Vall d'Hebron Hospital

Institut Català de la Salut

Generalitat de Catalunya Departament de Salut

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

32nd Congress of ECTRIMS
21st Annual Conference of RIMS
London, United Kingdom, 14- 17 September 2016

Teaching Course 8 - Improving the differential diagnosis of MS using MRI

"Multiple Sclerosis mimics"

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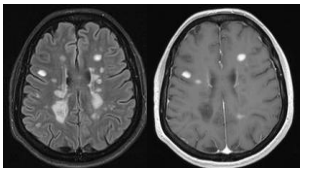
Magnims
Magnetic Resonance Imaging in Multiple Sclerosis
www.magnims.eu

MR imaging in MS

T2-weighted (FLAIR)



Post-contrast T1-weighted

- Highly sensitive for detecting MS plaques (white matter)
- Provide quantitative assessment of disease activity and severity
- Characterize disease course over time
- Monitor and predict treatment response
- Most important paraclinical tool for diagnosing and monitoring MS

Bakshi et al. Lancet Neurol 2008;7:615–25

Multifocal WM signal abnormalities: "white spots"

Incidental finding
- Virchow-Robin spaces
- normal population (5-10%)
- migraine (x4)

Hipoxic-ischemic vasculopathies
- small-vessel disease
- hyperhomocysthenimia
- CADASIL
- Susac's syndrome

Primary demyelinating diseases
- multiple sclerosis and variants
- ADEM
- neuromyelitis optica

Vasculitis
- primary
- sys… *…çet, APLAS*

Miscellaneous
- neurosarcoidosis
- Lyme disease
- PML
- metabolic: Fabry, Leber, xantomatosis, adult forms of leukodystrophy
- effects of radiation therapy or drugs
- lymphoma
- metastasic disease

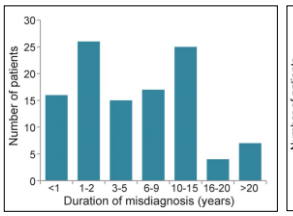
Brain MRI changes are not disease specific

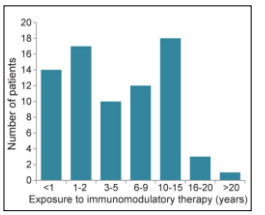
Sánchez Aliaga E, Barkhof F. Handb Clin Neurol 2014;122:291-316; Charil et al. Lancet Neurol 2006;5:841-52

Misdiagnosis of Multiple Sclerosis

•Neurologists at 4 academic MS centers submitted data on patients determined to have been misdiagnosed with MS.
•110 misdiagnosed patients:
- ✓51 (46%) "definite" misdiagnoses
- ✓59 (54%) "probable " misdiagnoses

70% received ≥ 1 DMD





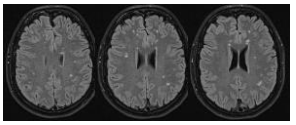
Solomon et al. Neurology 2016

Misdiagnosis of MS: overreliance on MRI interpretation, wrong application of DX criteria

- Frequent contemporary reason for misdiagnosis
- MRI features not considered in the context of appropiate clinical findings
- Overdiagnosis of RIS

- Incidental multifocal WM brain lesions on MRI

normal population aged 18-50 (5-10%)
migraine (x4)



Misdiagnosis has significant consequences:

- Clinical, psychosocial and scientific
- Health care system cost (overtreatment with DMTs; approx 40.000 subjects in US)

Fazekas et al. Eur Neurol. 1989; Solomon et al. Neurology 2016; Solomon et al. Curr Neurol Neurosci Rep 2013; Charil et al. Lancet Neurol 2006; Solomon et al. Neurology 2012; Rudick et al. Neurology 2013; Kim et al. Mult Scler. 2013

Diagnostic strategy in subjects with incidental multifocal brain T2 lesions of unknown origin

Comprehensive checklist for evaluation of WM spots

Systematic reading

- **Lesion distribution / involvement**
  - ✓subcortical/periventricular
  - ✓U-fibers
  - ✓cortical grey matter
  - ✓deep grey matter
  - ✓corpus callosum
  - ✓brainstem
  - ✓spinal cord
- **Lesion shape**
- **Enhancement pattern**
- **Features on special sequences: SWI**
- **Ancillary findings**
  - ✓microbleeds
  - ✓vascular abnormalities

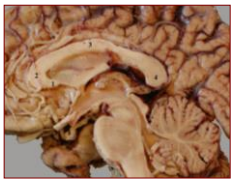
→

Brief and precise diagnostic impression that must consider:

