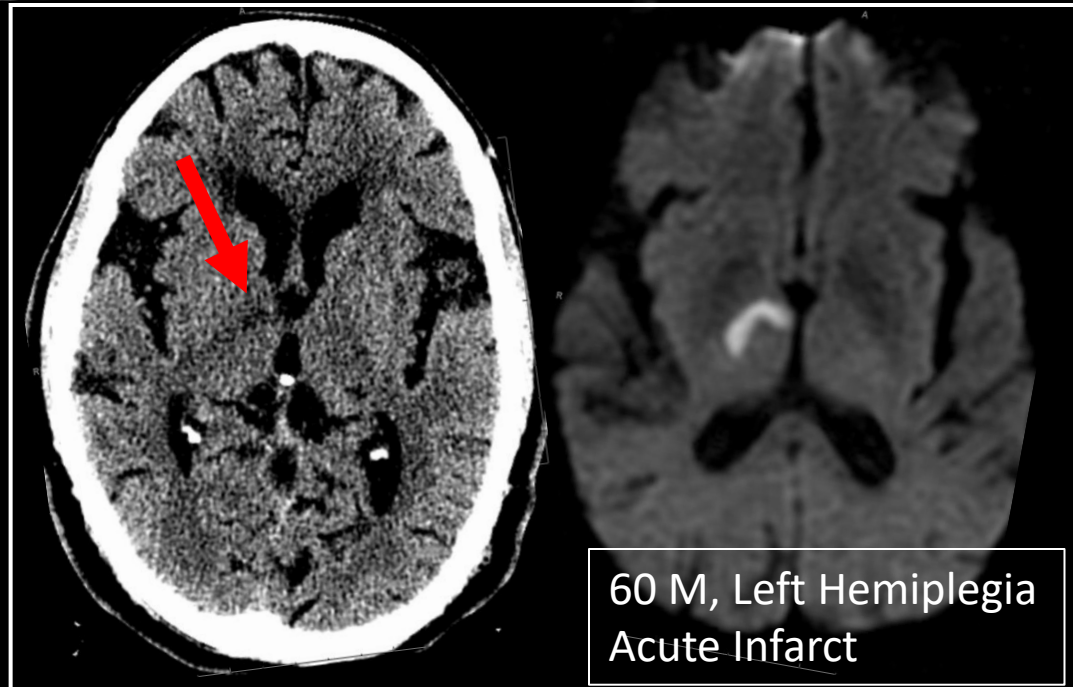
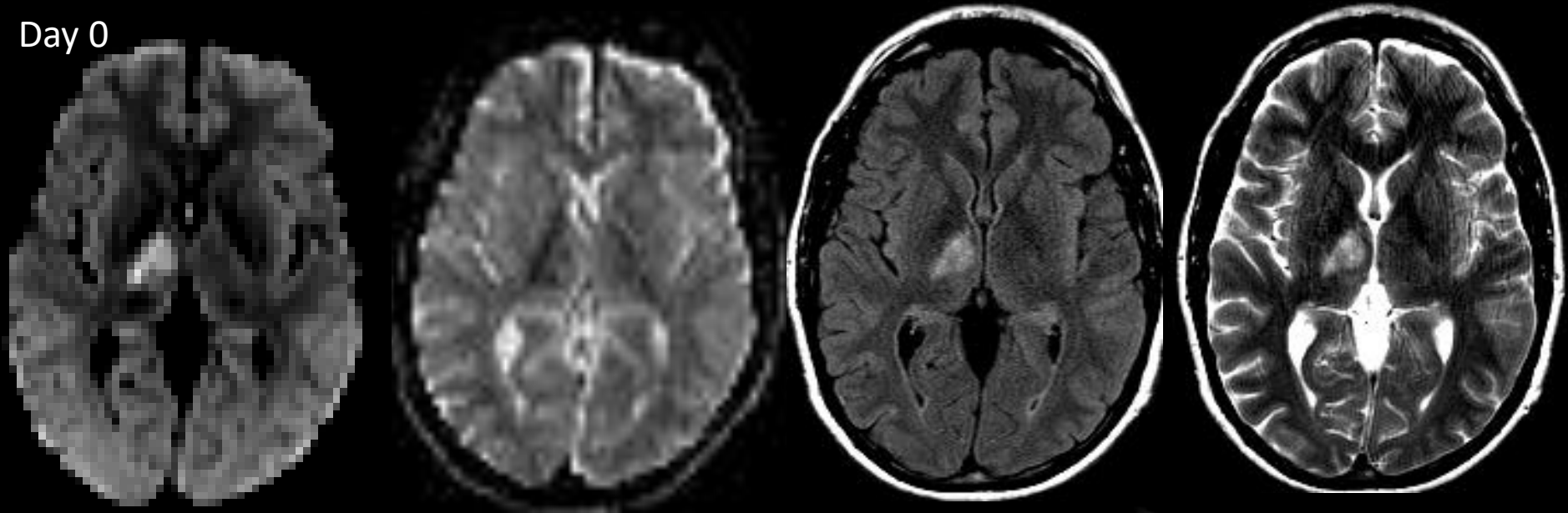
Day 60



