Vall d'Hebron Hospital

IX Congresso da SPNR
XLII Reunión Anual de la SENR
Lisboa
Parque das Nações
Escola Superior de Tecnologia da Saúde de Lisboa

Institut Català de la Salut
Generalitat de Catalunya Departament de Salut

"Use of brain MRI for differential diagnosis in multiple sclerosis"

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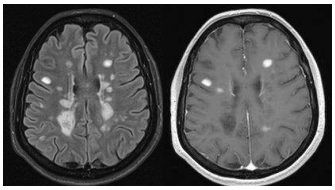
Conventional MRI measures T2 and CE T1-WI

T2-weighted



Post-contrast T1-weighted

- Highly sensitive for detecting MS plaques
- Provide quantitative assessment of inflammatory activity and lesion load
- Most important paraclinical tool for diagnosing and monitoring MS

Uses of MRI in Multiple Sclerosis

CIS patients

- **Diagnosis, prognosis (early conversion, frequency/severity of relapses, disability progression)**

Multiple sclerosis

- **Inflammation: disease activity, monitoring , prognosis, predicting treatment response**
- **Neurodegeneration: prognosis, predicting treatment response, neuroprotective effect**

Clinical trials

- **Stratifying study populations**
- **Primary endpoint (phase II clinical trials)**
- **Secondary endpoint (phase III clinical trials)**

Vall d'Hebron

Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Chris H. Polman, MD, PhD,[1] Stephen C. Reingold, PhD,[2] Brenda Banwell, MD,[3] Michel Clanet, MD,[4] Jeffrey A. Cohen, MD,[5] Massimo Filippi, MD,[6] Kazuo Fujihara, MD,[7] Eva Havrdova, MD, PhD,[8] Michael Hutchinson, MD,[9] Ludwig Kappos, MD,[10] Fred D. Lublin, MD,[11] Xavier Montalban, MD,[12] Paul O'Connor, MD,[13] Magnhild Sandberg-Wollheim, MD, PhD,[14] Alan J. Thompson, MD,[15] Emmanuelle Waubant, MD, PhD,[16] Brian Weinshenker, MD,[17] and Jerry S. Wolinsky, MD[18]

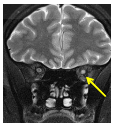
New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single scan. These revisions simplify the Criteria, preserve their diagnostic sensitivity and specificity, address their applicability across populations, and may allow earlier diagnosis and more uniform and widespread use.

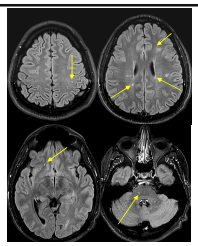
ANN NEUROL 2011;69:292–302

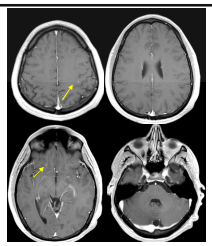
DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:	DIT Can Be Demonstrated by:
Periventricular	1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI
Juxtacortical	
Infratentorial	2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time
Spinal cord[b]	

Based on Swanton et al 2006, 2007.[22,27]
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.

29 year-old woman with unilateral optic neuritis







Clinical threshold

April 2010

Brain MR

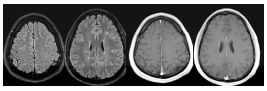
2010 McDonald criteria

Early diagnosis of MS with a single contrast-enhanced brain MRI

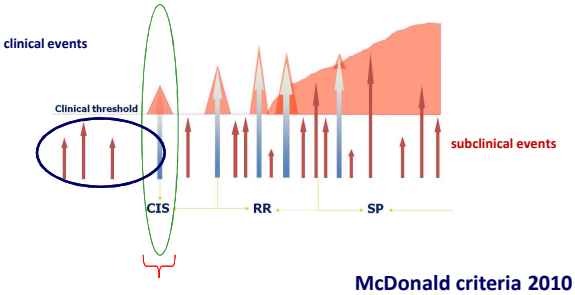
Rovira et al. Arch Neurol 2009

Optic neuritis

CIS



CIS MS



McDonald criteria 2010

2010 Diagnostic criteria: key points

Diagnostic Criteria for Multiple Sclerosis:
2010 Revisions to the McDonald Criteria

The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time can be established by a single MR scan.