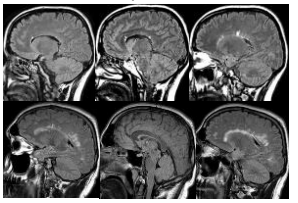
- ✓Demographics
- ✓Family history
- ✓Vascular risk factors
- ✓Clinical information and question
- ✓Lab findings

Kanecar et al. Radiol Clin N Am 2014; 52:241-61; Sánchez Aliaga E, Barkhof F. Handb Clin Neurol 2014;122:291-316

Corpus callosum involvement



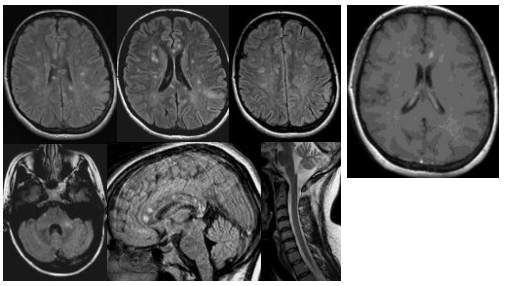
Multiple Sclerosis



Cerebrovascular disease

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

33 year-old woman with a three week clinical picture of behavioural disturbance, bradipsychia, sommnolence, headache, and memory loss



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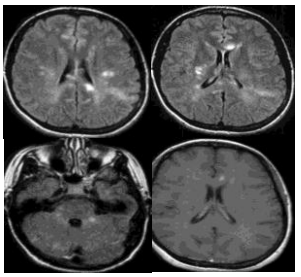
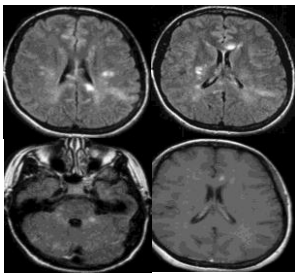


Does this patient fulfil the MRI diagnostic criteria for MS?

1- Yes
2- No

33 year-old woman with a three week clinical picture of behavioural disturbance, bradipsychia, sommnolence, headache, and memory loss



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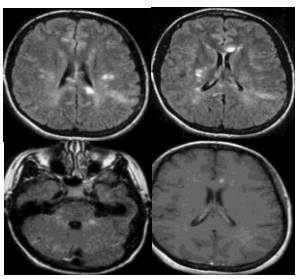
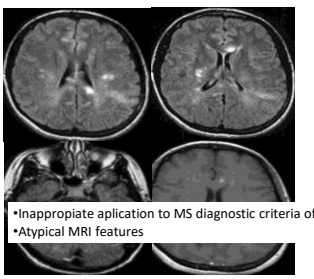


Diagnosis?

1- Multiple sclerosis
2- Devic disease
3- Susac syndrome
4- ADEM

33 year-old woman with a three week clinical picture of behavioural disturbance, bradipsychia, sommnolence, headache, and memory loss



Diagnosis?

1- Multiple sclerosis
2- Devic disease
3- Susac syndrome
4- ADEM

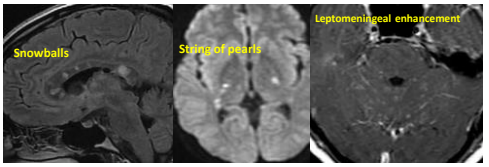
•Inappropiate aplication to MS diagnostic criteria of neurologic symptoms atypical for MS
•Atypical MRI features

Susac syndrome

Characteristic MRI features:

- Focal T2 white / grey matter lesions supra and infratentorial (infarcts)
  - Small and widespread
  - Enhancement
  - Diffusion restriction
  - Constant involvement of the corpus callosum (central)
  - Cortex, basal ganglia, brainstem amd cerebellum also involved
- Leptomeningeal enhancement (1/3)

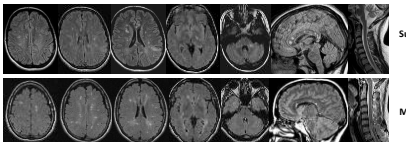
Susac et al. Neurology 2003



Courtesy F. Bonneville (Toulouse)

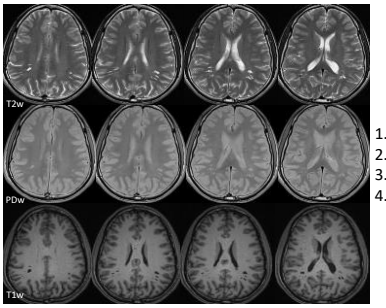
Susac syndrome vs Multiple Sclerosis

Features	Susac syndrome	Multiple sclerosis
Corpus callosum lesions	Constant and central	frequent, inferior
"String of pearls" in posterior limb of IC	frequent	rare
Leptomeningeal enhancement	33%	absent
Deep grey matter lesions	77%	rare (thalamus)
Diffusion restriction	yes (acute lesions)	rare (acute lesions)
Spinal cord lesions	absent	frequent



Rennebohm et al. J Neurol Sci 2010; Susac et al. Neurology 2003

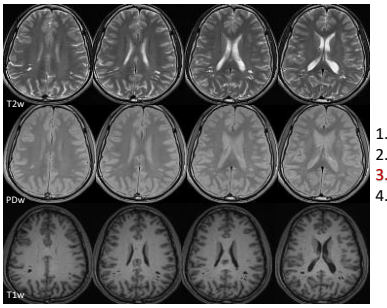
25 year-old woman
Migraine



Diagnosis?