Lymphoma mimicking acute infarct

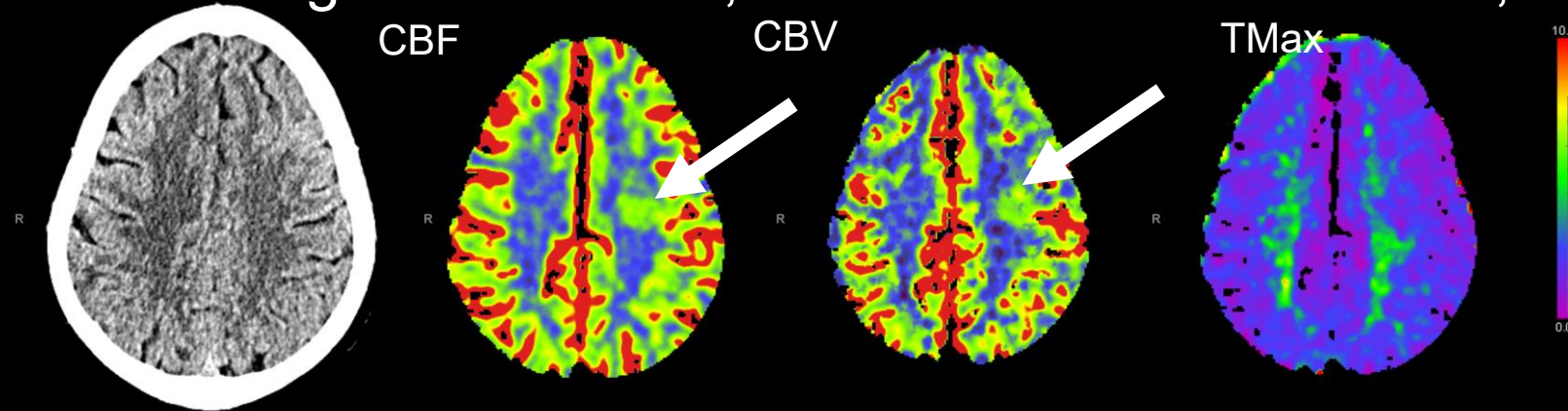
47M, Left facial and hand numbness with unsteady left lower extremity