This revision…

…simplifies the Criteria
…preserves their diagnostic specificity but increases the sensitivity
…addresses their applicability across populations (pediatric, Latino-America, Asian)
…may allow earlier diagnosis
…more uniform and widespread use

Polman et al., Ann Neurol 2011

Application of the 2010 McDonald MRI criteria

- Scans must be technically adequate
- The simplification and less restrictive McDonald criteria may ultimately compromise diagnostic specificity (overdiagnosis)
- Interpretation must be done by experts:
  - with knowledge of relevant clinical and laboratory information
  - with enough skills to recognize the full range of brain and spinal cord MS imaging abnormalities
  - familiar with atypical features that should raise the diagnosis of other diseases ("red flags")

MRI and the diagnosis of multiple sclerosis: expanding the concept of "no better explanation"

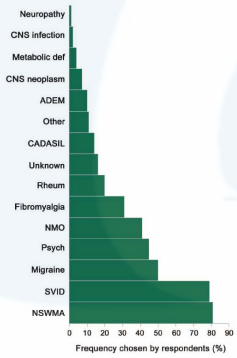
Lancet Neurol 2006; 5: 841–52

Arnaud Charil, Tarek A Yousry, Marco Rovaris, Frederik Barkhof, Nicola De Stefano, Franz Fazekas, David H Miller, Xavier Montalban, Jack H Simon, Chris Polman, Massimo Filippi

Misdiagnosis of MS

- Common (academic institutions)
- Mainly due to overuse and improper interpretation of MRI (non specific findings)
- >25% under treatment (difficult to take away)

Increase specificity of MRI findings is highly required



Solomon et al. Neurology 2012

Situations in which misdiagnosis may occur

Situation	Pitfalls
•Preclinical diagnosis	•Incidental MRI findings suggest MS normal population aged 18-50 (5-10%) migraine (x4)
•Diagnosis at first symptom	•Difficult when clinical presentation is atypical
•MS mimics	•e.g. Vasculitis, lymphoma, hipoxic-ischemic vasculopathies, sarcoidosis, Lyme disease…

Misdiagnosis has significant consequences:

- Patient care
- Health care system cost (overtreatment)

Modified from Rudick and Miller. Neurology 2013
Kim et al. Mult Scler J 2013

According to the 2010 McDonald criteria does this patient fulfils criteria for dissemination in space and time?

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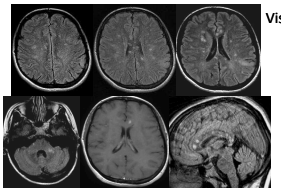

Visual loss right eye

1. Yes
2. No

According to the 2010 McDonald criteria does this patient fulfils criteria for dissemination in space and time?

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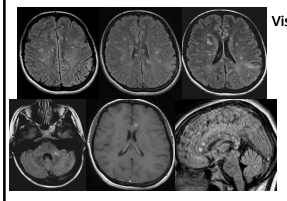

Visual loss right eye

1. **Yes**
2. No

Would you establish a diagnosis of multiple sclerosis?

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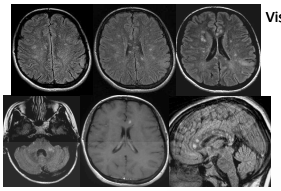

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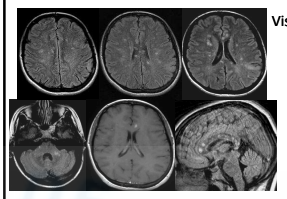

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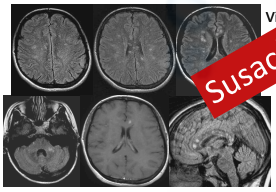
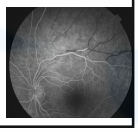


