CURSO NACIONAL DE
NEURORRADIOLOGÍA

S.E.N.R
Sociedad Española
de Neurorradiología

Radiología en la Patología Neurodegenerativa, Desmielinizante e Infecciosa del SNC

15 y 16 de febrero de 2024 | MADRID

Sede: CINESA. C/ Fuencarral 136

Resonancia Magnética en la Esclerosis Múltiple

Àlex Rovira
Secció de Neurorradiologia. Servei de Radiologia
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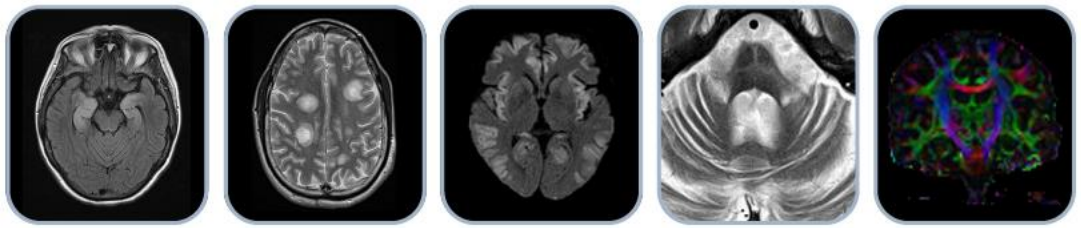
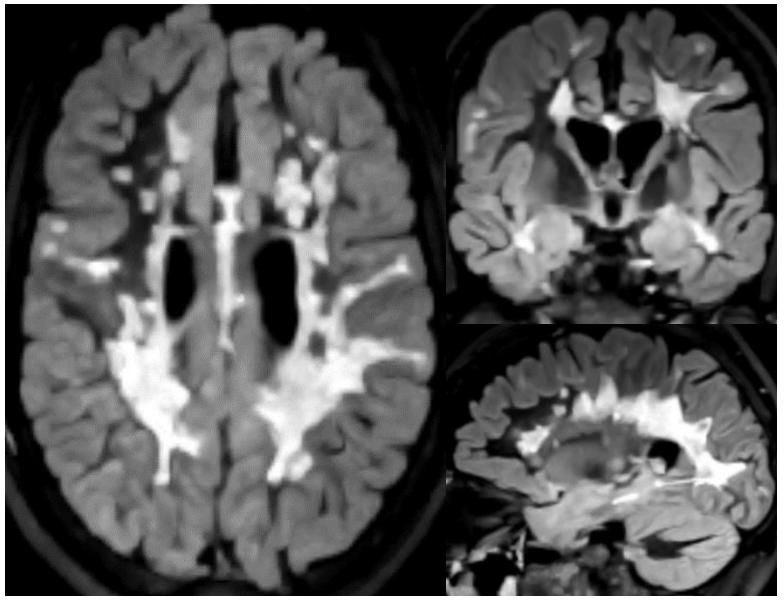


MRI in Multiple Sclerosis (MS)

Objective measure



Powerful tool across the whole spectrum of MS management in the clinical setting:

- Diagnosis
- Prediction of prognosis
- Monitoring disease activity/ clinical status / treatment response
- Early detection of treatment –related adverse events
- Outcome measure in trials of disease modifying therapies (DMTs)

Most important paraclinical tool for diagnosing and monitoring MS

1. *Rovira A et al. Nat Rev Neurol. 2015;11:471–82;* ***2.*** *Wattjes M et al. Nat Rev Neurol. 2015;11:597–606.*

Multifocal white matter abnormalities

Modified from F. Barkhof

Hypoxic-ischaemic

Hypertension, diabetes

Migraine

Incidental (young adults)

Age-related WM changes

Small-vessel disease

CADASIL

Inflammatory

Sarcoidosis

Susac

Lyme

MS

ADEM

PACNS

Systemic vasculitis

NMOSD

MOGAD

Other

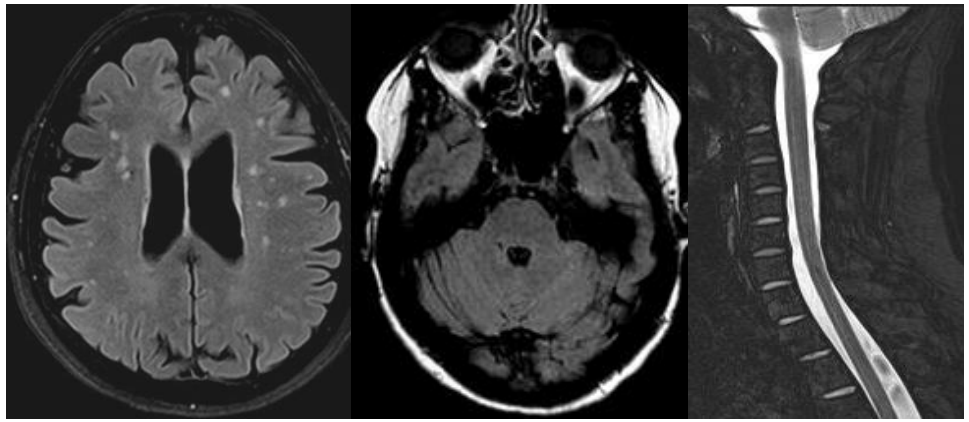
Primary CNS lymphoma

PML

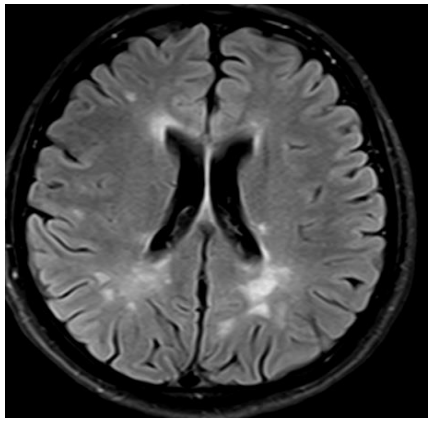
Leber

Leukodystrophies

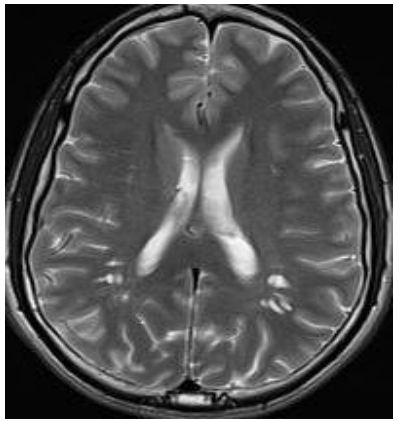
Virchow-Robin spaces



Incidental



MS



Virchow-Robin

Misdiagnosis of multiple sclerosis

	Cedars (n = 19)	UCLA (n = 24)
MS misdiagnosed by neurologist	14 (74%)	20 (83%)
MS misdiagnosed by non-neurologist	4 (21%)	2 (8%)
Under care of neurologist for MS but specialty of physician who made the misdiagnosis unknown	1 (5%)	2 (8%)
Years from misdiagnosis to evaluation at Cedars or UCLA (mean)	0.1–20 (4.1)	0.1–19 (4.0)
CSF[a] analyzed prior to or during evaluation at Cedars or UCLA	14 (74%)	20 (83%)
Oligoclonal bands unique to CSF	4 (29%)	3 (13%)
Other CSF abnormalities	1 (5%)	1 (4%)
Normal CSF	6 (32%)	11 (46%)
CSF Results unavailable	3 (16%)	5 (21%)
Clinical syndrome atypical for MS	14 (74%)	16 (67%)
Normal exam	3 (16%)	3 (13%)
Radiographic red flags	15 (79%)	20 (83%)
Normal brain and spinal cord MRIs	4 (21%)	2 (8%)

Almost one in five patients (19%) referred to two academic MS centers with an established diagnosis of MS did not have MS.

Final diagnoses of the 43 patients misdiagnosed with MS.

Migraine	
Migraine with nonspecific white matter changes	5
Migraine with normal MRI	1
Migraine and cervical stenosis	1
Autoimmune	
Radiologically isolated syndrome (Browne et al., 2014)	4
Neuromyelitis optica spectrum disorder	2
Transverse myelitis, infectious or post-infectious	2
Lupus (no myelitis)	2
Stiff-person syndrome with anti-GAD antibody	1
Anti-Calcium channel antibody with confluent white matter changes	1
Myasthenia gravis	1
Miscellaneous	
Cervical spondylosis with stenosis	3
Peripheral neuropathy	3
Optic neuropathy (without optic neuritis)	3
Fibromyalgia	2
Pre-syncope and small vessel ischemic disease	1
Bell's palsy	1
Psoriasis, hypothyroidism, and small vessel ischemic disease	1
Encephalitis, infectious	1
Asymptomatic demyelinating changes likely due to TNF alpha inhibitor	1
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes	1
Myelopathy, copper deficiency	1
Evaluation ongoing or lost to follow-up, most likely diagnosis:	
Cobalt poisoning	1
Pompe (glycogen storage disease type II)	1
Hypercoagulable state	1
Central nervous system vasculitis	1
Hereditary spastic paraplegia	1

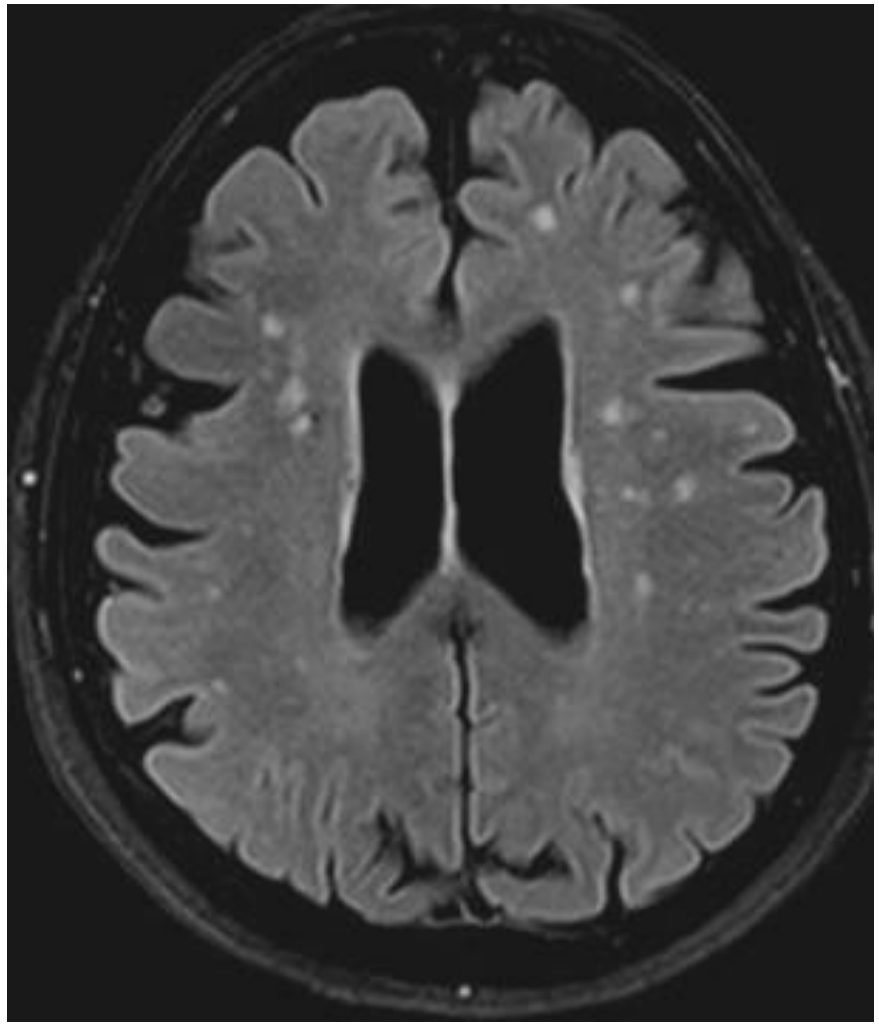
Kaisey et al. Mult Scler Rel Dis 2019

Multifocal white matter abnormalities in young adults

MRI focal white matter lesions (incidental, vascular?)
Prevalence 5–10% (20–40 years)

- Focal WMLs involving the subcortical frontal white matter
- Small and nonconfluent
- Stable over time
- Weak (or NO) association with vascular risk factors
- More prevalent in **migraine** headaches
- No associated lesions posterior fossa, spinal cord

Multiple sclerosis
Prevalence <0,1% (20–40 years)



***WML**, white matter lesion.*

Charil A et al. Lancet Neurol 2006;5:841–52; Image courtesy of Dr Rovira.

Diagnosis of MS: Identifying typical lesions

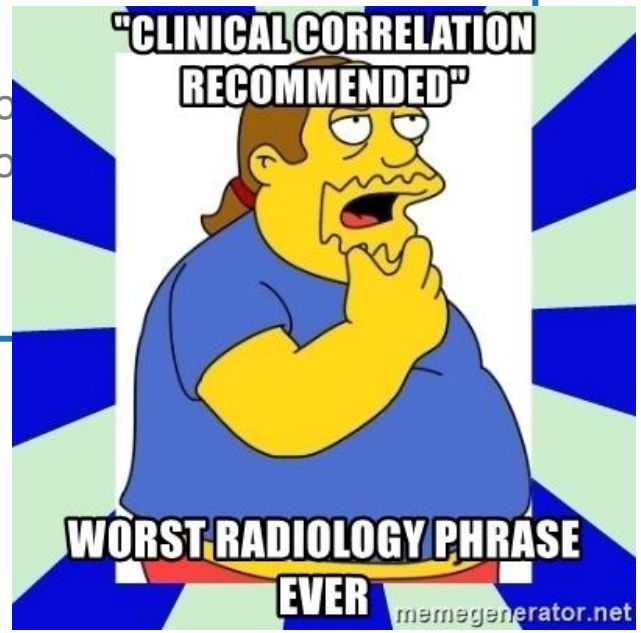
Comprehensive checklist for evaluation of focal lesions

Systematic reading

- **Lesion distribution / involvement**
  - Subcortical/periventricular
  - U-fibres
  - Cortical grey matter
  - Deep grey matter
  - Corpus callosum
  - Brainstem
  - Spinal cord
- **Lesion shape**
- **Central vein sign, hypointense rims (SWI)**
- **Enhancement pattern**

Brief and precise diagnostic impression that must consider:

- Demographics
- Family history
- Vascular risk facto
- Clinical informatio
- Lab findings

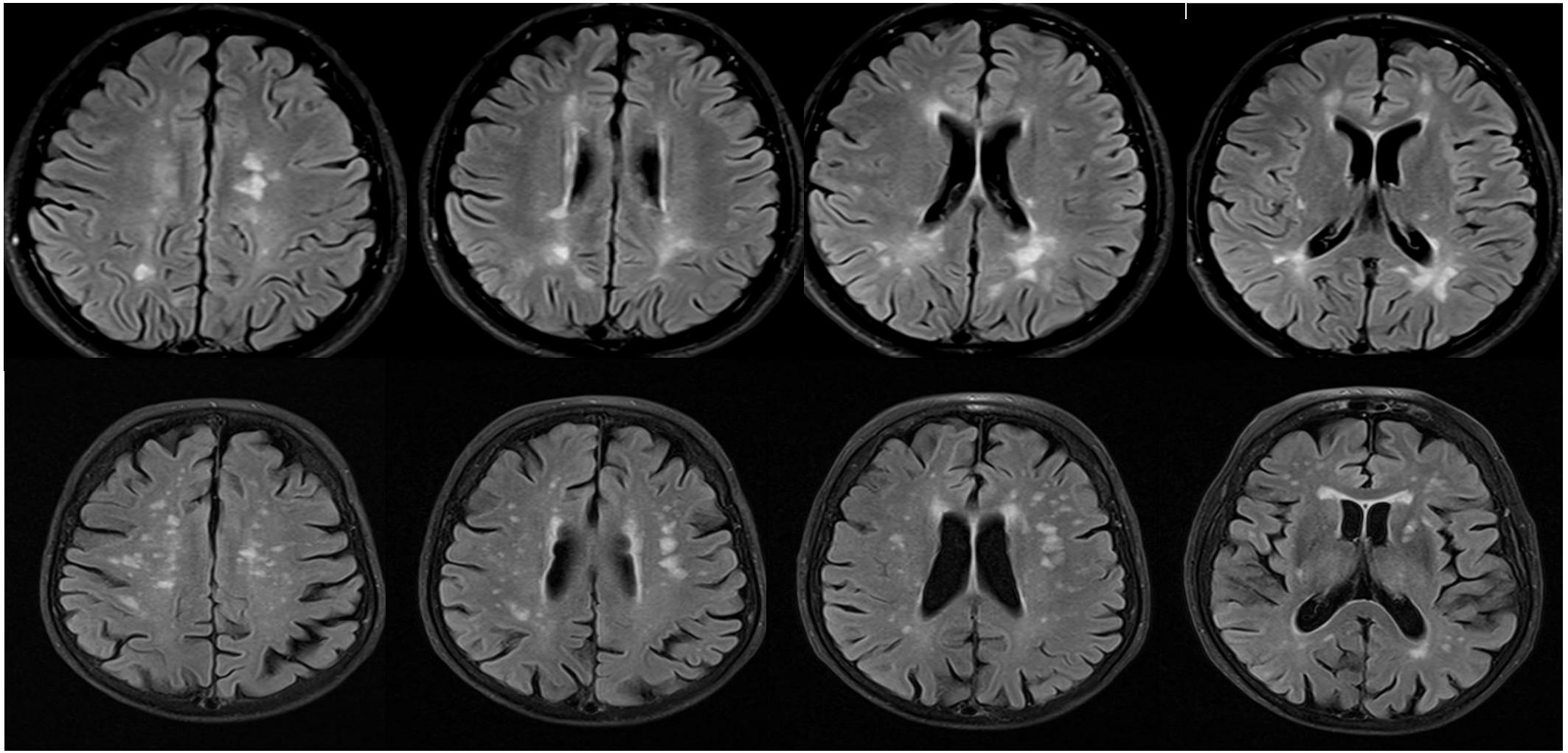


SWI, *susceptibility weighted imaging.*

Rovira A et al. Nat Rev Neurol. 2015;11:471–82.