Day 0

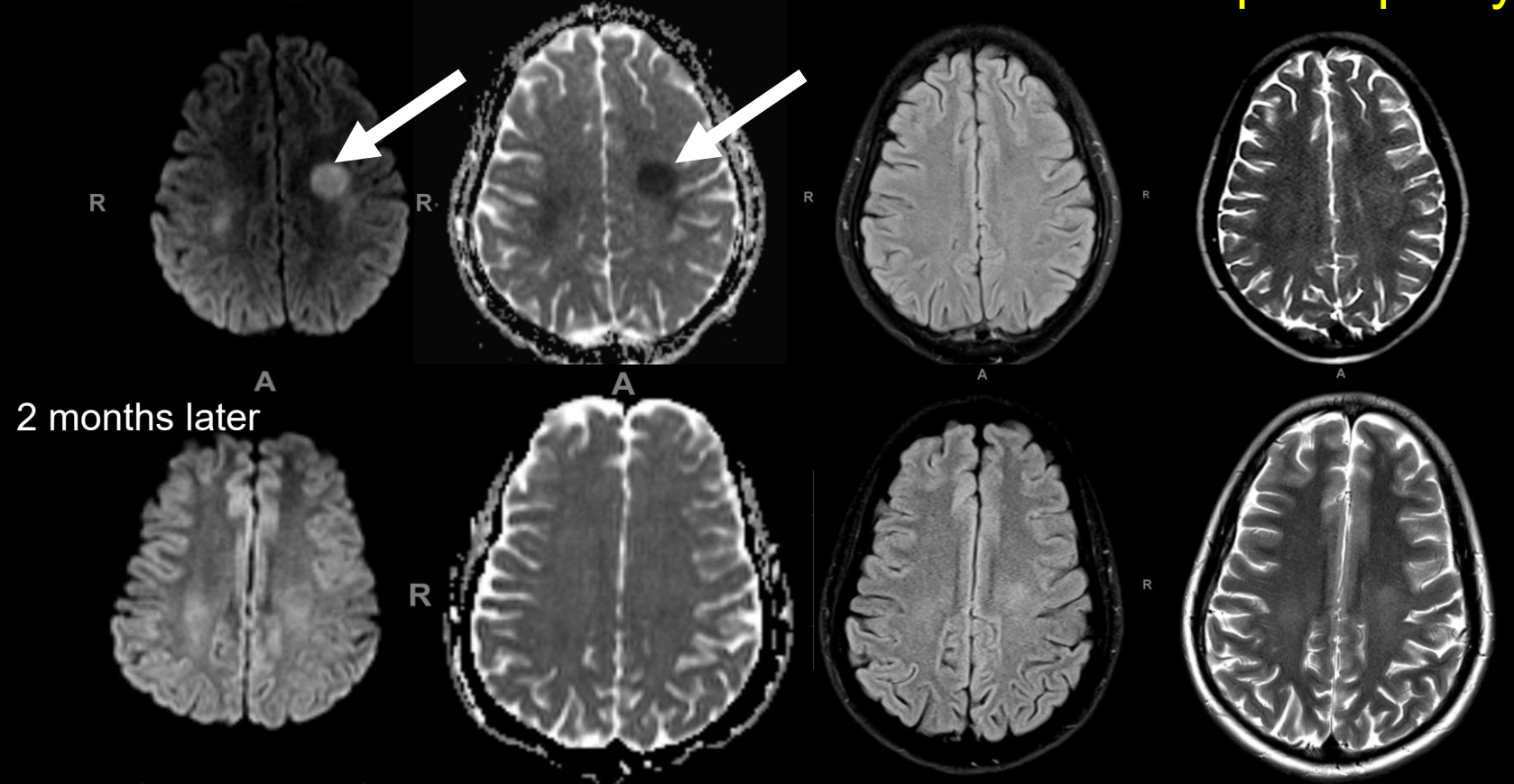


60 M, Left Hemiplegia
Acute Infarct

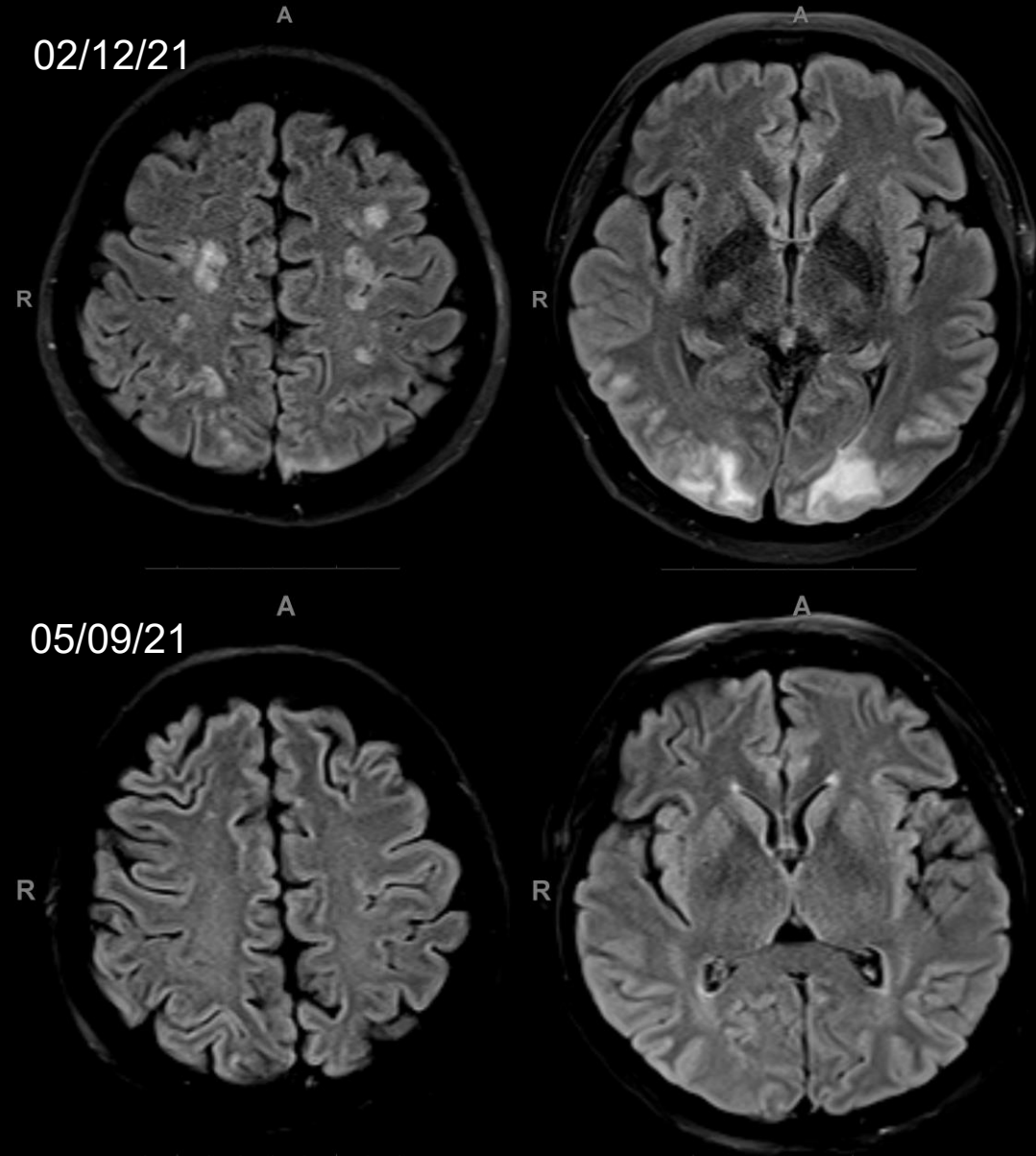
19 M, leukemia receiving methotrexate, Rt arm and face weakness, acute stroke



Methotrexate induced leukoencephalopathy



52 M, myelodysplastic syndrome, on tacrolimus



Posterior reversible encephalopathy syndrome (PRES)