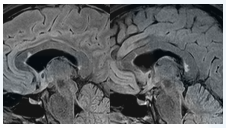
Susac´s syndrome

1. Yes
2. **No**



Sensorineural hearing loss, branch retinal artery occlusions

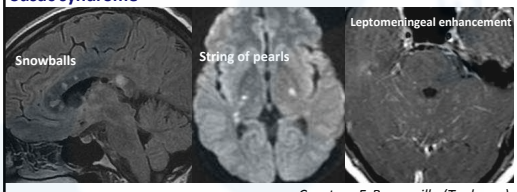
MS



- Lesions involve centrally the CC (100%)
- "String of pearls" in posterior limb of IC
- Leptomeningeal enhancement

Susac syndrome

Rennebohm et al. J Neurol Sci 2010



Courtesy F. Bonneville (Toulouse)

Diagnostic strategy in patients with multifocal brain T2 lesions of unknown origin

- ✓ Demographic data
- ✓ Family history
- ✓ Vascular risk factor profile
- ✓ Clinical information / CSF analysis
- ✓ Full range of imaging abnormalities
  - **Distribution (perivenular) and shape of lesions**
  - **Signal pattern**
  - **Involvement:**
    - ***cortical grey matter***
    - ***callososeptal interface***
    - ***U-fibers***
    - ***brainstem***
    - ***spinal cord***

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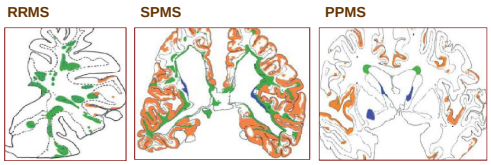
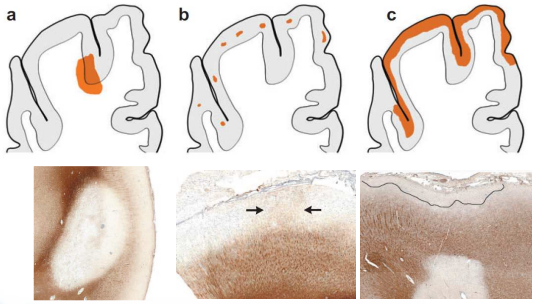
Cortical gray matter involvement in MS



focal demyelinated plaques in the white matter
cortical demyelination
demyelinated lesions in the deep grey matter

Kutzelnigg et al. Brain 2005

Cortical gray matter involvement in MS



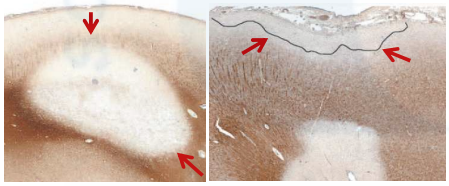
Trapp and Nave. Ann Rev Neurosci 2008
Lucchinetti et al. NEJM 2012

Cortical gray matter involvement in MS
Post-mortem imaging

Sensitivity depends on lesion type

cMRI detects <10% of pure intracortical lesions
Higher detection of mixed lesions

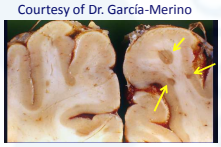
Geurts et al. J Neurol 2008



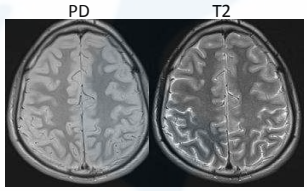
mixed lesion subpial lesion

MRI features in MS
Juxtacortical lesions

Courtesy of Dr. García-Merino



PD T2



MRI features in MS
Juxtacortical lesions

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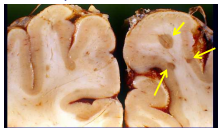
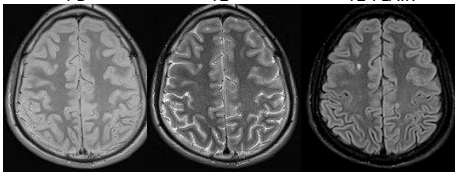
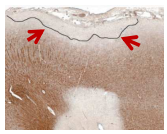


PD T2 T2-FLAIR

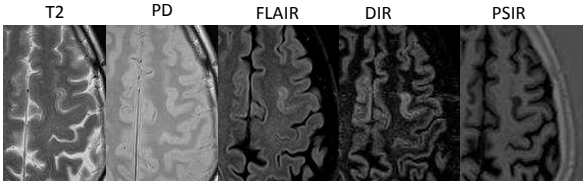


Cortical lesions in CIS (3T)