Distribution pattern

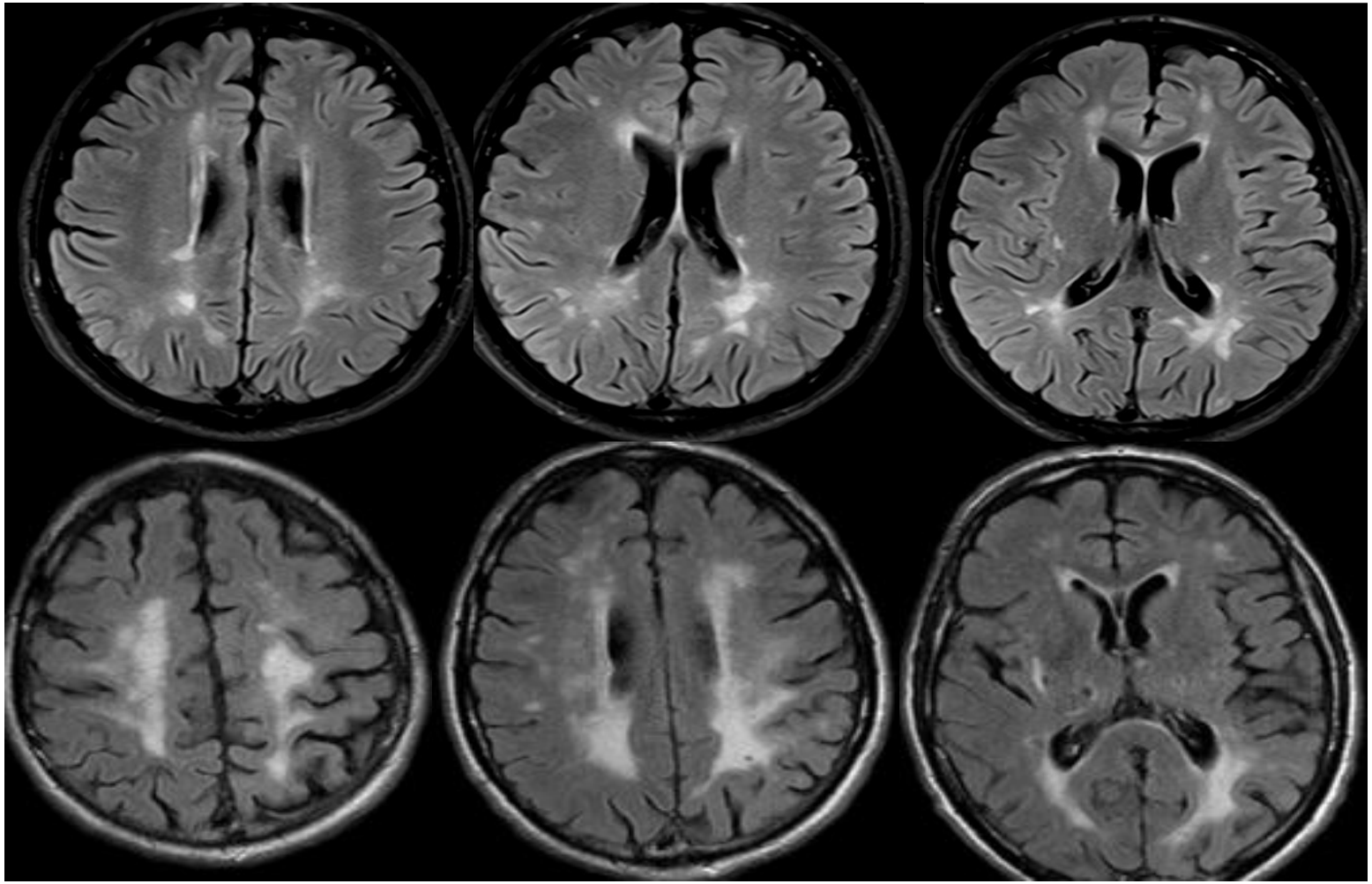
Multiple sclerosis



Age-related white matter changes

Distribution pattern

Multiple sclerosis



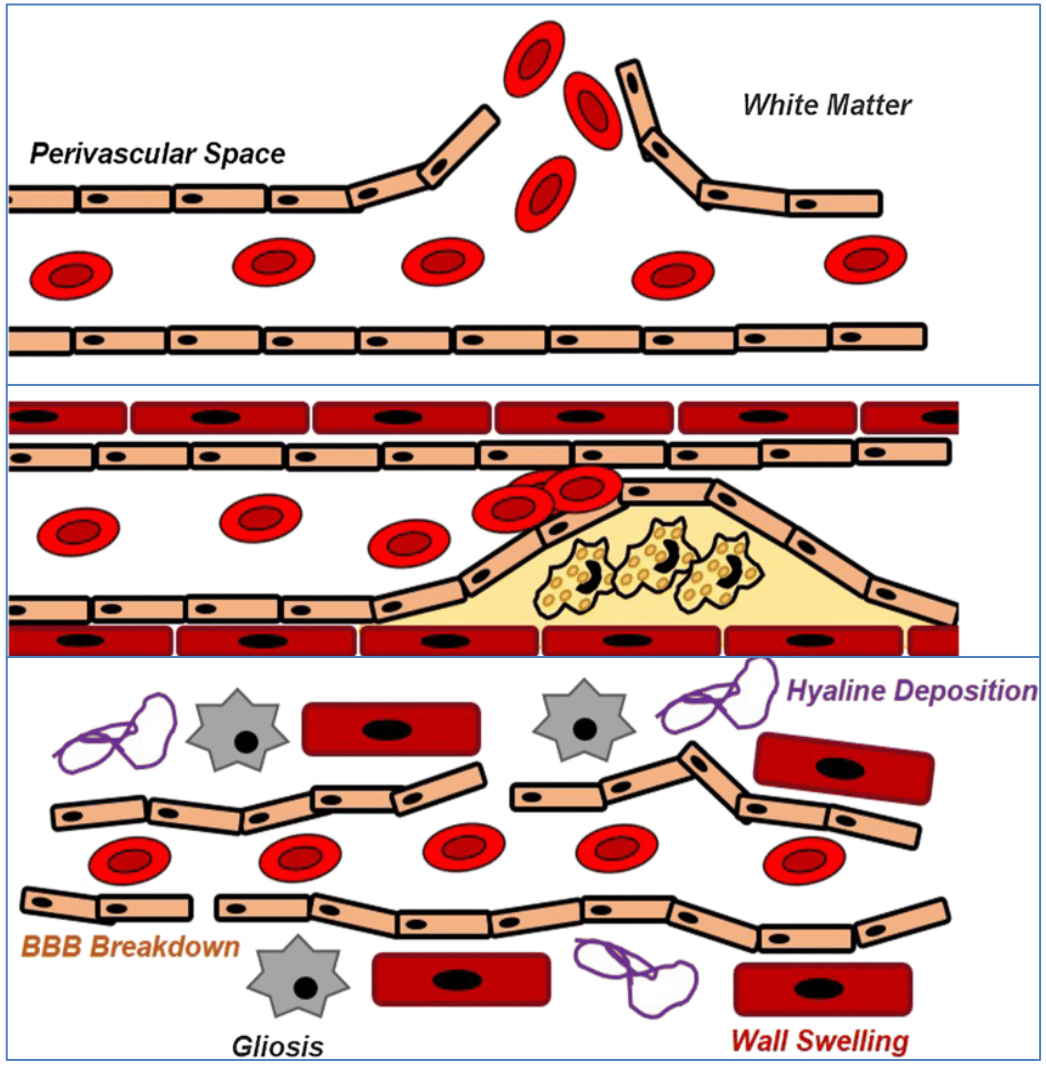
Small vessel disease

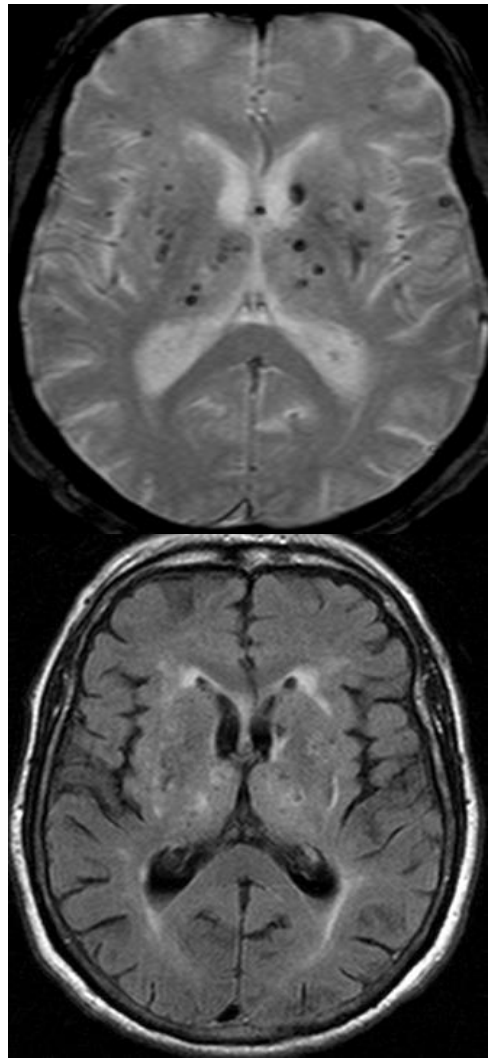
Lipohyalinotic small-vessel disease: MRI findings

Microbleeds

Microinfarcts

Leukoaraiosis
(white matter lypohyalinosis)