1. Multiple sclerosis
2. RIS
3. Virchow-Robin spaces
4. Vasculitis

25 year-old woman
Migraine



Diagnosis?

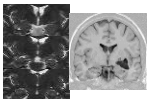
1. Multiple sclerosis
2. RIS
3. Virchow-Robin spaces
4. Vasculitis

Dilated Virchow-Robin spaces

- Virchow-Robin spaces (VRs) surround the walls of vessels as they course from the subarachnoid space through the brain parenchyma
- Appear in all age groups (small)
- Higher frequency and size with advancing age
- Signal intensity almost identical to that of CSF
- Associated with: neuropsychiatric disorders, MS, mild traumatic brain injury, and small-vessel disease

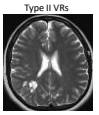
R. M. Kwee, and T. C. Kwee. Radiographics 2007; Law et al. AJNR 2005; Wuerfel et al. Brain 2008; Doubal et al. Stroke 2010; Kilsdonk et al. MSJ 2015

Type I VRs



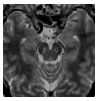
Along the lenticulostriate arteries entering the basal ganglia through the anterior perforated substance

Type II VRs



Along the paths of the perforating medullary arteries as they enter the cortical gray matter over the high convexities and extend into the white matter

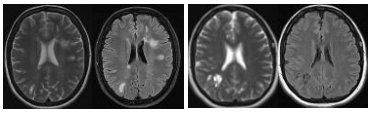
Type III VRs



In the midbrain

Dilated Virchow-Robin spaces vs Multiple Sclerosis*

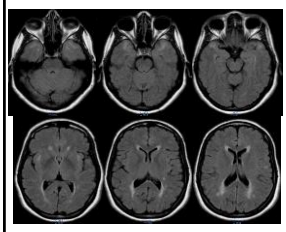
Features	Dilated Virchow-Robin spaces	Multiple sclerosis
Periventricular lesions	absent	yes
Spinal cord lesions	absent	yes
Signal intensity	CSF-like	high (T2-FLAIR)
Shape	ovoid/linear	ovoid
SVD (infarcts, DM, microbleeds)	+/-	absent
Contrast enhancement	absent	+/-



* An association with MS has been described.

1. Tarasoff-Conway et al. Nat Rev Neurol 2015; 2. Law et al. AJNR 2005; 3. Wuerfel et al. Brain 2008; 4. Kilsdonk et al. MSJ 2015

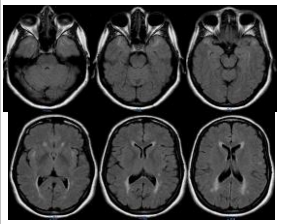
46 year-old woman with a five month clinical picture of recurrent headache



Key MRI feature for the diagnosis?

1. Posterior periventricular lesions
2. Involvement of the anterior temporal lobe
3. Involvement of the internal capsule
4. All of the above

46 year-old woman with a five month clinical picture of recurrent headache



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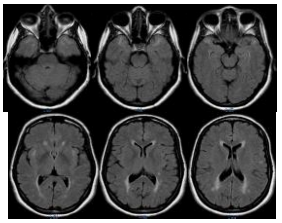

1. Multiple sclerosis
2. Lupus
3. Susac syndrome
4. CADASIL

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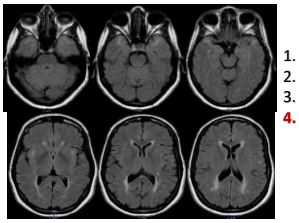
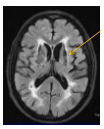


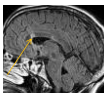
1. Multiple sclerosis
2. Lupus
3. Susac syndrome
4. **CADASIL**