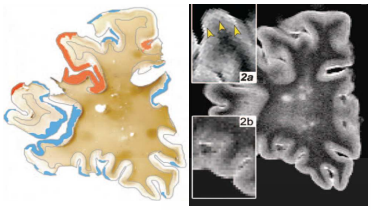
subpial lesion

T2 PD FLAIR DIR PSIR



Cortical gray matter involvement in MS
Post-mortem imaging

Sensitivity depends on lesion size (1.5T): 13.3 mm vs 6.9mm, p = 0.001
No differences in terms of histopathology



MRI visible
MRI invisible

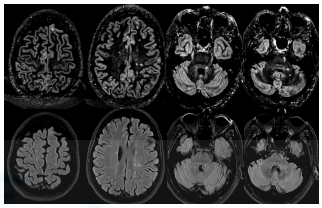
Visible lesions correlate with overall number of lesions r = 0.96

Seewan et al. Mult Scler J 2011

Double inversion-recovery (DIR) sequences

- ✓ Selective saturation of CSF and white matter
- ✓ Improve visualization of cortical-juxtacortical lesions
- ✓ Increase in cortical lesions associated with cognitive impairment
- ✓ Low signal/noise (3,0T)
- ✓ Artifacts (false positives) archi/paleocortex

DIR
FLAIR



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

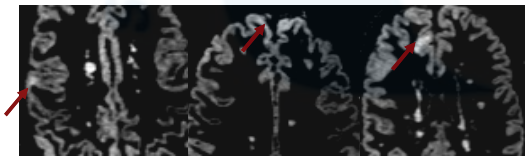
Double inversion-recovery (DIR) sequences

- Low interobserver concordance (cortico-juxtacortical lesions) (5 observers)

Geurts et al. Neurology 2011

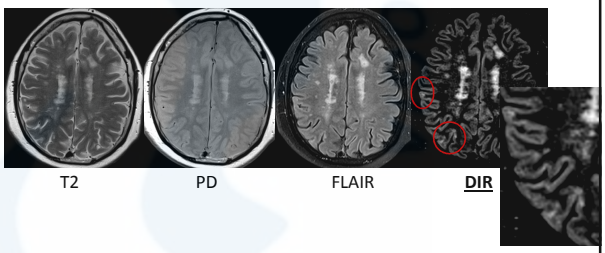
19.4% lesions (5)
39.5% lesions (4-5)
54.0% lesions (3-5)

Better concordance for mixed lesions (juxtacortical)
Worst concordance for pure cortical lesions



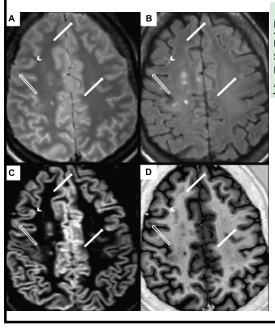
Cortical / juxtacortical lesions

Double-inversion recovery sequences (3.0T)



T2 PD FLAIR **DIR**

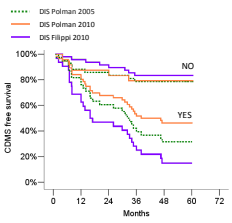
Detection of cortical MS lesions with phase-sensitive inversion recovery MRI (PSIR)

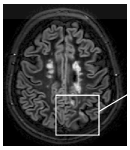


MS sub-type	DIR		PSIR	
	IC	LC	IC	LC
PP (n=15)	3.7±4.6	6.1±4.8	12.3±8.8	11.6±12.7
SP (n=15)	6.5±5.3	12.2±9.6	21.3±10.0	20.8±13.6
RR (n=30)	6.6±3.9	5.5±7.6	19.5±9.2	10.5±11.4
All (n=60)	5.9±4.5	7.3±8.0	18.1±9.8	13.4±12.9