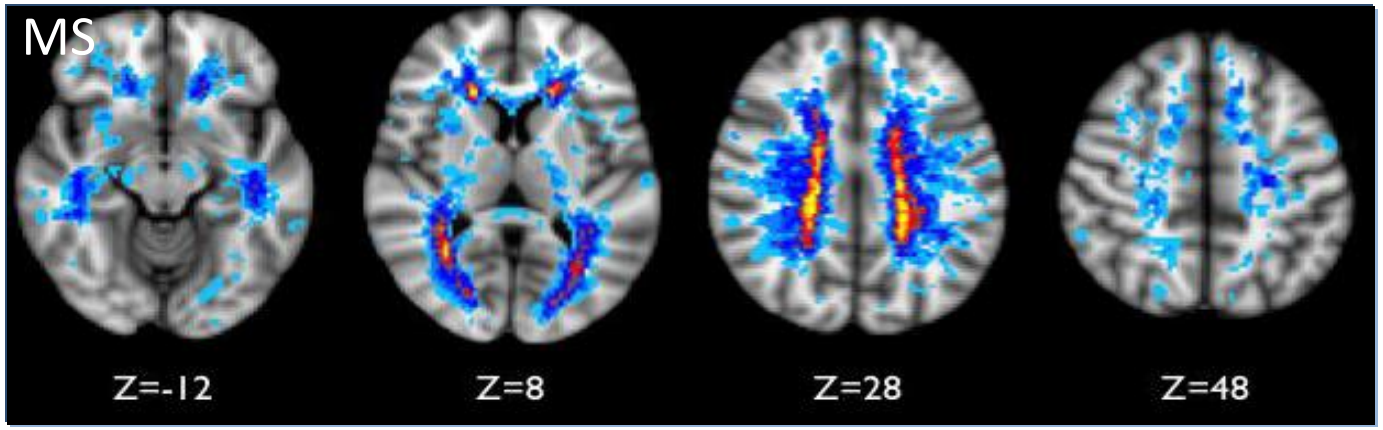


T2* GRE

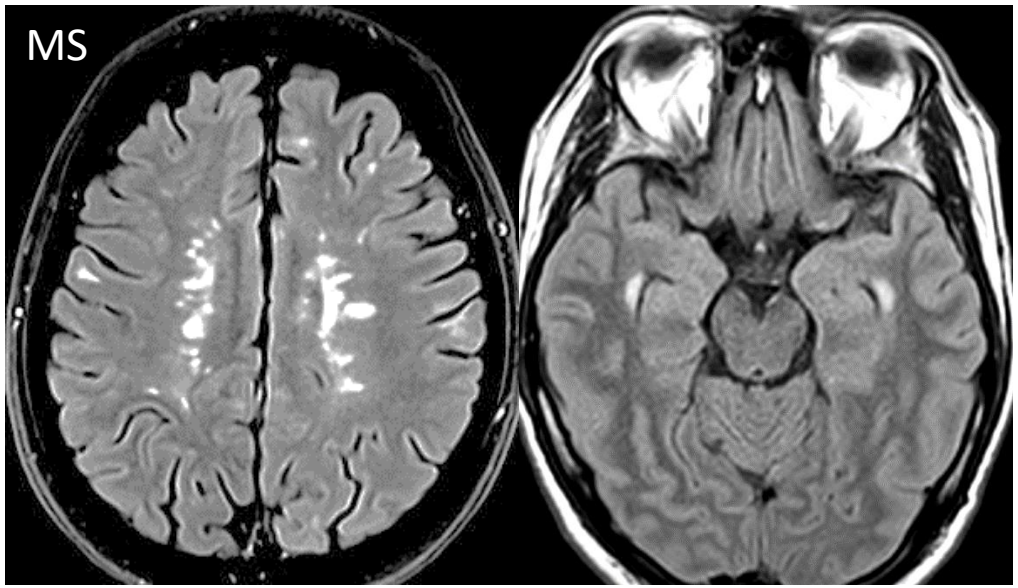
T2-FLAIR

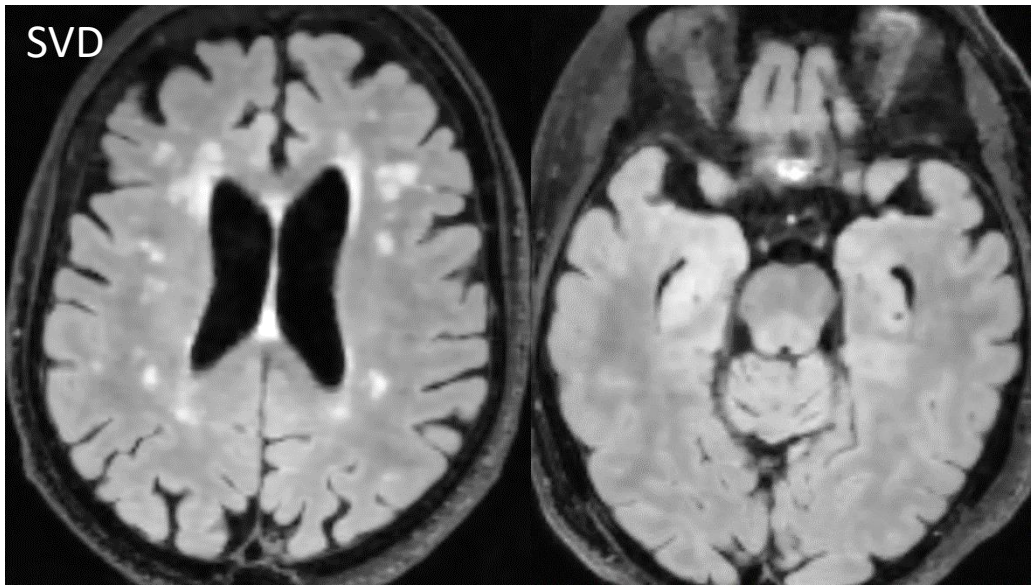
Brain MR imaging features: MS

Matthews et al. Neurology 2013

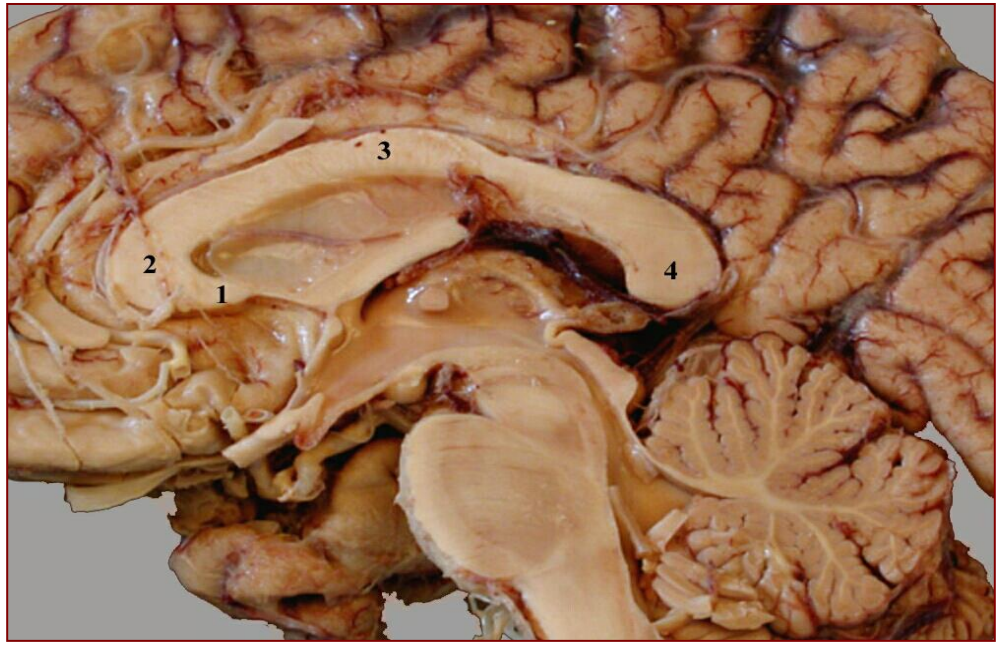


Periventricular and in inferior temporal lobe

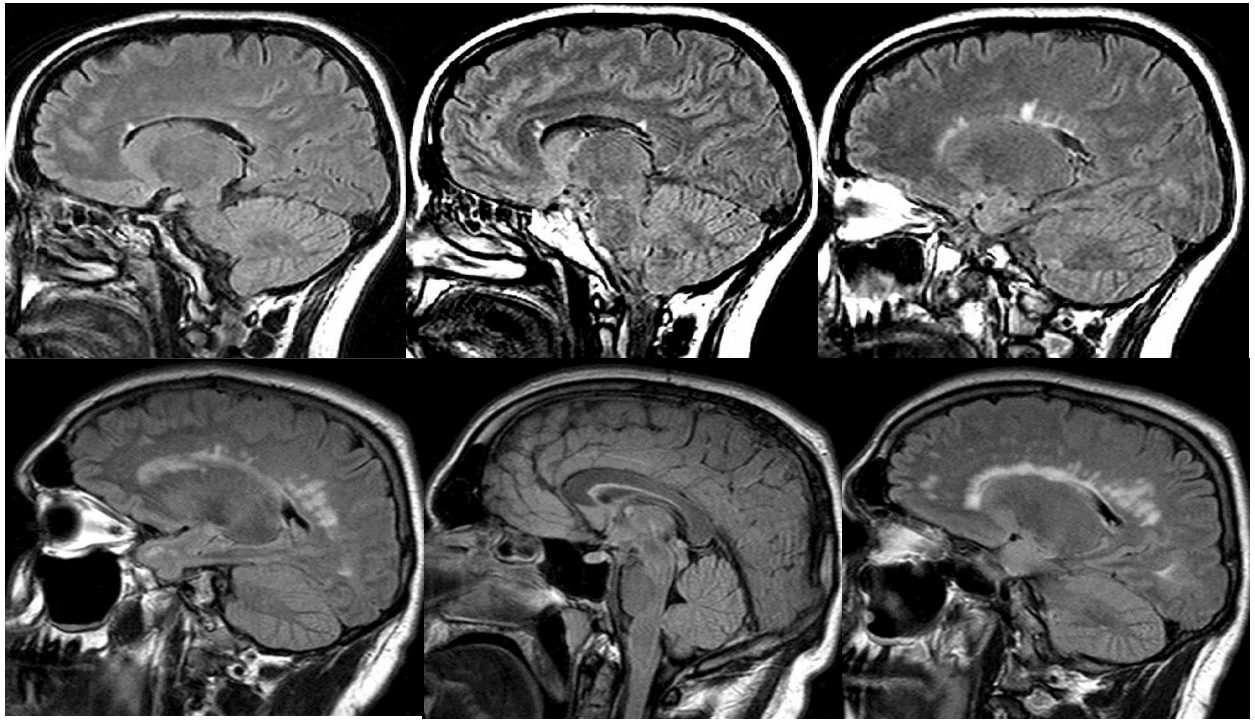




Corpus callosum involvement



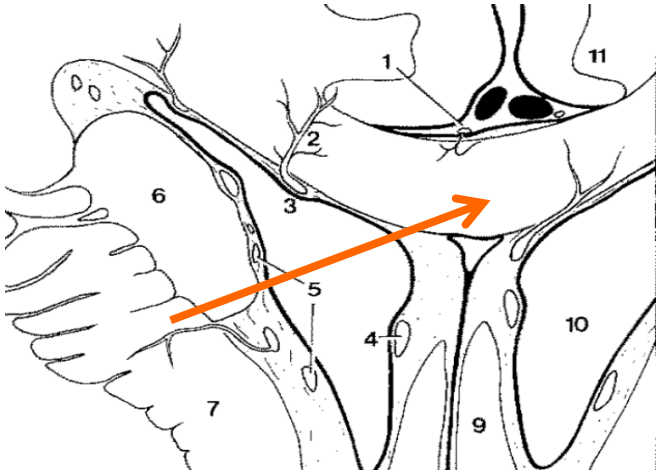
Multiple Sclerosis



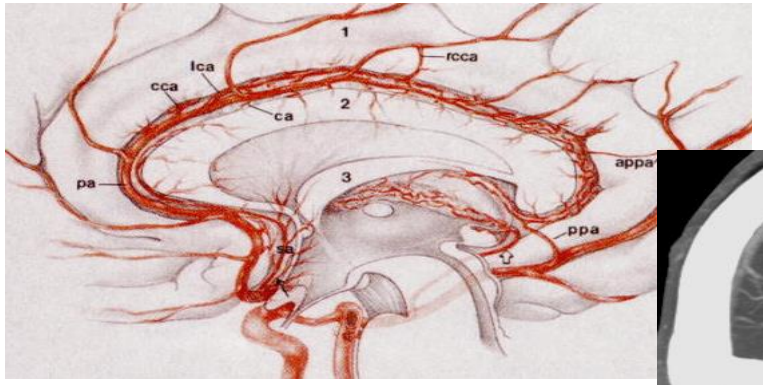
Cerebrovascular disease

Gean-Marton et al. 1991;180:215-221; Simon et al. Radiology 1986;160:363-367

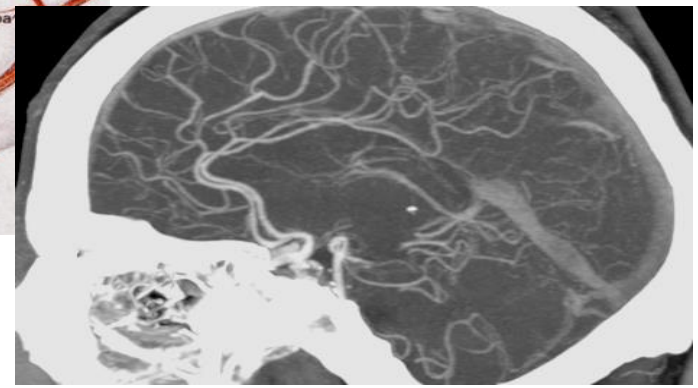
Corpus callosum involvement

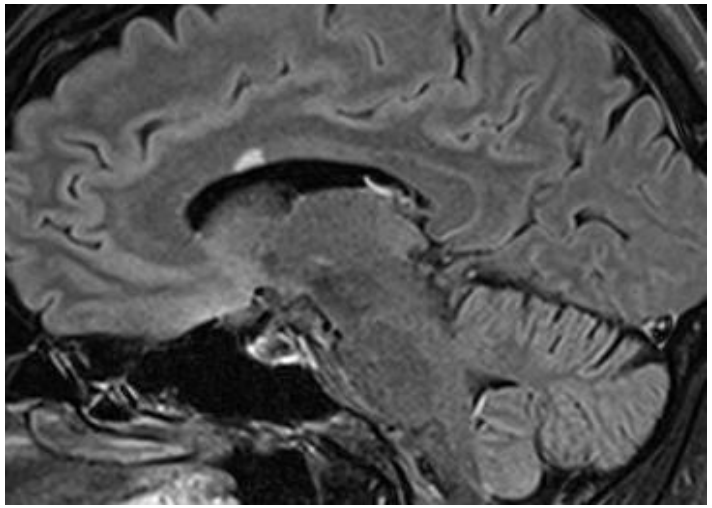


R Wotfram-Gabel et al. Surg Radiol Anat 1992;14:17-21

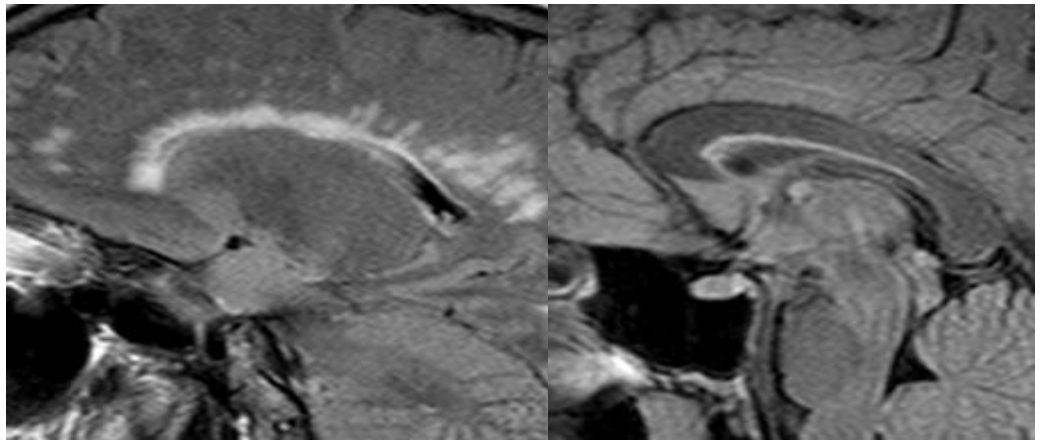


Türe et al. Neurosurgery. 1996;39:1075-84



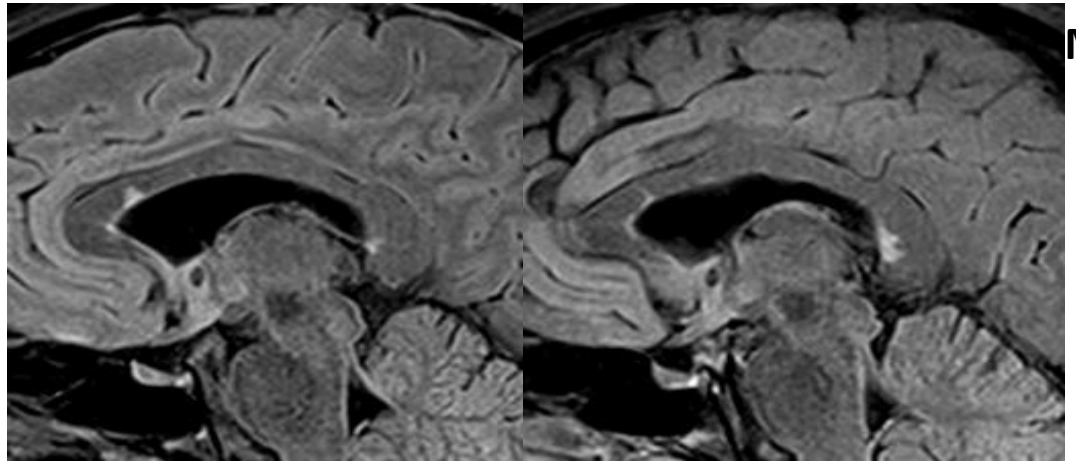


MS

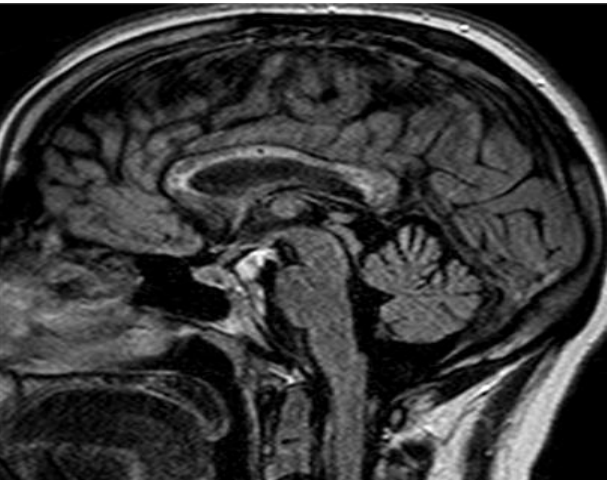


Vascular lesions

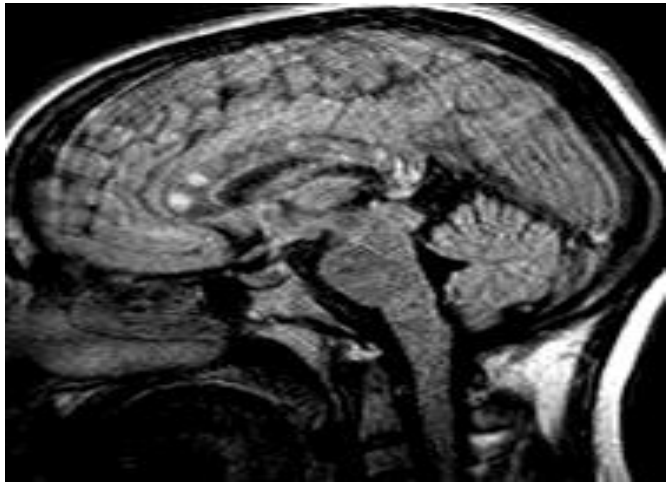
Corpus callosum involvement



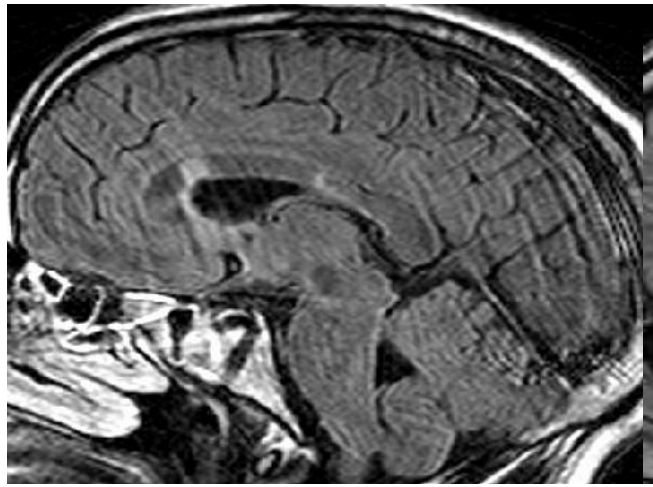
MS



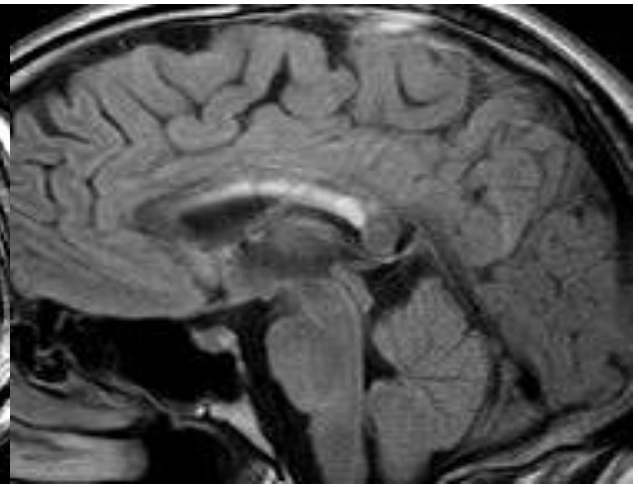
Small-vessel disease
(diabetes)



SUSAC
(100%)



CADASIL
(40%)

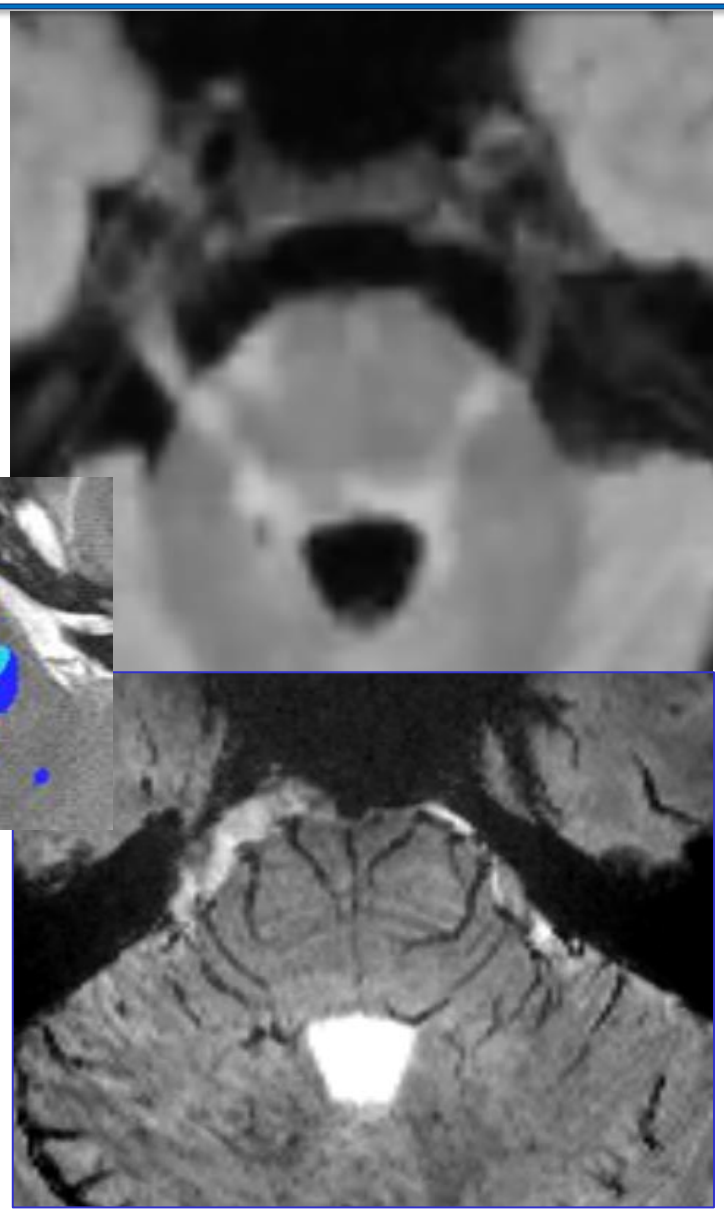


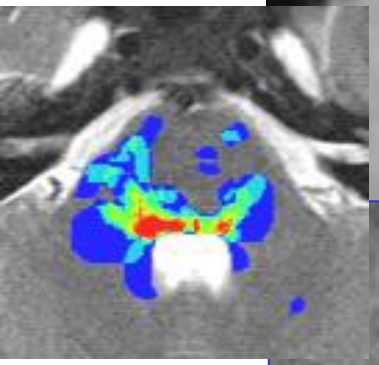
NMOSD
(30%)

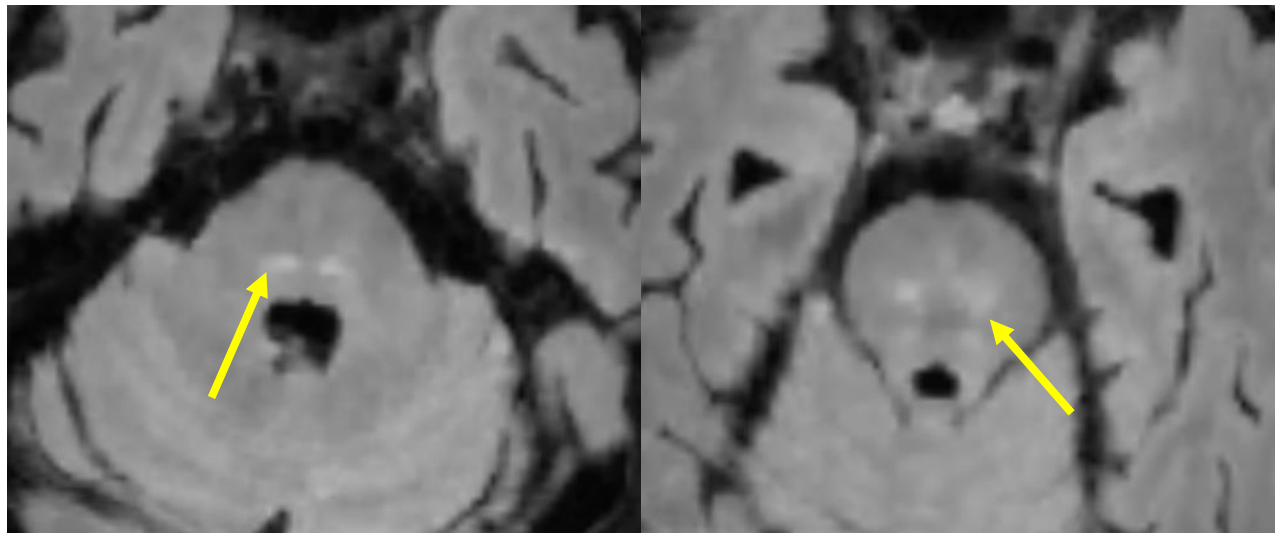
Uchino et al. Eur Radiol 2006;16:905-14; Susac et al. Neurology 2003;61:1783-7; O'Sullivan et al. Neurology 2001;56;628-34