PRES

Hypertension

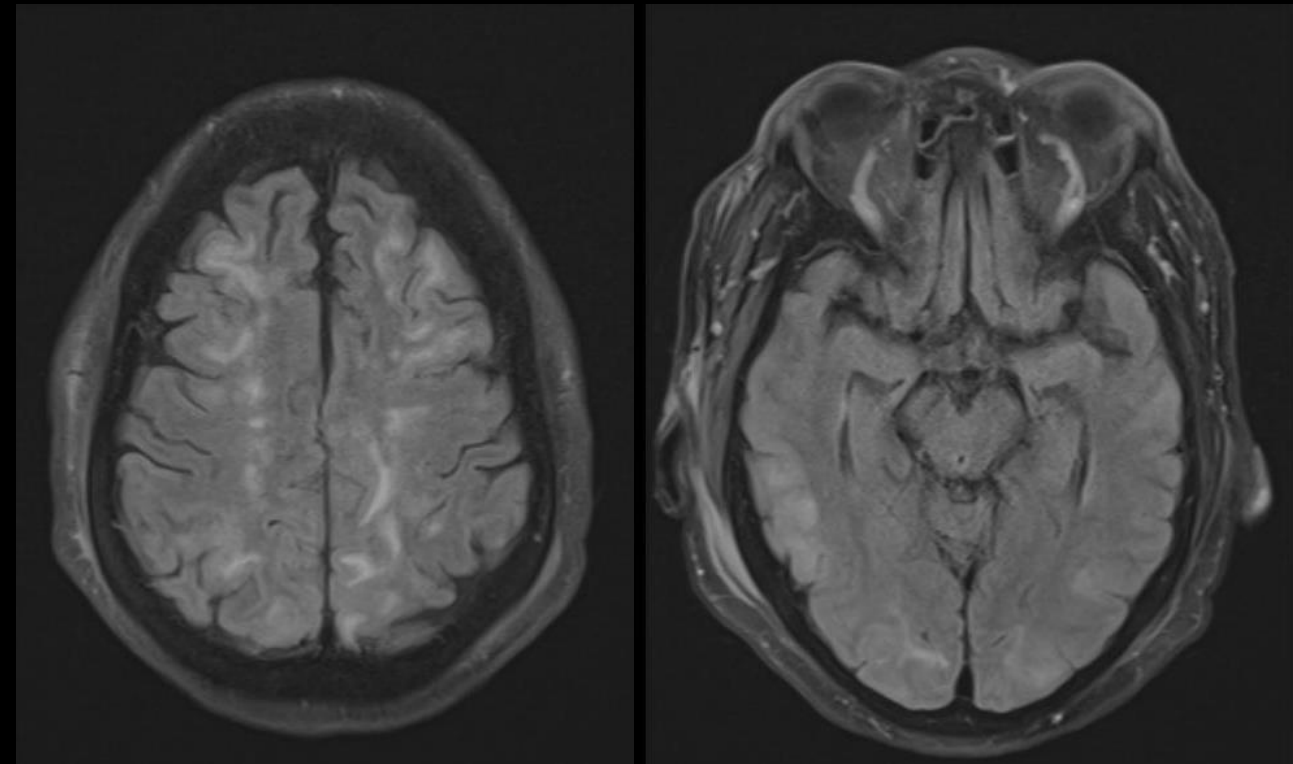
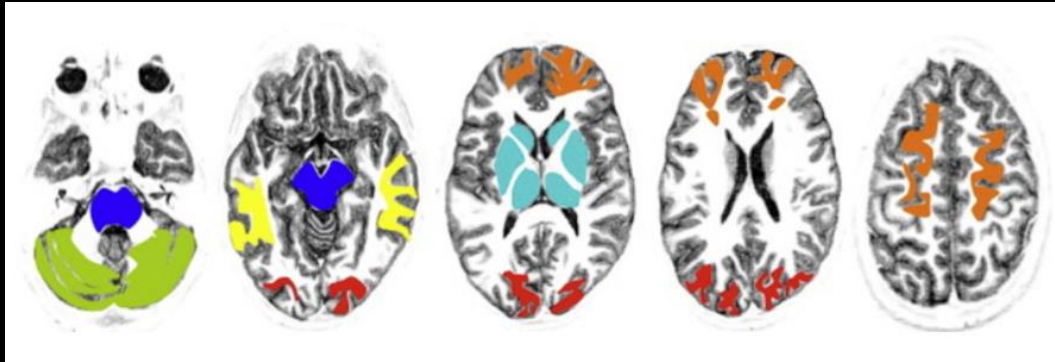
Chemotherapy/immunosuppression

Eclampsia/pre-eclampsia

Systemic disorders (many)



Not just posterior – commonly involves frontal lobes



Take home points

- Context and history is essential
- New diagnostic criteria for MS – know the five brain regions and the paraclinical tools
- Recognize when something isn't just routine small vessel disease