Sethi et al. JNNP 2012

Cortical lesions in CIS and diagnostic criteria





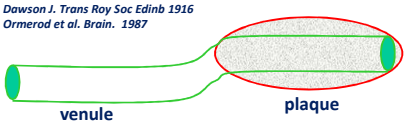
At least 2 of the following:
- *1 enhancing or 1 spinal cord lesion*
- *1 infratentorial lesion*
- *1 cortical lesion*

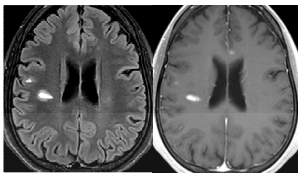
	Sensitivity	Specificity	Accuracy	OR
DIS Polman 2005	**74 %**	**73%**	**74%**	**7.9**
DIS Polman 2010	**86%**	**42%**	**61%**	**4.3**
DIS Filippi 2010	**77%**	**93%**	**86%**	**47.3**

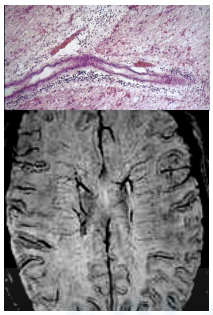
Filippi et al. Neurology 2010

Perivenular topography of MS plaques
"Dawson's fingers"

Dawson J. Trans Roy Soc Edinb 1916
Ormerod et al. Brain. 1987





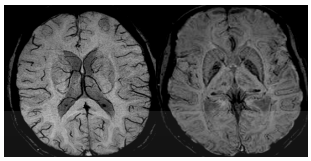


HR MR venography (SWI)

Susceptibility-weighted MR imaging

- Novel MR technique described by Haacke et al. (MRM 2004)
- Contrast based on the differences in "Magnetic Susceptibility" properties of tissues
- Increases sensitivity and conspicuity of MRI for detecting iron containing tissues and small veins (high concentration of deoxihemoglobin) due to their paramagnetic properties

Veins visibility

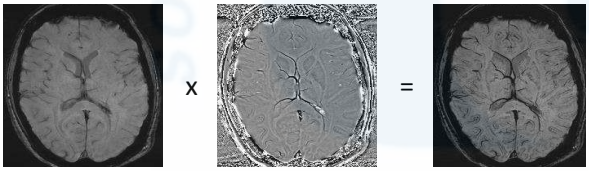


Iron within basal ganglia and thalami (low signal)

Susceptibility-weighted images

Susceptibility-weighted MR imaging

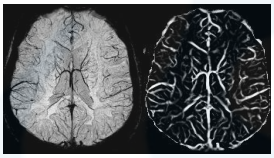
- High resolution 3D GE sequence (TE: 24ms)
- Velocity compensanted
- Magnitude image is multiplied by unwrapped and filtered phase image



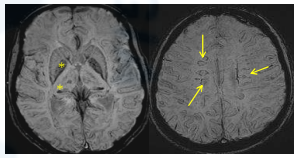
Magnitude | Phase (unwrapped and filtered) | SWI

Susceptibility-weighted MR imaging
Applications in Multiple Sclerosis

- Assessment of brain **venous vasculature visibility due to the paramagnetic effect of** deoxihemoglobin (signal loss): inverse BOLD effect
- Assessment of **Iron deposition**: deep grey matter, focal lesions



Veins mapping



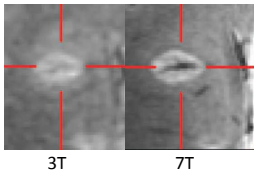
Iron deposition: deep grey matter (arterisk), focal lesions (arrows)

Susceptibility-weighted MR imaging
Central vein visibility

•Tan et al. identified a central vein in 45% of focal lesions (1.5T)

Tan et al. Am J Neuroradiol 2000

•Presence of central vein is almost constant in periventricular lesions at 7T



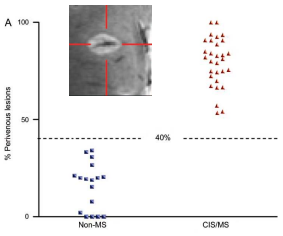
3T 7T

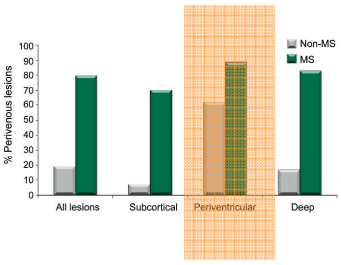
A central vessel could be identified in:
- •45% of visible lesions using 3T
- •87% of visible lesions using 7T
- •8% of incidental WM lesions at 7T