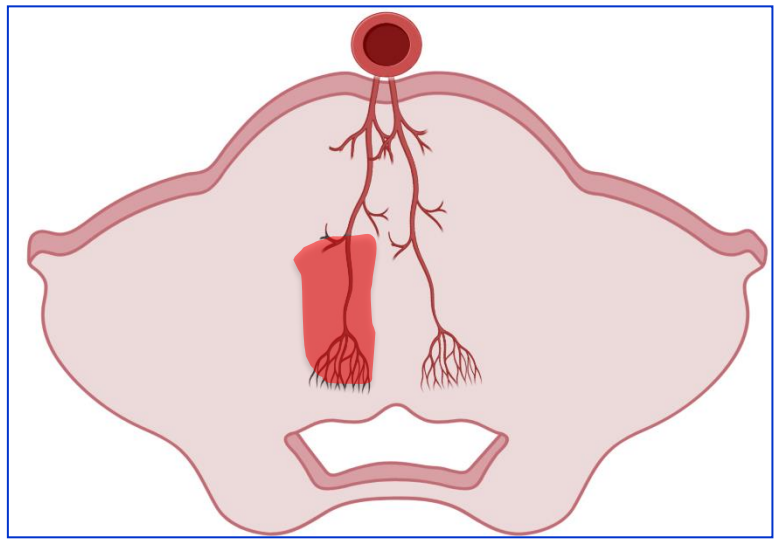
Brainstem involvement

MS







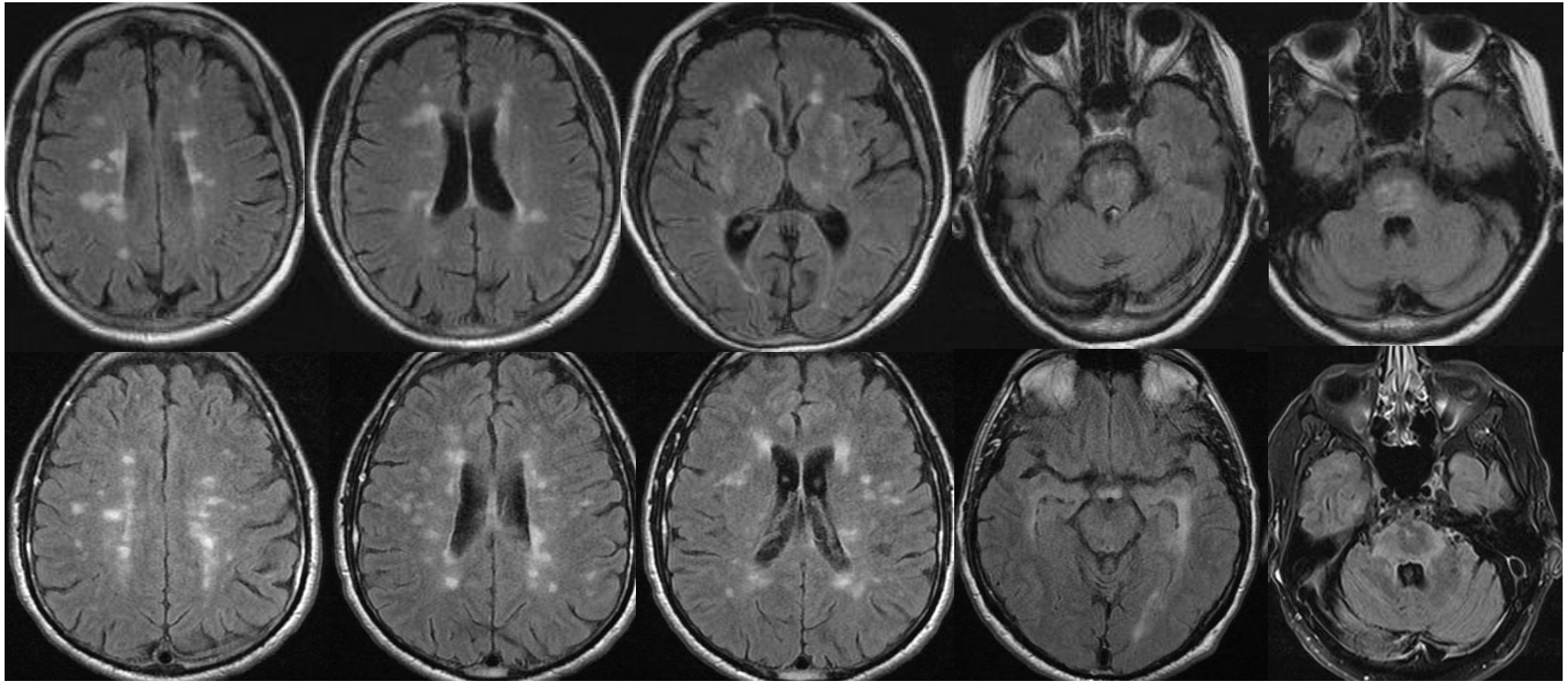


Small-vessel disease

T2 Hyperintensity of Medial Lemniscus Is an Indicator of Small-Vessel Disease

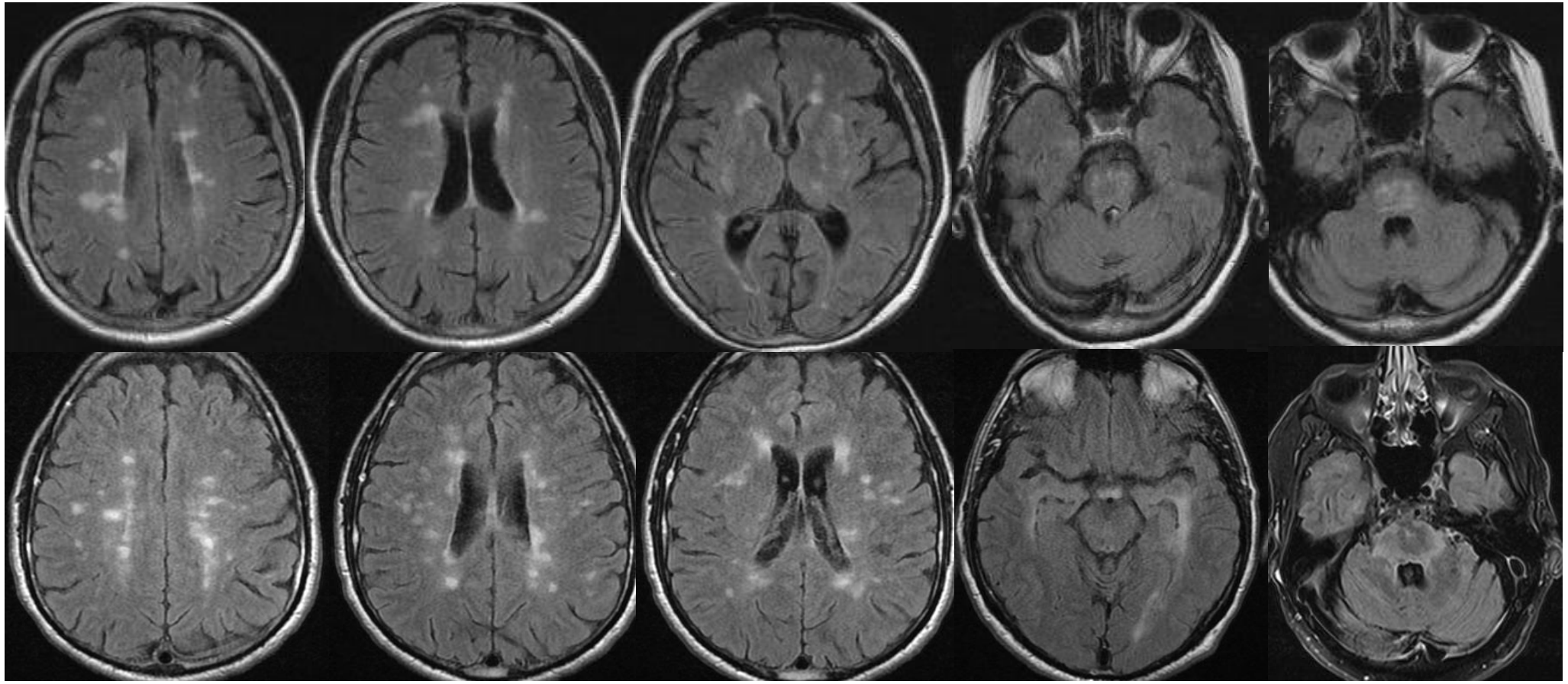
Erro et al. Eur J Neurol 2005; Erbay et al. AJR 2012

Multifocal White Matter Abnormalities



Multifocal White Matter Abnormalities

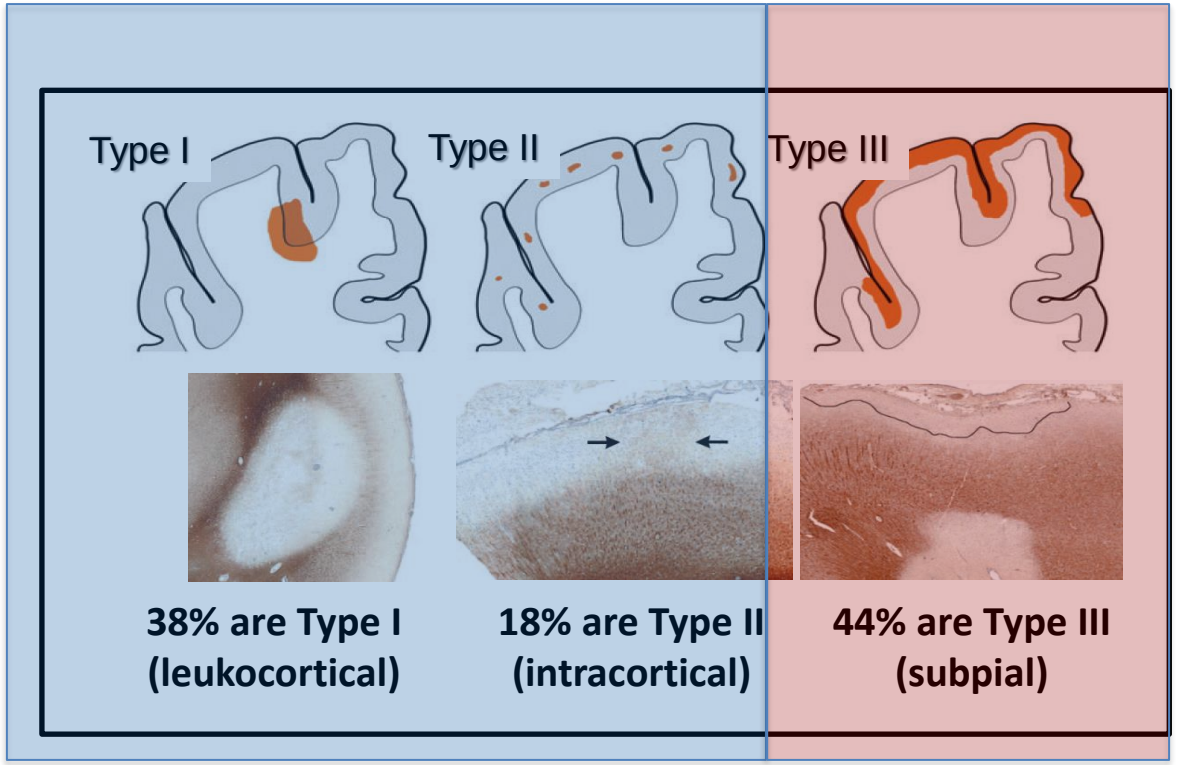
Small-vessel disease + MS



MS

Focal lesions in grey matter: 90% of MS autopsy cases show cortical demyelination

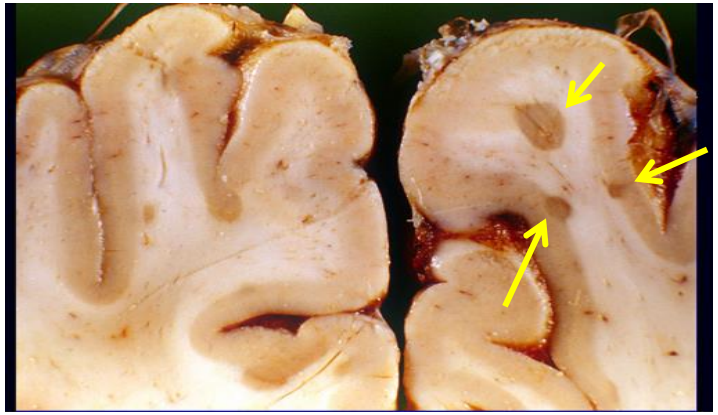
- Characterised by:
  - demyelination[1]
  - microglial activation[1]
  - often meningeal inflammation[2,3]
- Less often associated with[4]
  - immune cell influx
  - complement activation
  - BBB leakage
- Difficult to detect by MRI[5]
- Three types of cortical lesion*[6]

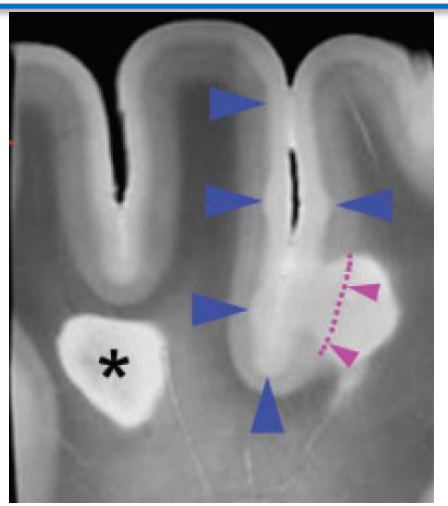


*Based on post-mortem tissue samples taken from 22 patients with MS. Leukocortical Type I lesions involve neocortex and subcortical white matter; intracortical Type II lesions are confined to the neocortex and often located around a vessel; subpial Type III lesions extend from the pial surface into the neocortex. 1. Peterson JW *et al. Ann Neurol* 2001; 2. Lucchinetti CF *et al. N Engl J Med* 2011; 3. Magliozzi R *et al. Ann Neurol* 2010; 4. Klaver R *et al. Prion* 2013; 5. Filippi M *et al. Neurology* 2010; 6. Wegner C *et al. Neurology* 2006

Cortical lesiones: type I (juxtacortical)

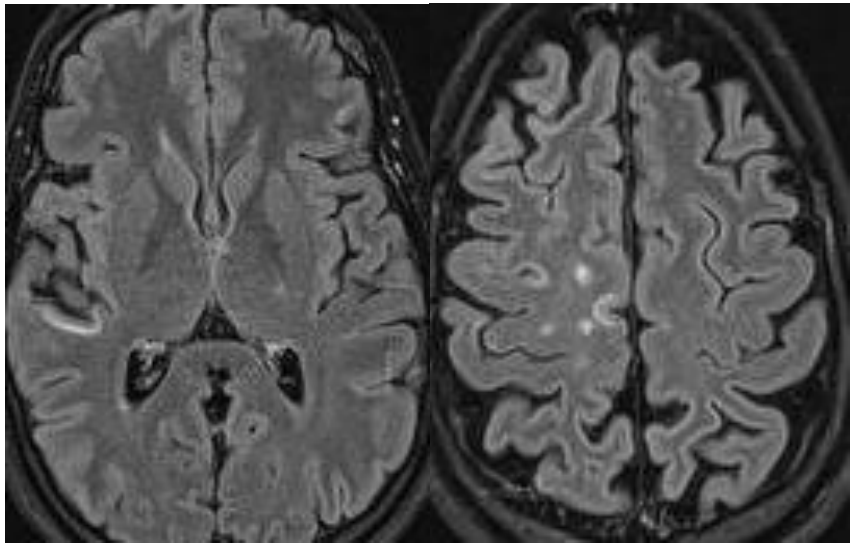
Courtesy of Dr. García-Merino

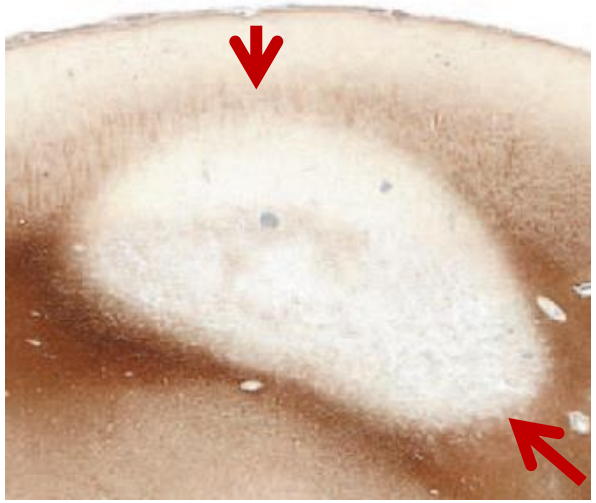




9T MRI (T2)
Schmierer et al. Brain 2010

T2-FLAIR





leukocortical lesion

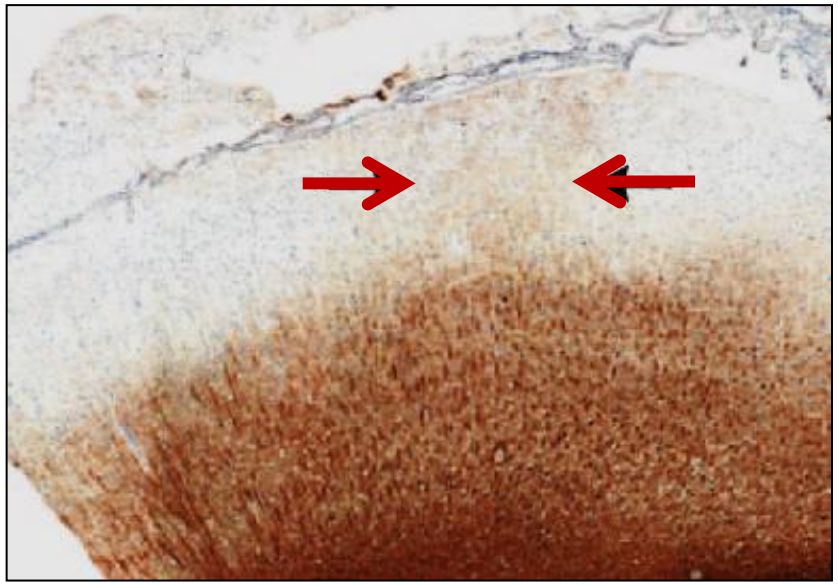
Lucchinetti et al. NEJM 2011;365:2188-97

Cortical lesiones: type II

Lesions within the cerebral cortex that do not extend to juxta-cortical white matter

- cMRI detects <10% of type II lesions (very small size)
- Improved sensitivity by using DIR or heavily 3D T1-weighted sequences

Intracortical lesion



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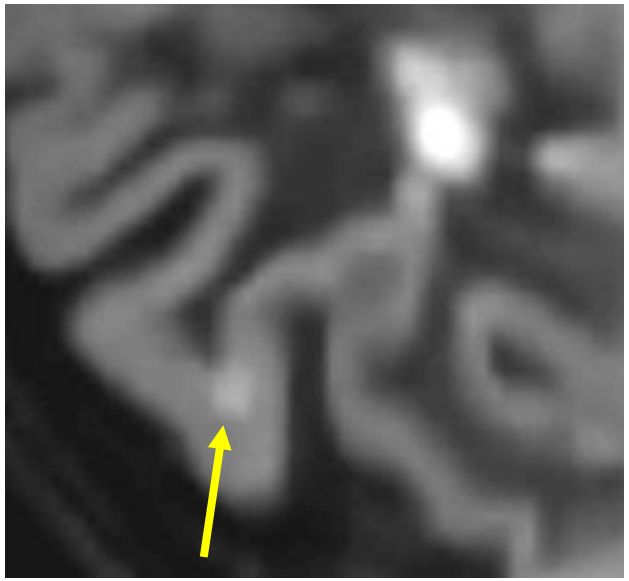
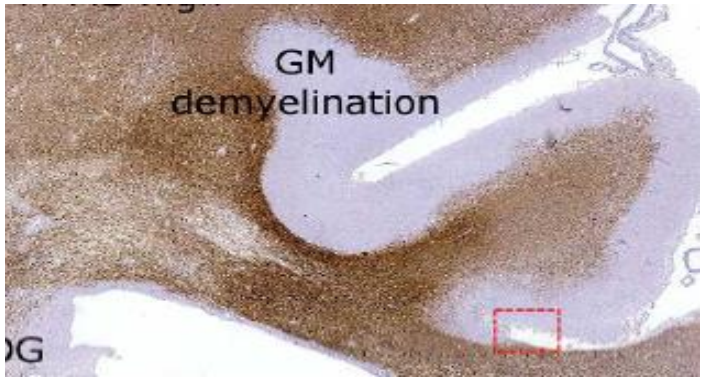
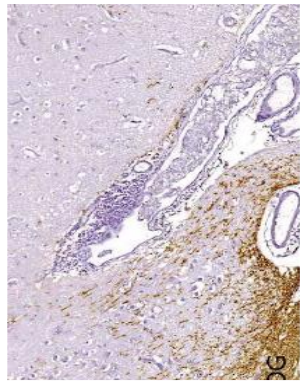


Geurts et al. J Neurol 2008; Wattjes et al. Am J Neuroradiol 2006; Geurts et al. Radiology 2005; Roosendaal et al. Mult Scler 2009

Subpial demyelination: cortical lesiones type III



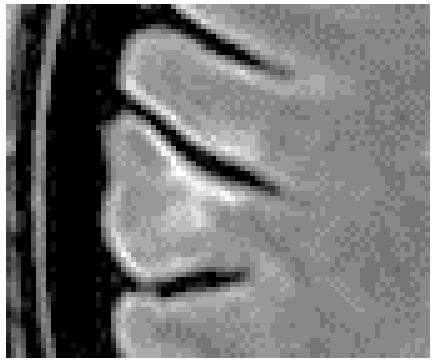
Subpial demyelination



Meningeal inflammation (B and T cells)

Lesion type	Number	Mean lesion size (mm^2)	Percentage of total demyelinated Area
1 (mixed WML/GML)	17	29.2	14.4
2	18	2.4	1.2
3	65	35.5	67.0
4	9	66.2	17.3
Intracortical lesions (2–4)	92	32.1	85.6

Bo et al. J Neuropathol Exp Neurol 2003

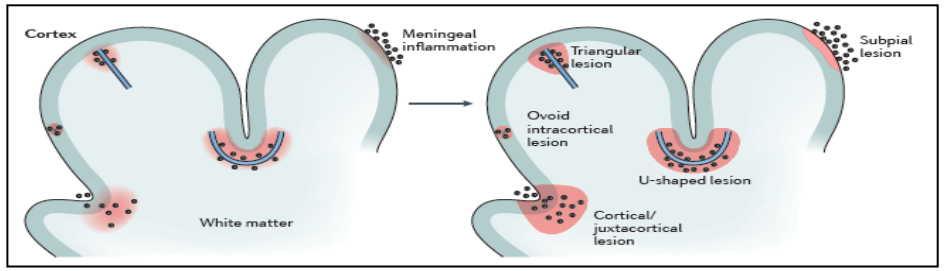


Most common cortical lesion

Affects the largest cortical area

A common appearance:

- long ribbons of subpial demyelination, often affecting several adjacent gyri
- wedge-shaped, with the basis at the surface of the brain

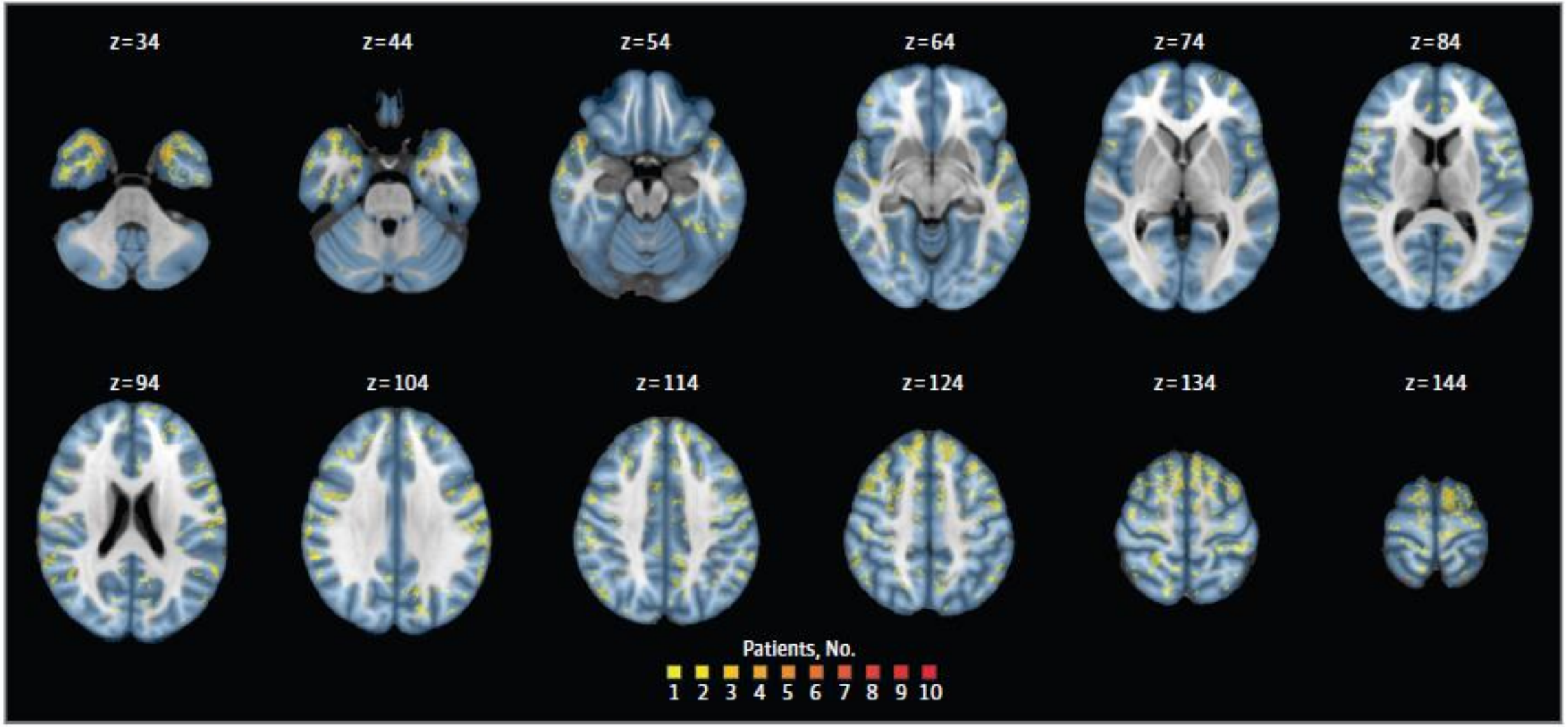


Absinta et al. Nat Rev Neurol 2016

Absinta et al. Neurology 2017; Absinta et al. Neurology 2015; Howell et al. Brain 2013; Lucchinetti et al. 2011

Cortical lesions: topography

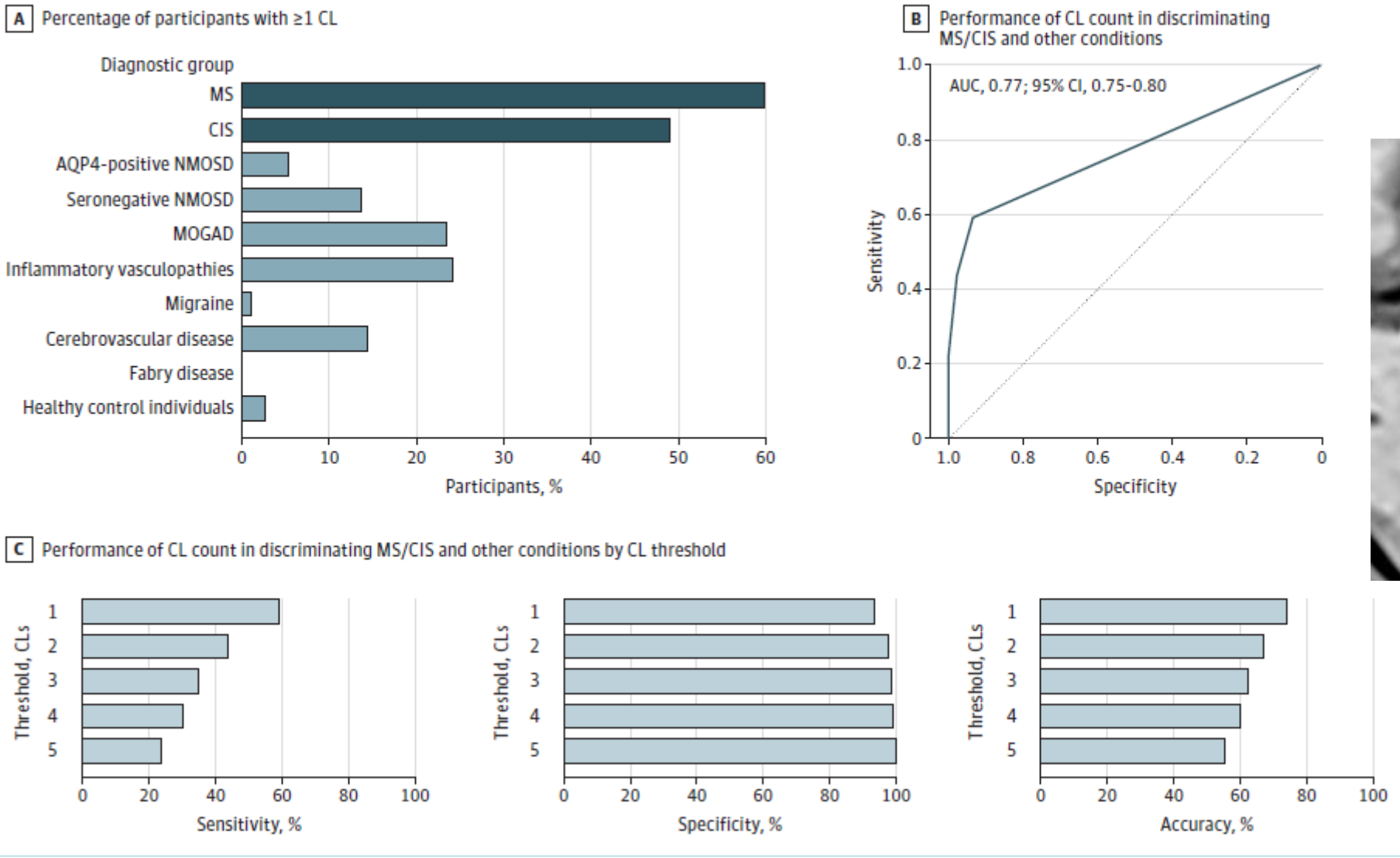
Figure 2. Cortical Lesion Probability Map in Patients With Multiple Sclerosis (MS)/Clinically Isolated Syndrome (CIS)

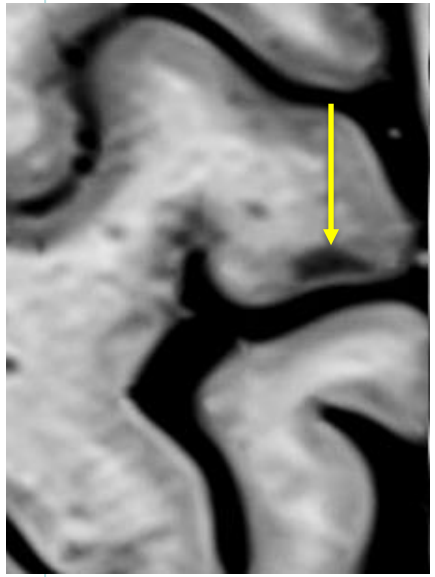


Cagol et al. JAMA Neurol 2023

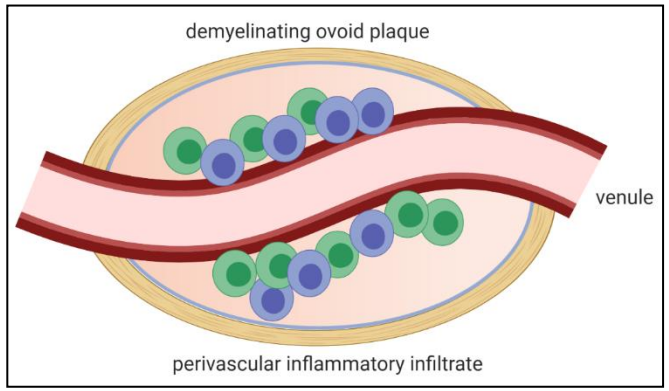
Cortical lesions: diagnostic performance

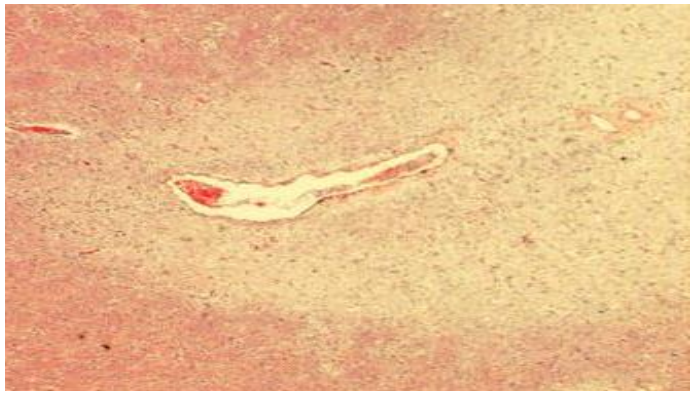
Figure 1. Cortical Lesions (CLs) for Discrimination Between Multiple Sclerosis (MS)/Clinically Isolated Syndrome (CIS) and Other Diagnoses

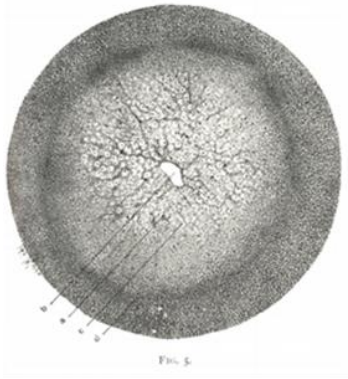




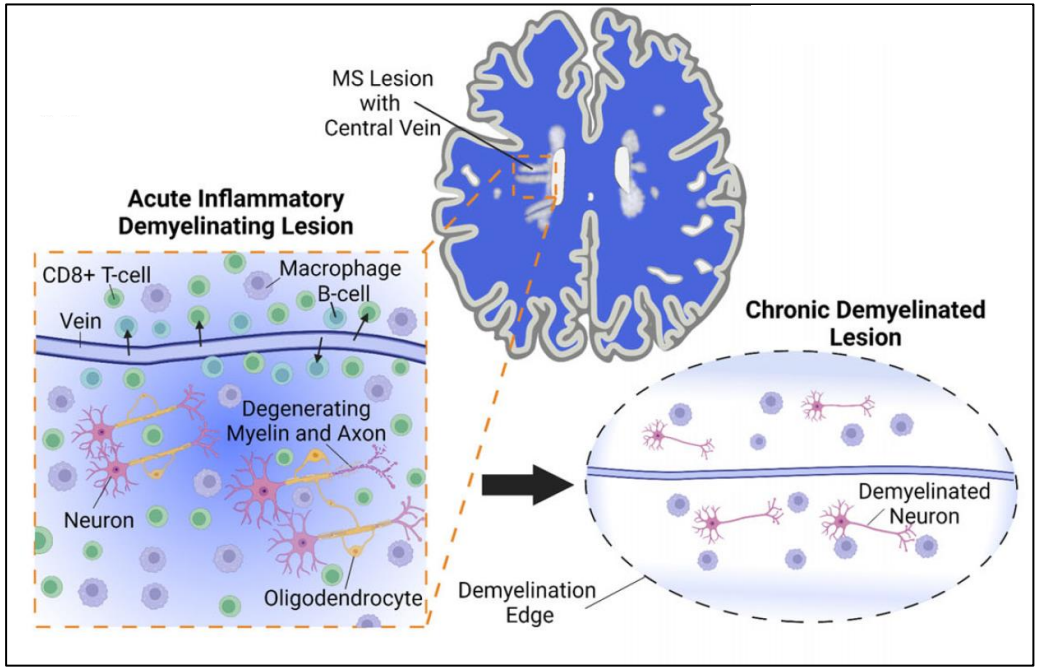
Ovoid shape: Dawson finger





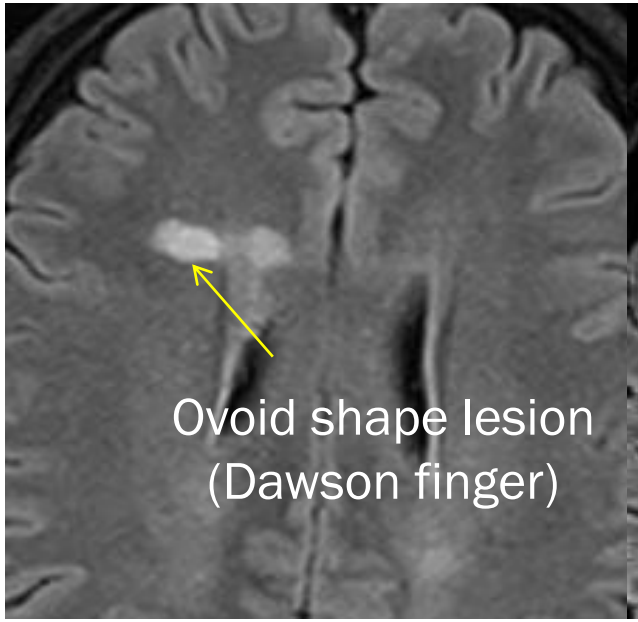


Dawson J. Trans Roy Soc Edinb 1916; 50:517-740
Horowitz et al. Am J Neuroradiol 1989;10:303-5

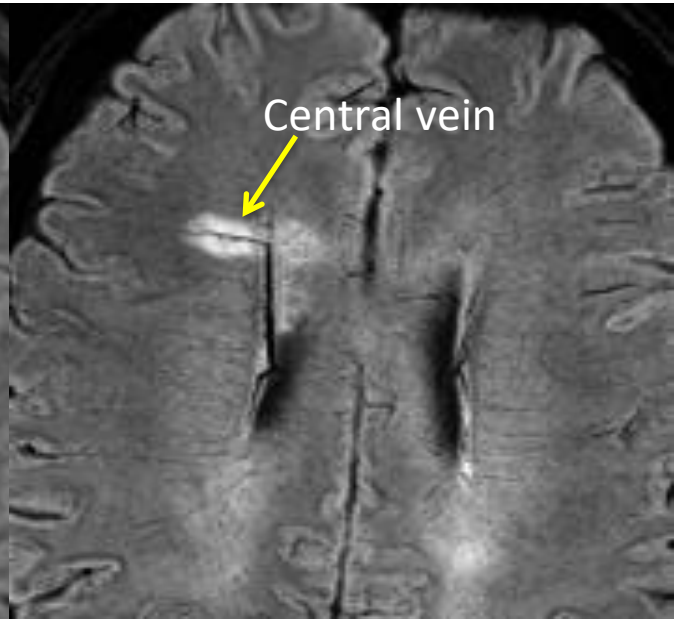


Gill et al., Eur J Immunol 2023

FLAIR

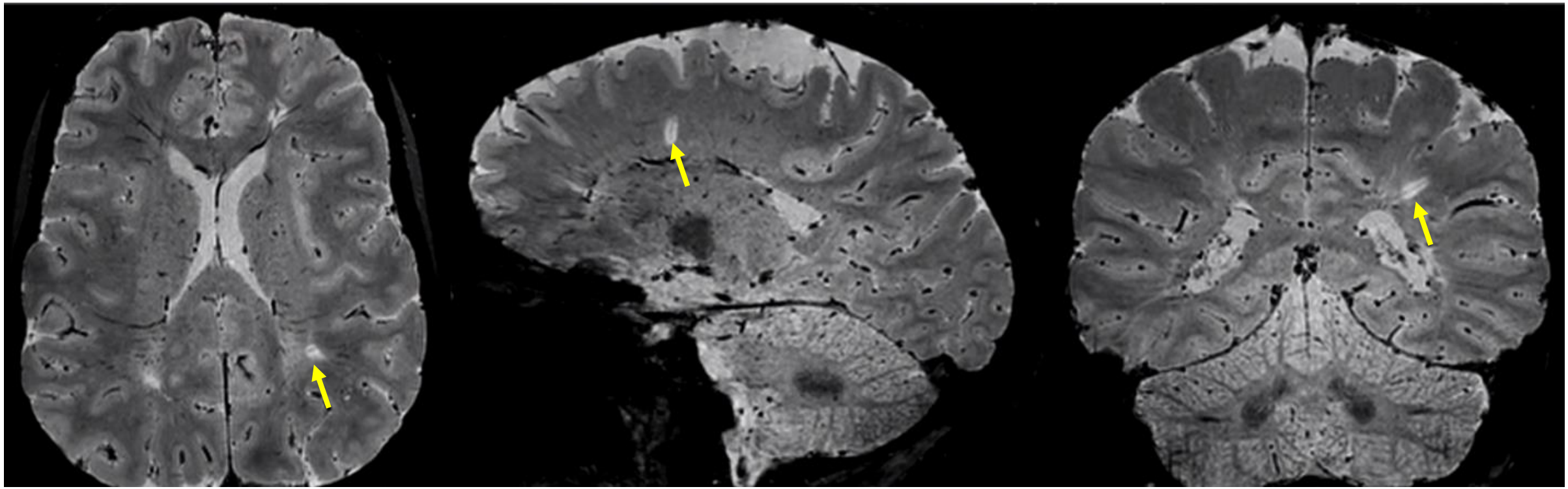


SWI (3T)



Central vein sign: 3D T2*w Segmented EPI GRE (T2*-EPI)