Tallantyre et al. Invest Radiol 2009

Susceptibility-weighted MR imaging
Central vein visibility

7T

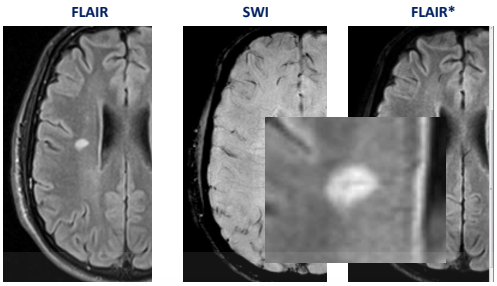




Presence of a central vein could be a marker to discriminate between MS and incidental WM lesions

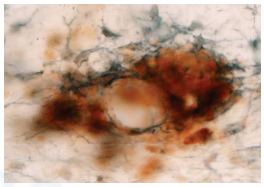
Tallantyre et al. Neurology 2011

FLAIR* sequence (3T)
Central vein visibility

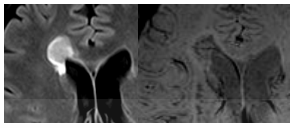


Iron deposition within lesions (MS)

- ✓ Extravasation of RBCs across the BBB (macrophages): microbleeds
- ✓ Enhanced uptake of microglia
  - Up-regulation of transferrin receptor expresion
  - Phagocytosis myelin/OG debris (macrophages)

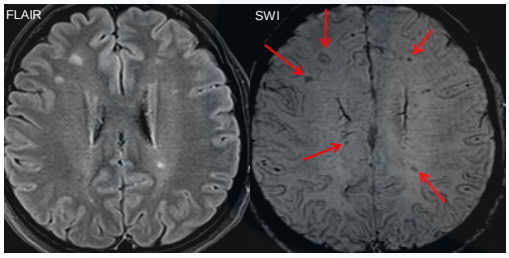


Williams et al. BMC Neuroscience 2011
Williams et al. J Neurochem 2012

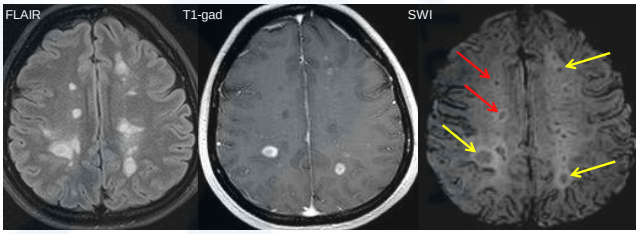


An iron labeled vessel with associated microgliosis and double labeled cells revealing iron deposits within reactive microglia

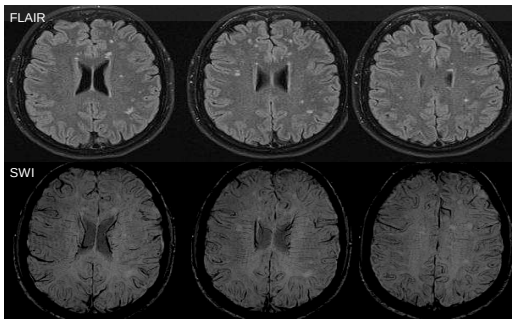
Intralesional susceptibility signal (ISS) in CIS



Intralesional susceptibility signal (ISS) in CIS



No Intralesional susceptibility signal (ISS) in migraine



Conclusions

➢Conventional MRI techniques, which are **highly sensitive** for detecting CNS demyelinating plaques, are recognized as the most important paraclinical tool for diagnosing MS

➢Incidental findings and vascular lesions may mimick MS

➢MRI pattern in MS is usually relatively specific when the full range of signal abnormalities are taken into consideration

➢Non-conventional techniques improve the **specificity** of MRI in selected cases

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