Sati et al. Mult Scler J 2014



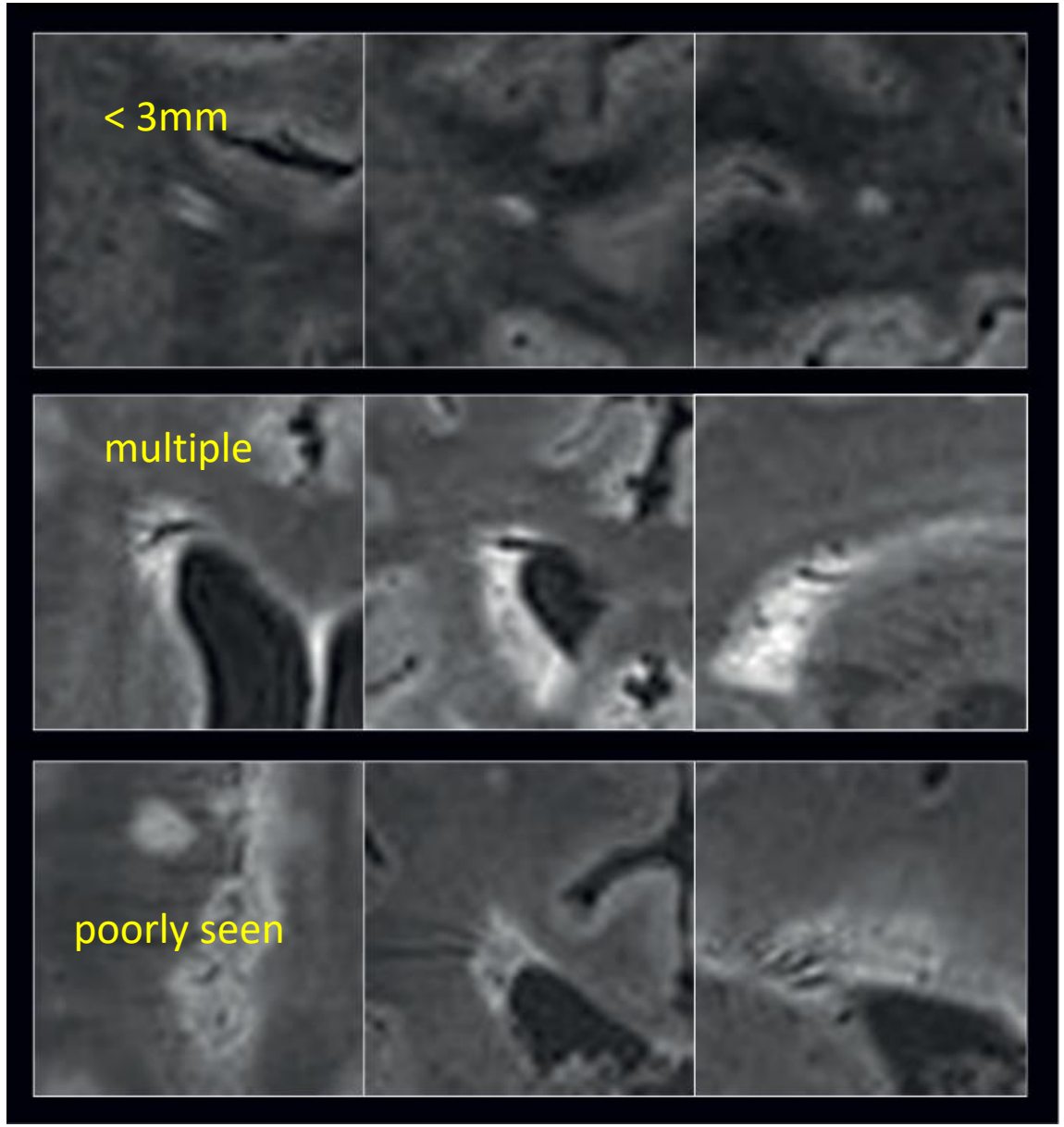
- 3T Magnet
- 650 µm isotropic voxels
- Whole brain coverage in 6 minutes

NAIMS criteria

- Thin hypointense line or small dot
- Visualized in at least two perpendicular planes (and appear as a thin line in at least one plane)
- Small apparent ven diameter (<2mm)
- Runs partially/entirely through the lesion
- Positioned centrally in the lesion

Sati et al. Nat Rev Neurol 2016

Central vein sign: 3D T2*w Segmented EPI GRE (T2*-EPI)



NAIMS exclusion criteria

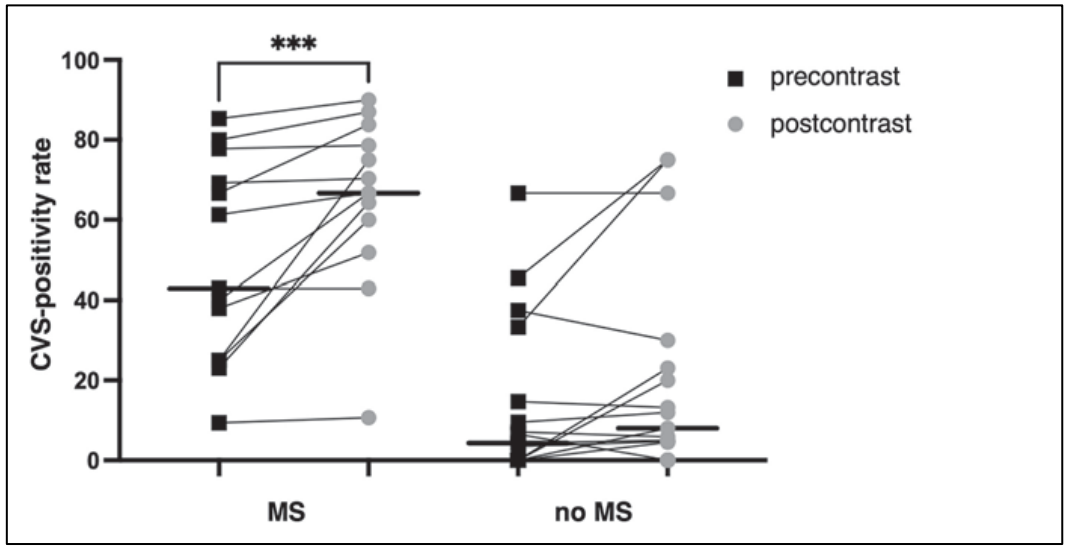
- Lesion is <3mm in diameter
- Confluent lesions
- Lesion has multiple veins
- Lesion is poorly visible

Sati et al. Nat Rev Neurol 2016

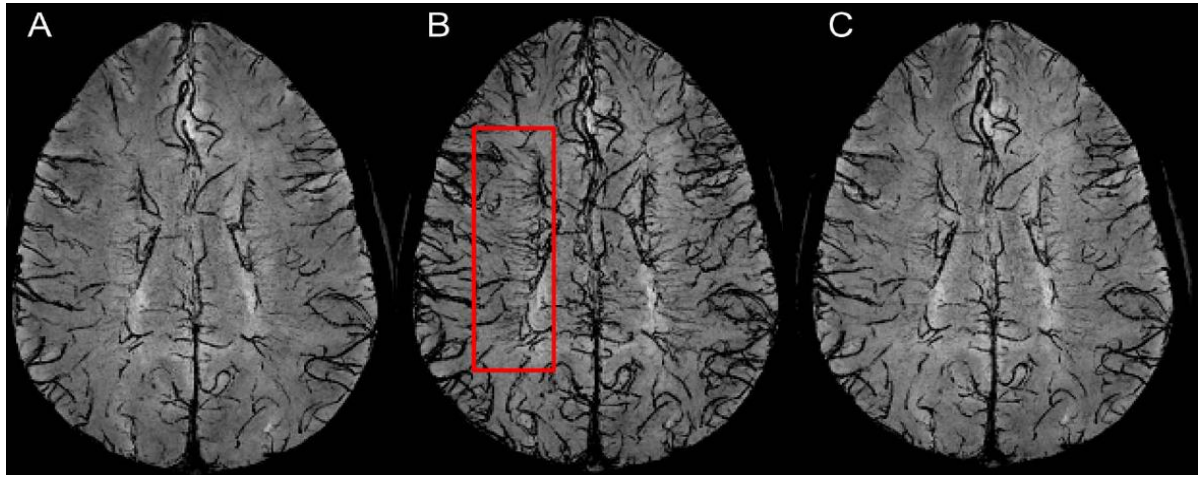
Central vein sign (CVS): effect of using GBCA

3T magnets

- Fraction of WML that were CVS-positive on pre-contrast and post-contrast images was 48% and 58% (MS) an 7% and 10% (no-MS)
- Median patient-level CVS-positivity rate on pre-contrast and post-contrast images was 43% and 67% (MS) and 4% and 8% (non-MS)



Daboul et al. AJR 2023



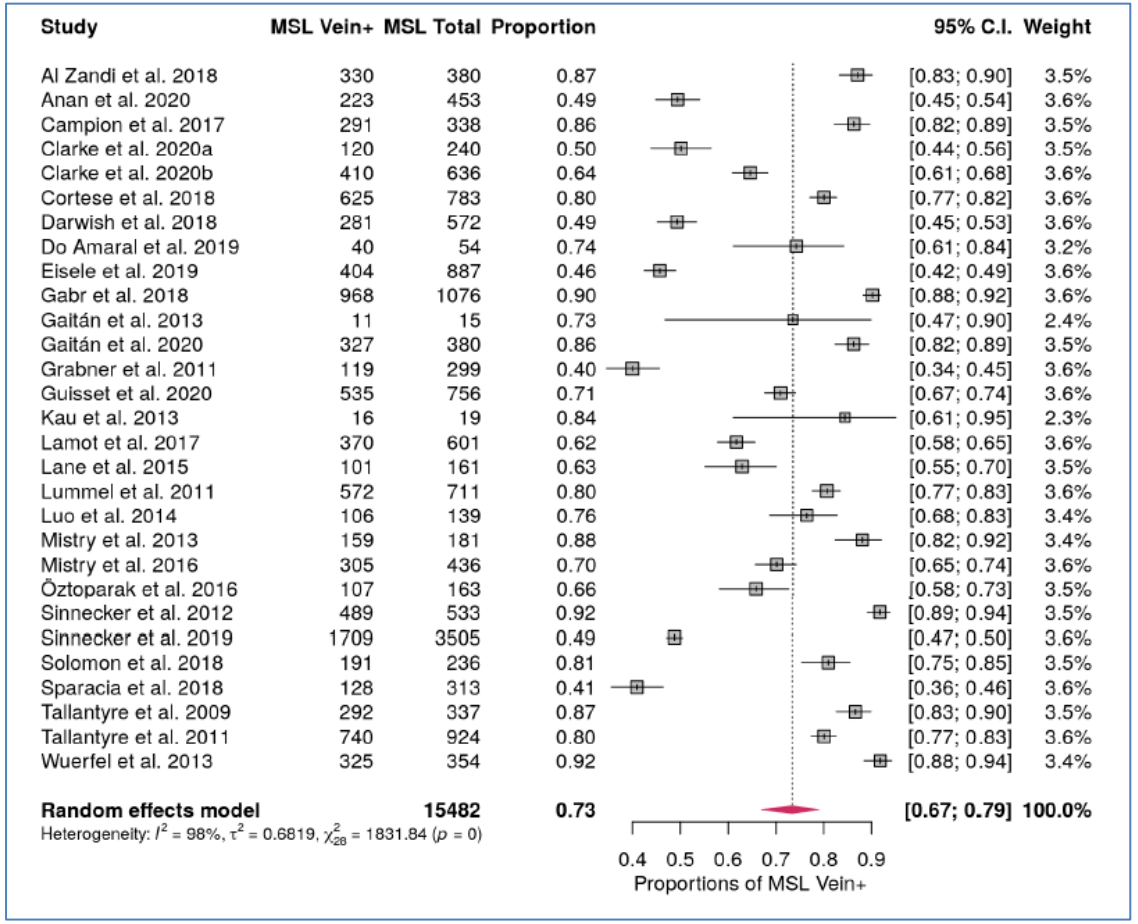
Pre-injection During injection Post-injection (15 min)

Sati et al., Mult Scler. 2014

Central vein sign (CVS): Systematic review and meta-analysis

- CVS in the MS population was **73%.**
- Diagnostic performance in MS cases, providing a pooled **specificity of 92% and a sensitivity of 95%.**
- The optimal **cut-off value was 40%** with excellent accuracy calculated by the area under the ROC (0.946).
- The 3D-EPI sequences showed both a higher pooled proportion compared to other sequences
- The 1.5 Tesla (T) scanners showed a lower (**58%**) proportion of MS lesions with a CVS compared to both 3T (**74%**) and 7T (**82%**).

Up to August 24, 2020
35 studies for quantitative analysis)

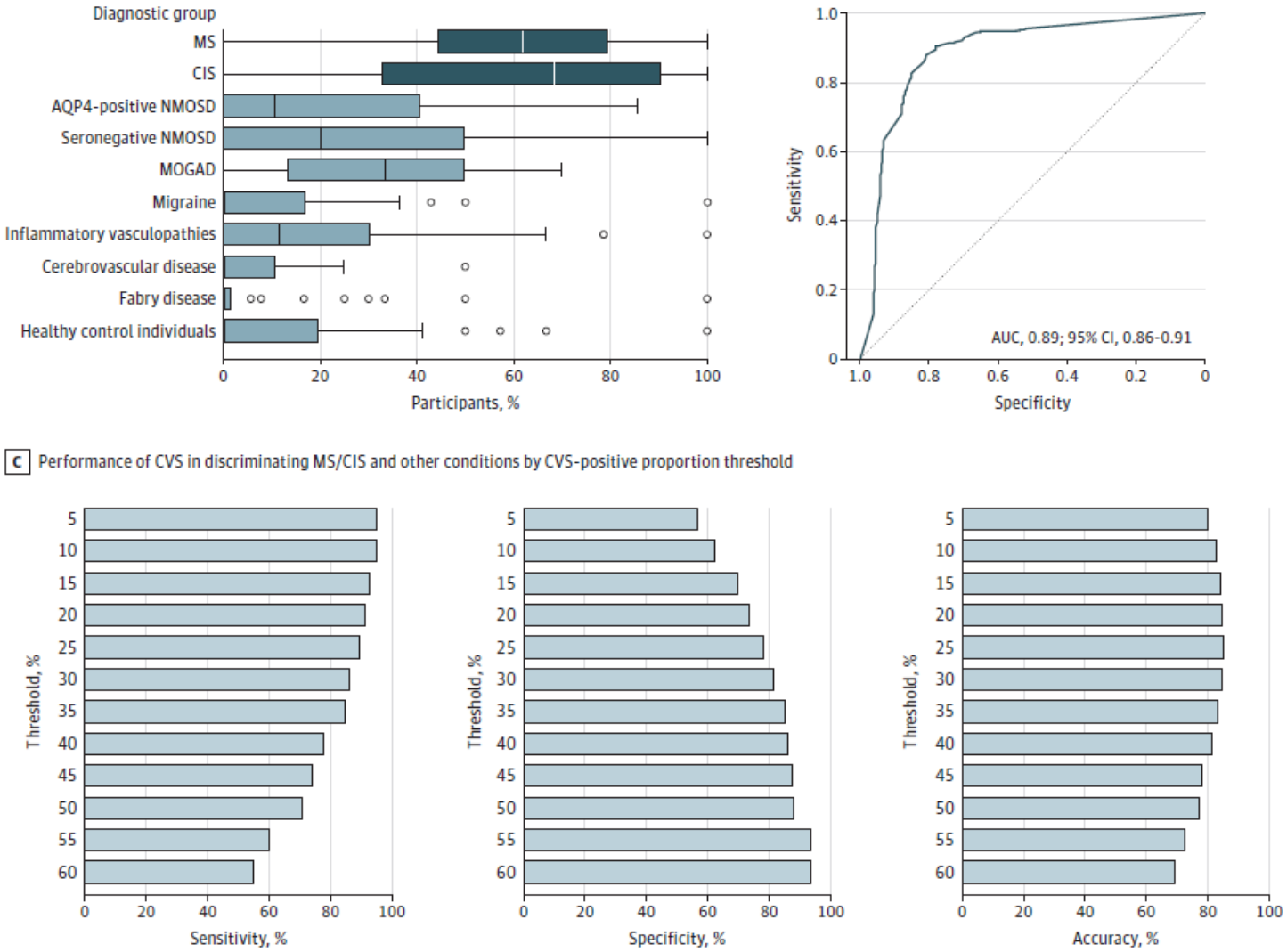


MS: multiple sclerosis; ROC: Receiver operating characteristic; EPI: echo planar imaging

Castellaro et al. Diagnostics 2020

Central vein sign: diagnostic performance

Figure 3. Central Vein Sign (CVS) for Discrimination Between Multiple Sclerosis (MS)/Clinically Isolated Syndrome (CIS) and Other Diagnoses



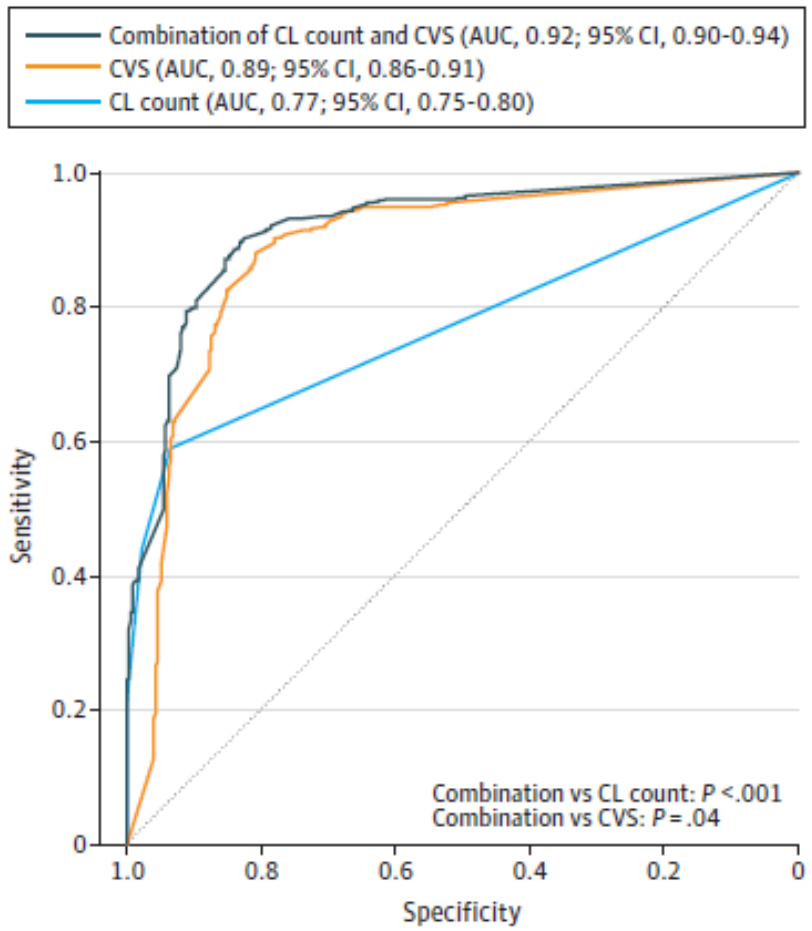
Magnims

Magnetic Resonance Imaging in Multiple Sclerosis

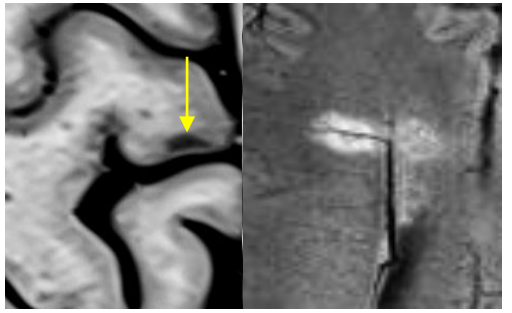
Cagol et al. JAMA Neurol 2024

Cortical lesions plus central vein sign: diagnostic performance

Figure 4. Combination of Cortical Lesions (CLs) and Central Vein Sign (CVS) for Discrimination Between Multiple Sclerosis/Clinically Isolated Syndrome and Other Diagnoses



Magnims
Magnetic Resonance Imaging in Multiple Sclerosis



In MS differential diagnosis:

- The presence of CLs on 3T MRI images provided high specificity and low sensitivity
- The 40% CVS rule yielded high specificity and moderate
- sensitivity.
- **CVS and CLs** outperformed the presence of infratentorial, periventricular, and juxtacortical WMLs in supporting the differentiation between MS/CIS and non-MS conditions.

CVS and CLs, as assessed on dedicated MRI sequences, may be valuable tools to optimize the accuracy of MS diagnosis.

Cagol et al. JAMA Neurol 2024

Central vein sign: assessment

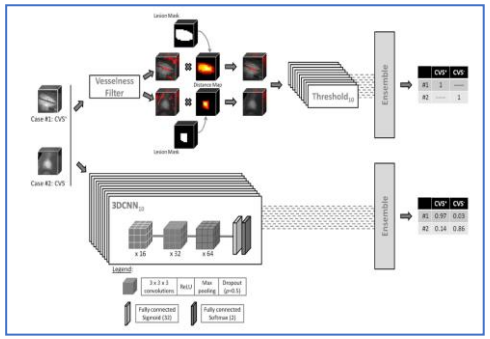
Rating methods

> 40% WML CVS positive:

- Time consuming (assess all lesions)
- High variability
- Automated tools

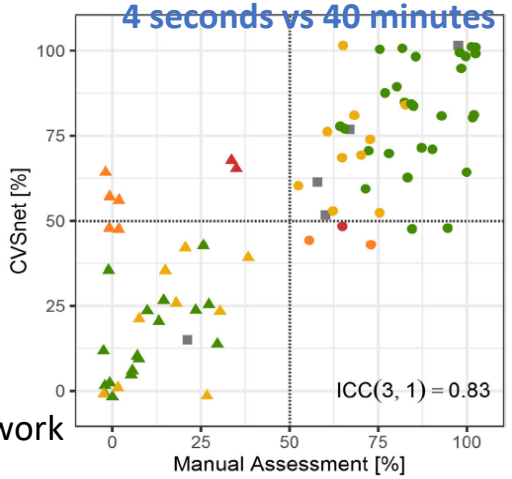
Maggi et al. NMR Biomed 2020

Automatic assessment



3D Convolutional Neural Network

4 seconds vs 40 minutes



Simplified methods

Select 3

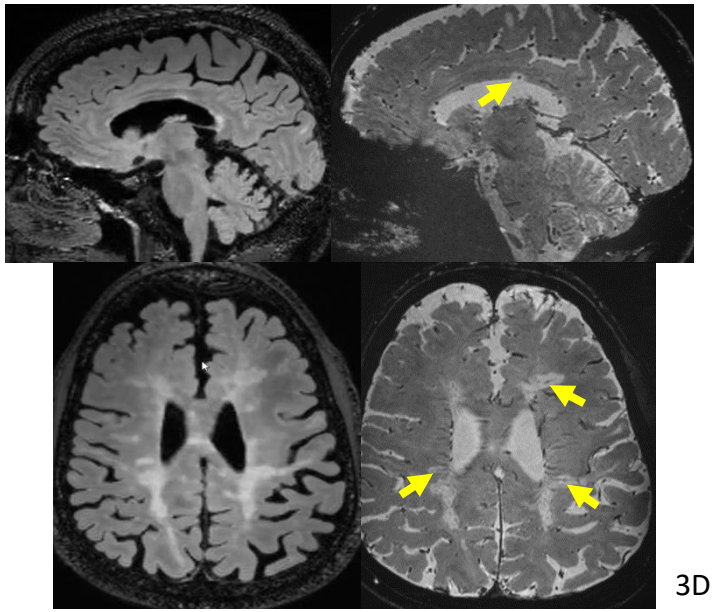
- Patients with < 3 lesions excluded
- Positive if 3/3 are CVS+ OR 2/3 are CVS+

Select 3*

- Patients with < 3 lesions excluded
- Evaluate if at least 3 lesions are CVS+

Rule of 6 / Select 6*

- Evaluate if at least 6 lesions are CVS+
- If <6 WM lesions, positive if CVS+ > CVS-
- Some studies: positive if 6/10 lesions are CVS+



3D EPI GRE with Gad

Mistry et al. JAMA Neurol 2013; Solomon et al. MSJ 2018; Dworkin AJNR 2019; Maggi et al. Ann Neurol 2018; Maggi et l. NMR Biomed 2020; Maggi et al. MSJ 2020

Central vein sign: assessment

Simplified methods: validation

Simplified methods

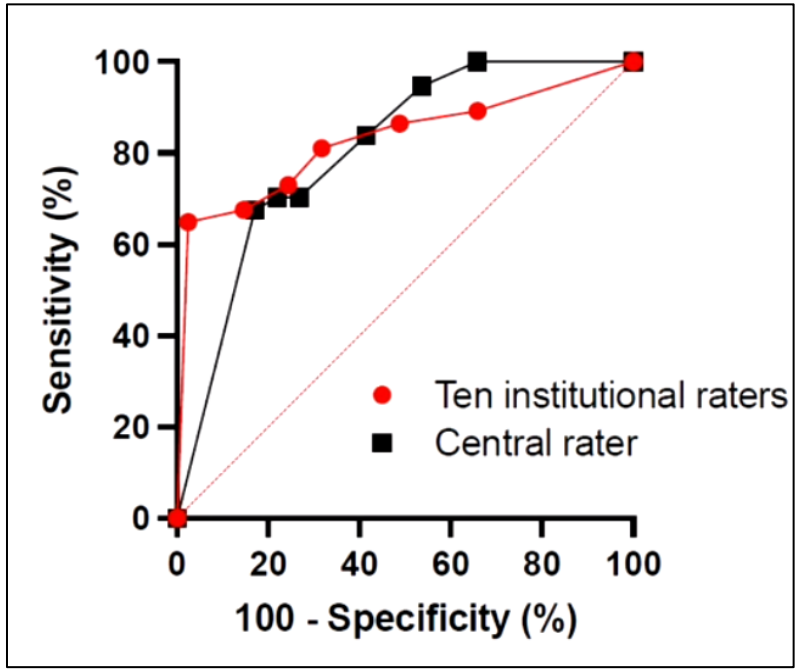
Select 3
- Patients with < 3 lesions excluded
- Positive if 3/3 are CVS+ OR 2/3 are CVS+

Select 3*
- Patients with < 3 lesions excluded
- Evaluate if at least 3 lesions are CVS+

Rule of 6 / Select 6*
- Evaluate if at least 6 lesions are CVS+
- If <6 WM lesions, positive if CVS+ > CVS-
- Some studies: positive if 6/10 lesions are CVS+

NAIMS group: N=78, 10 sites, T2*EPI

Method	Sensitivity	Specificity
40% Threshold	92%	75%
50% Threshold	89%	80%
Select-3*	81%	64%
Select-6*	65%	93%

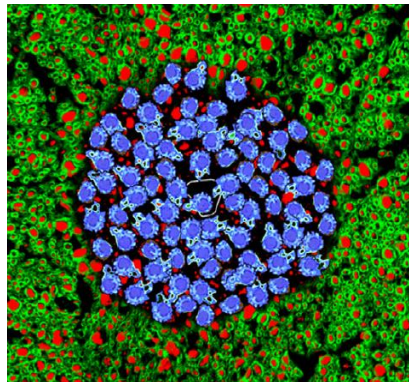


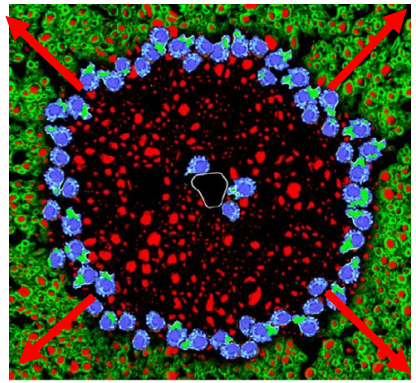
Daboul et al. Mult Scler 2024

Pathological Evolution of Inflammatory-mediated Demyelination of Brain White Matter in MS

Acute MS lesion: An early event in white matter demyelination is the entry of immune cells **(blue)** from the blood

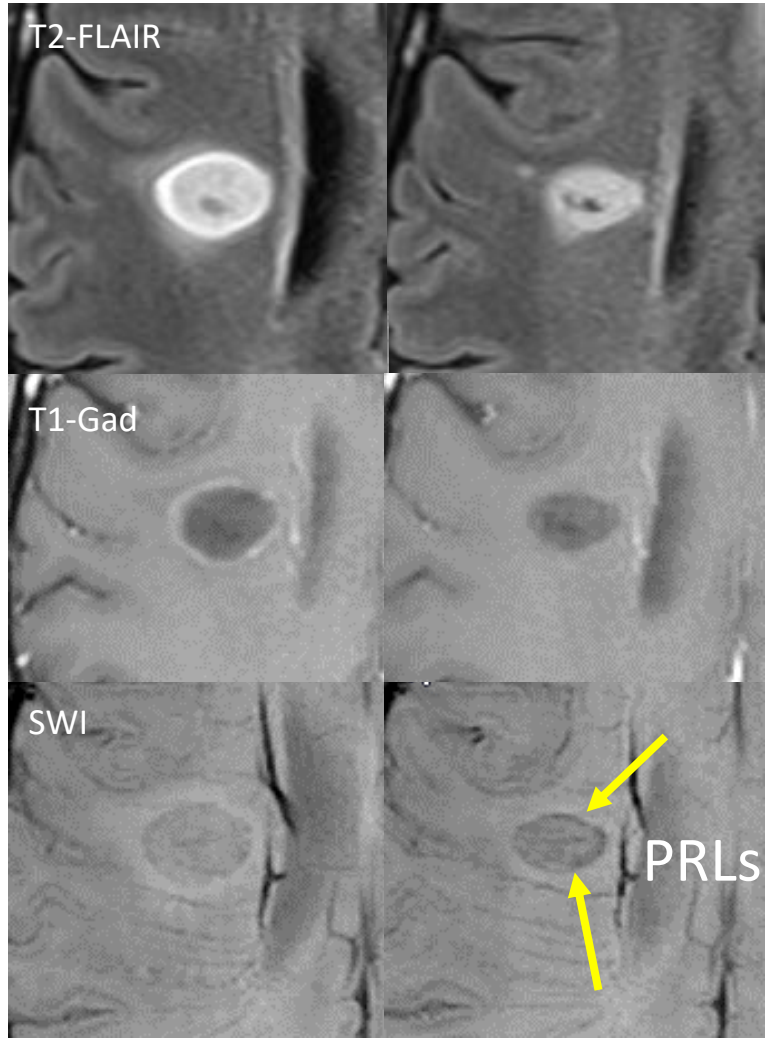
Chronic active MS lesion: With time, the immune cells disappear from the center of the MS lesion but remain at the border of the lesion where they slowly expand the area of demyelination





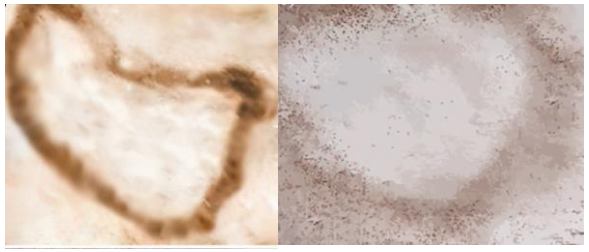
Goodin et al. Mult Scler Rel Dis 2016; 6:10-20

Rim of activated microglía containing myelin degradation products



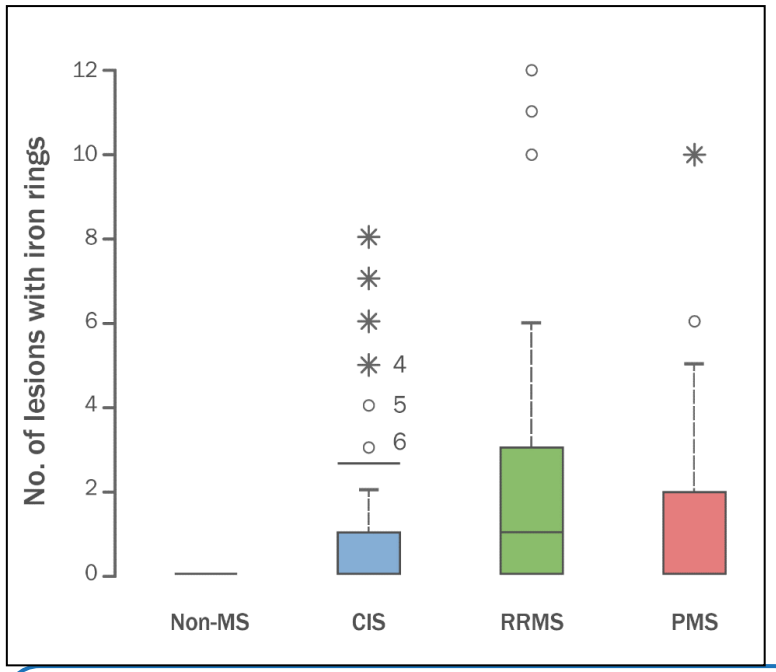
Baseline **6 months**

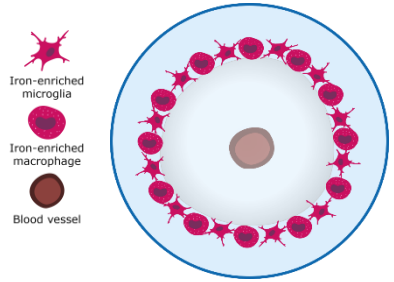
Paramagnetic rim lesions (PRLs): MS versus other CNS disorders



Iron Microglia, Macrophages

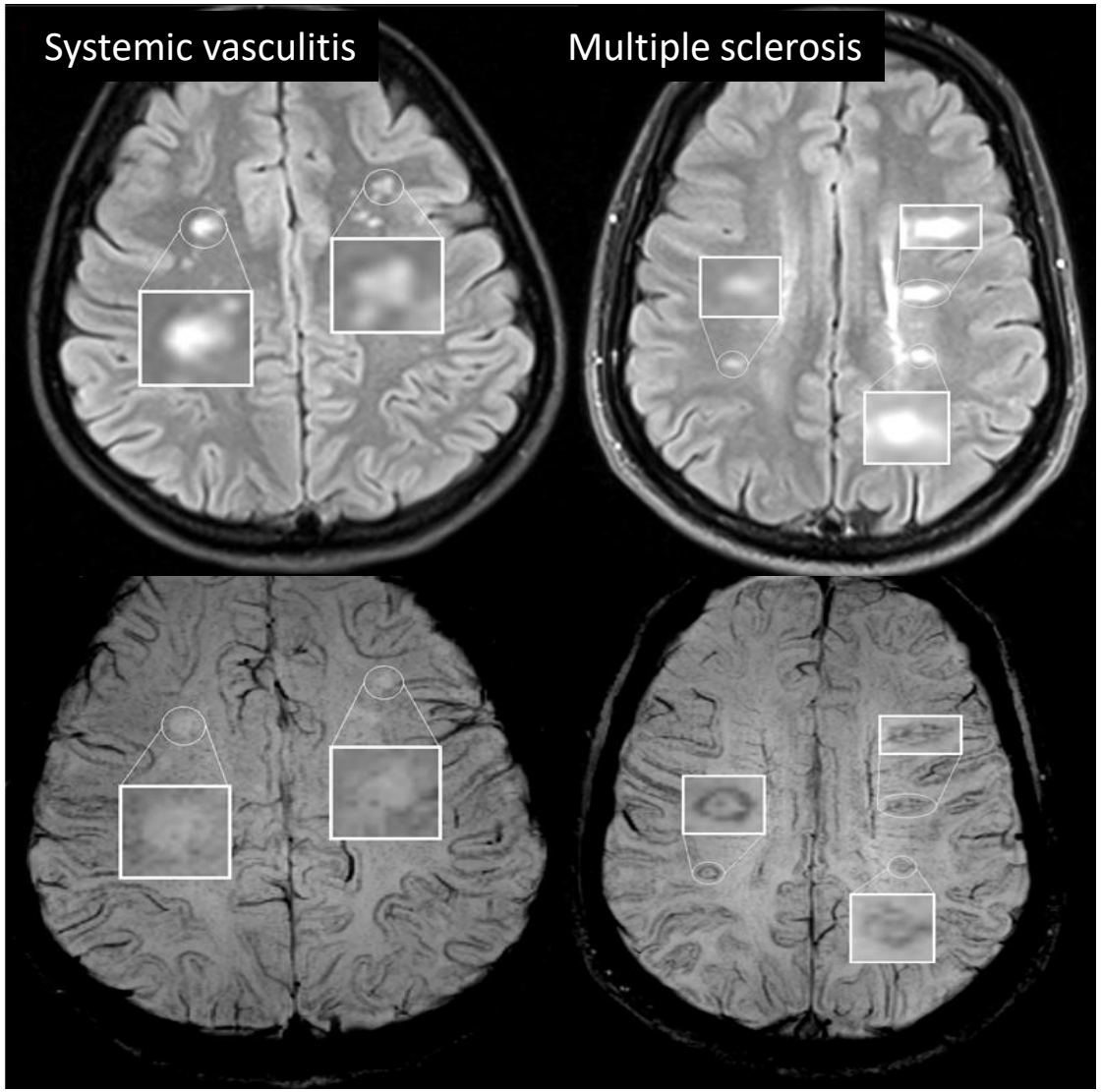
Calvi et al. Mult Scler J 2020





Maggi P et al. Neurology 2021

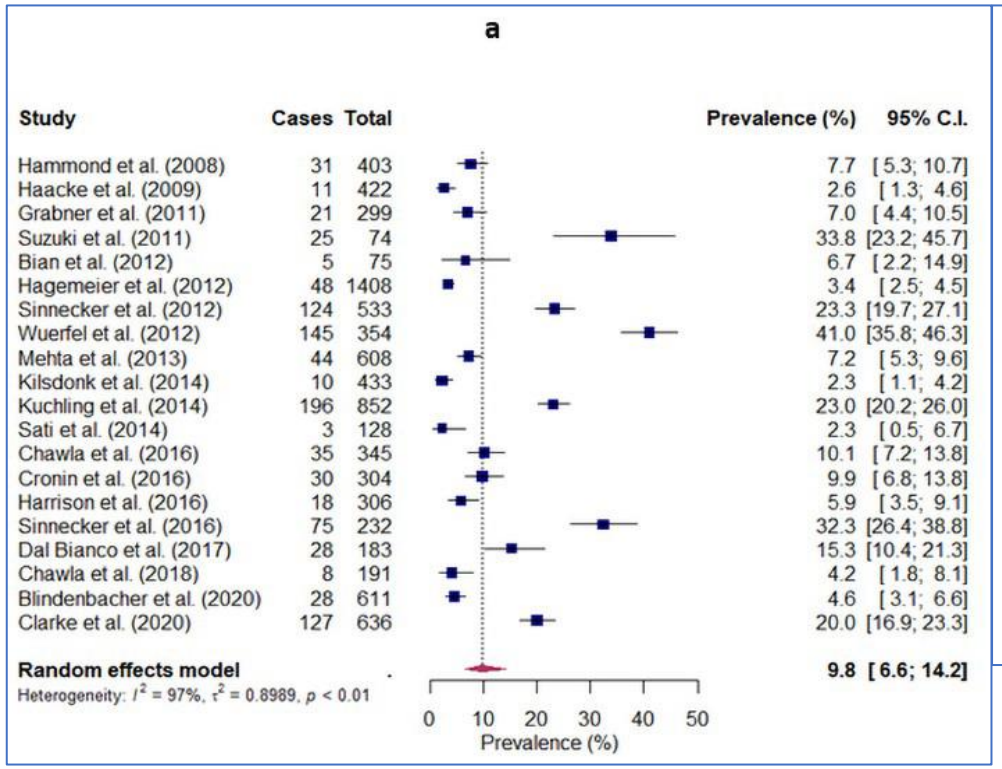
- 48% of CIS, 59% of RRMS and 39% of PMS patients had at least one lesion with an iron rim**

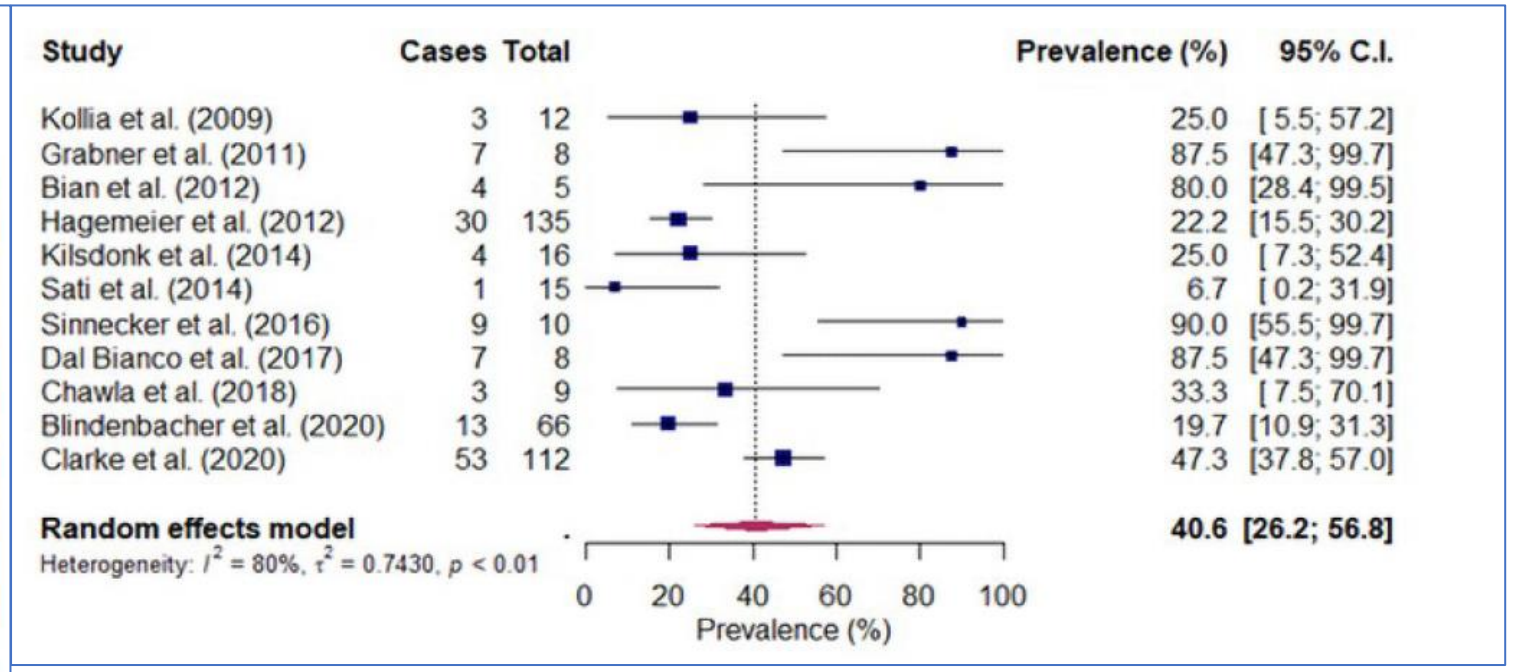


Clarke MA et al. AJNR Am J Neuroradiol. 2020

Paramagnetic rim lesions: Systematic review and Meta-analysis

29 studies comprising 1230 patients

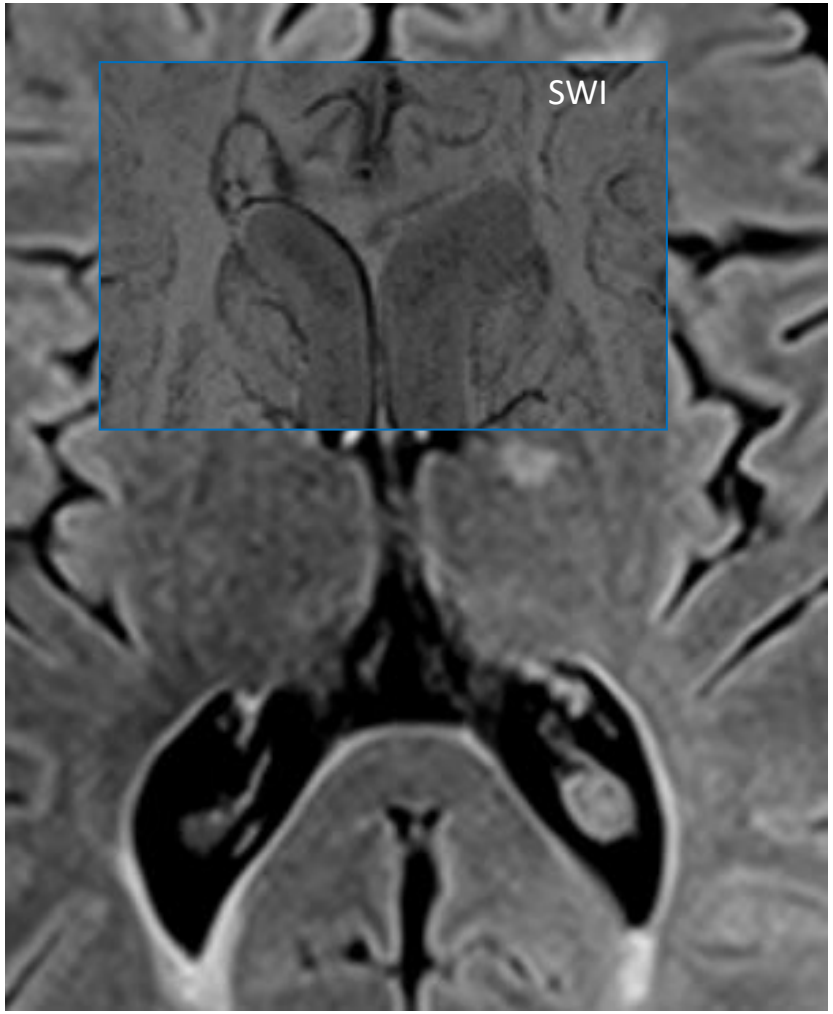




- Pooled prevalences of **9.8%** and **40.6%** for rim lesions at lesion-level and patient-level
- Significant variation across studies
- Clear guidelines should be introduced to standardize their assessment

Kwong et al. PlosOne 2021

Association of Paramagnetic Rim Lesions with Disability



Rim Category:	No Detected Rims	1–3 Rims	≥4 Rims	Statistical Analysis[a]
Demographic and Clinical Data				
No. (%)	84 (44)	66 (34)	42 (22)	NA
Clinical phenotype, No. (%)				
CIS/RR	61 (73)	46 (70)	24 (57)	Fisher 2x3 *P* = 0.20, NS
SP	16 (19)	14 (21)	10 (24)	
PP	7 (8)	6 (9)	8 (19)	
Sex, Female, No. (%)	59 (70)	45 (68)		Fisher 2x3 *P* = 0.90, NS
Age, mean (SD), years	47.3 (14.5)	47.2 (11.4)	44.3 (11.1)	ANOVA *P* = 0.40, NS
Disease duration, mean (SD), years	13.4 (12.5)	12.9 (9.9)	12.2 (8.3)	ANOVA *P* = 0.80, NS
Patients never treated, No. (%)	27/84 (32)	11/66 (17)	5/42 (12)	Fisher 2x3 *P* = 0.01
African American, No. (%)	10 (12)	12 (18)	10 (24)	Fisher 2x3 *P* = 0.20, NS
*HLA-DRB1**15:01, No. (%)	29/64 (45)	15/54 (28)	13/33 (41)	Fisher 2x3 *P* =0 .10, NS
EDSS score, median (range)	1.5 (0–7.5)*	2 (0–8)&	3 (1–7.5)*&	ANOVA *P* =0 .002
MSSS score, mean (SD)	3.0 (2.5)*	3.4 (2.5)&	4.9 (2.5) *&	ANOVA *P* <0 .001
PASAT score, mean (SD)	49.9 (8.6)*	48.4 (9.9)	44.6 (11.9)*	ANOVA *P* = 0.03
SDMT score, mean (SD)	53.4 (12.3)*	48.3 (13.4)	43.7 (17.8)*	ANOVA *P* = 0.001

*a Statistical significance at P < 0.05 level in Bonferroni post hoc analysis is referred with symbols: * for the comparison No rim vs ≥4 rims rims group; & for the comparison 1–3 rims vs ≥4 rims group.*

CIS, clinically isolated syndrome; EDSS, Expanded Disability Status Scale; HLA, human leukocyte antigen; MSSS, MS Severity Score; NS, not significant; PASAT, Paced Auditory Serial Addition Test; PP, primary progressive; RR, relapsing-remitting; SDMT, Symbol Digit Modalities Test; SP, secondary progressive.

Modified from Absinta M et al. JAMA Neurol. doi:10.1001/jamaneurol.2019.2399.

- **Over 50% of MS patients have at least one PRL**
- **WM rarefaction occurs at the paramagnetic lesion's edge**
- **Higher number of PRLs correlates with:**
  - More aggressive disease
  - More severe cognitive decline and disability at a younger age
  - Lower brain volume

Absinta et al. JAMA Neurol 2019; Absinta et al. J Clin Invest 2016; Lassmann et al. Front Neuroimmunol 2019

MS diagnosis: McDonald 2017 criteria

Dissemination in space (DIS)

- **≥1 T2 lesion* in 2 out of 4 regions of the CNS**
  - Periventricular
  - Juxtacortical
  - Infratentorial
  - Spinal cord

Dissemination in time (DIT)

- Simultaneous presence of Gd+ and non-enhancing lesions at any time
- New T2 and/or Gd+ lesion on follow-up MRI
  - Compared to reference (baseline) MRI
- Demonstration of DIS and presence of CSF specific oligoclonal bands

CNS= central nervous system; Gd=gadolinium, CSF=cerebrospinal fluid

*Gd not needed for demonstration of DIS

Thompson AJ et al. Lancet Neurol 2018

MS Diagnostic Criteria 2023 (in preparation)

Proposed revisions

- **DIT** is not longer needed for diagnosis
- Need for paraclinical evidence to diagnose MS
- **Optic nerve** may serve as a fifth topography
- Updated DIS criteria
- Addition of **CVS** and **PRLs** as optional paraclinical tools for diagnosis in certain situations
- **RIS is MS** in specific situations
- More strict features for confirming diagnosis in individuals over 50 years, or with headache disorders (including migraine), or with vascular disorders
- Laboratory tests (anti-MOG ab) for confirming diagnosis in children and adolescents
- Additional imaging features for PPMS diagnosis
- kFLCs as another tool to support diagnosis

2023 McDonald Criteria Review
29 Nov-2 Dec 2023
Barcelona, ES

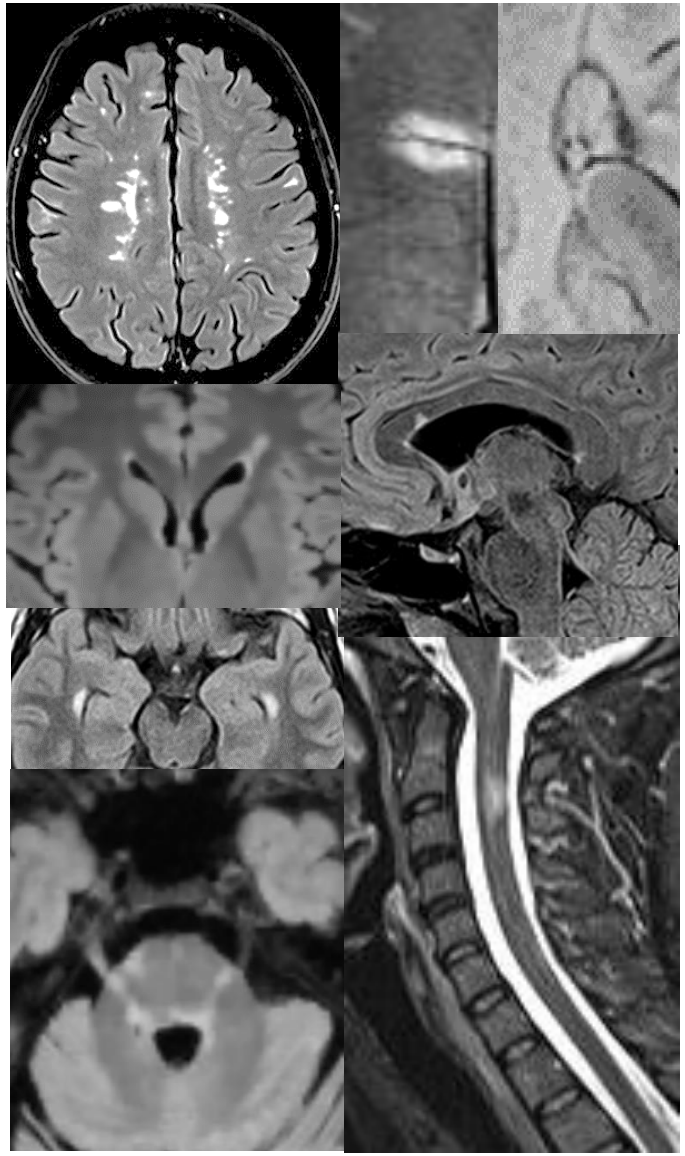
An Initiative of the International Advisory Committee on Clinical Trials in MS

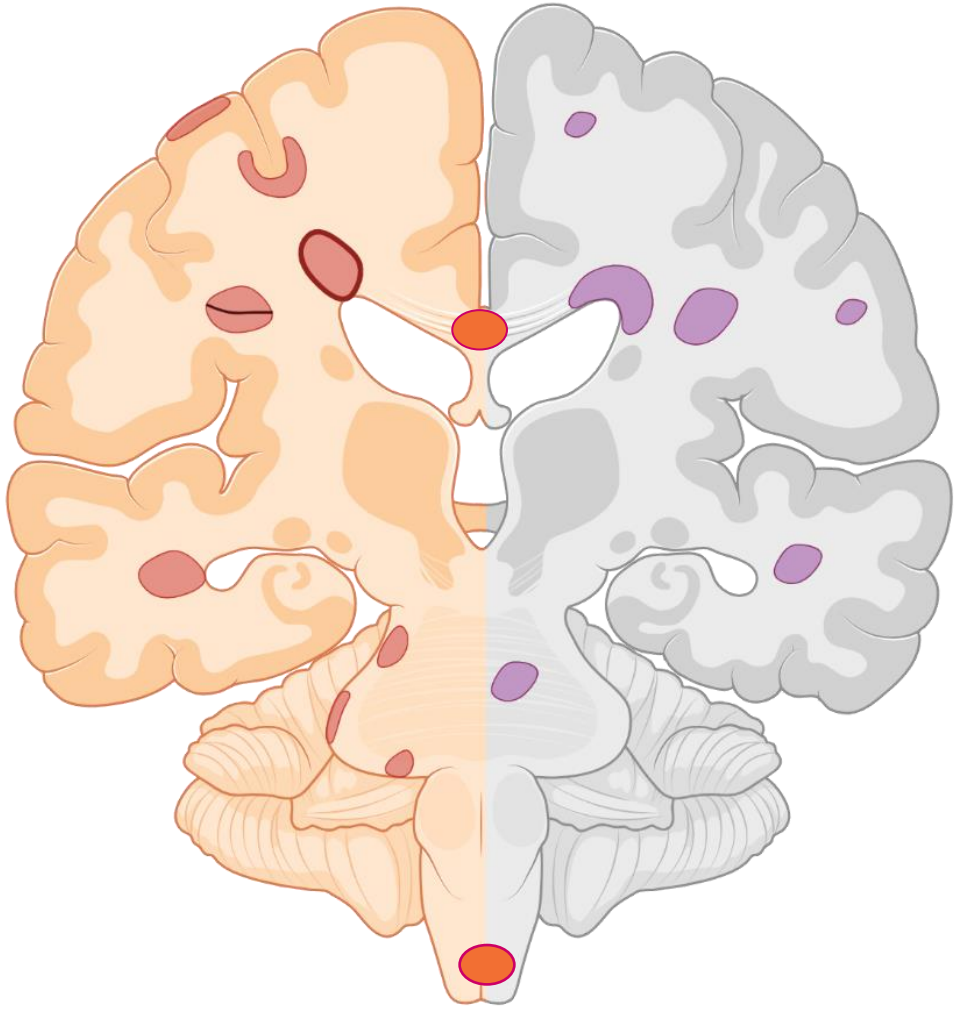
2023 McDonald Diagnostic Criteria Review Meeting
Barcelona, Spain

International Advisory Committee on Clinical Trials in MS | ECTRIMS | MS National Multiple Sclerosis Society

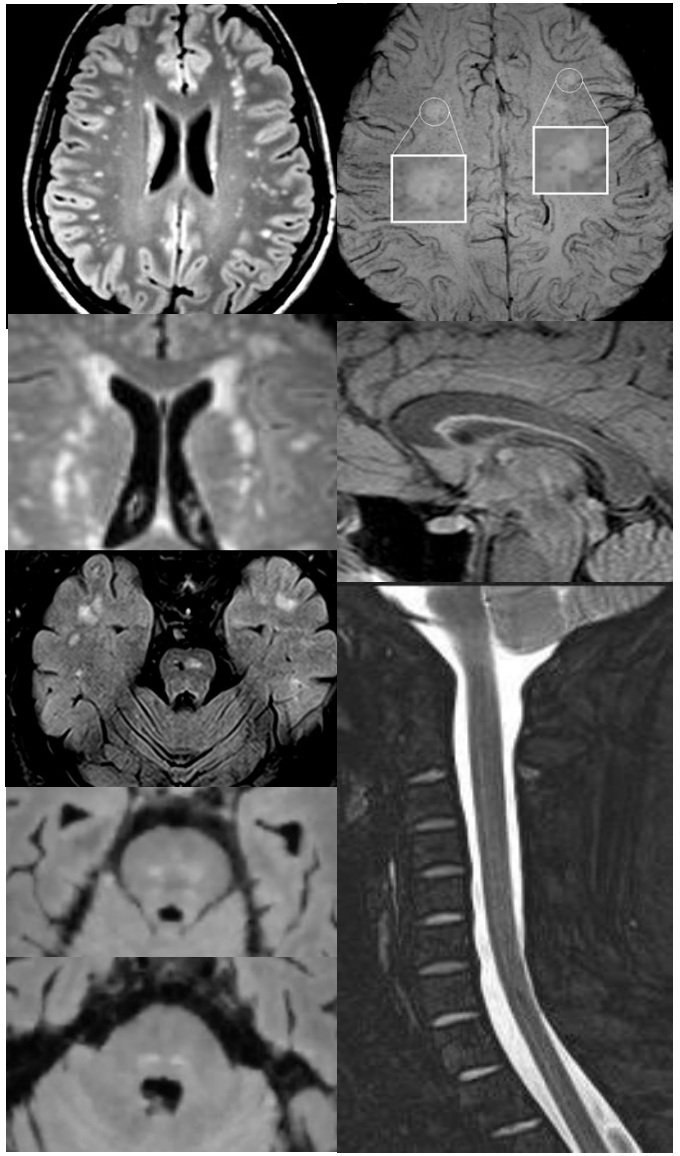
Typical imaging features

MS





SVD



Summary

- Wide variety of causes may present with multifocal white matter lesions
- MRI is the preferred imaging technique for diagnostic workup
- Radiological interpretation with demographic, clinical history, and lab findings (work together radiologists and neurologists)
- Standardized brain (spinal cord) MRI protocol
- Comprehensive checklist for evaluation of white matter spots is crucial
- Spinal cord and susceptibility-based imaging (CVS, PRLs) improve diagnostic specificity