CADASIL

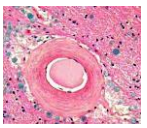
Summary of radiological features

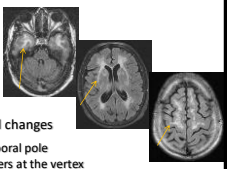


Multiple lacunar infarcts

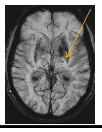


Involvement of corpus callosum





Microbleeds on T2* or SWI



Diffuse white matter T2 signal changes

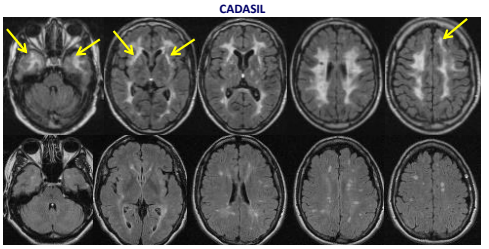
- Temporal pole
- U fibers at the vertex
- External capsule /insular region

Van den Boom et al. Radiology 2003;229:683-90; Singhal et al. Am J Neuroradiol 2005;26:2481-7

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CADASIL

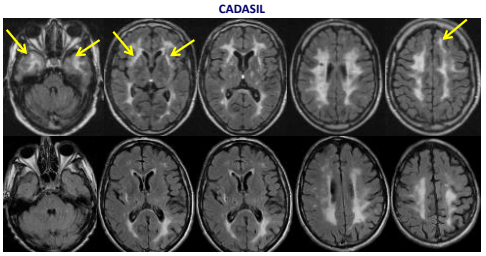


Multiple sclerosis

CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

CADASIL



Small vessel disease

Central nervous system vasculitis

Which of the following MRI features distinguish CNS vasculitis from Multiple Sclerosis?

1. Spinal cord involvement
2. Pseudotumoral lesions
3. Leptomeningeal enhancement
4. Restricted diffusivity in acute lesions

Central nervous system vasculitis

Which of the following MRI features distinguish CNS vasculitis from Multiple Sclerosis?

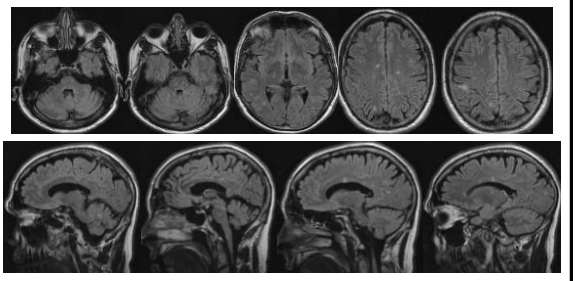
1. Spinal cord involvement
2. Pseudotumoral lesions
3. **Leptomeningeal enhancement**
4. Restricted diffusivity in acute lesions

Primary angiitis of the CNS

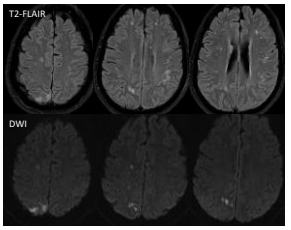
MRI features (non specific):

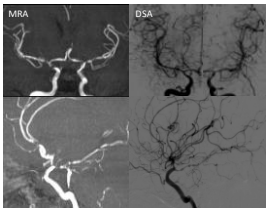
- Abnormal in 90-100% of patients (diagnosis unlikely if MRI is normal)
- Diffuse / focal supratentorial areas of increased signal on T2W images
- Multiple cortical / subcortical infarcts
- Pseudotumoral lesions
- Gadolinium enhancement in one-third of cases; leptomeningeal enhancement may occur in 10% to 15%
- Restricted diffusion suggestive of acute stroke
- Concentric vessel-wall thickening and intramural enhancement (fat supressed CE - T1W)

Primary angiitis of the CNS



Primary angiitis of the CNS



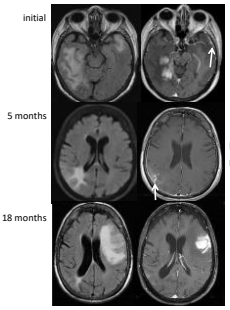


Classic angiographic vasculitis pattern

- ✓ multiple focal or long segmental areas of narrowing of small and medium vessels
- ✓ poor correlation between DSA and MRA
- ✓ MRA provides false negative results in more than 1/3

Primary angiitis of the CNS

Pseudotumoral, relapsing



Brain biopsy revealed evidence of necrotising lymphocytic vasculitis.

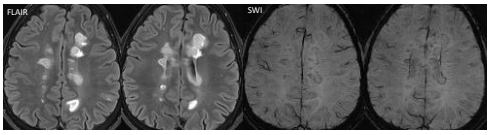
PACNS vs Multiple Sclerosis

Features	PACNS	Multiple sclerosis
Multifocal / diffuse WM brain lesions	Frequent (almost 100%)	frequent
Cortical/subcortical infarcts	yes	absent
Dural masess	+/-	absent
Pseudotumoral lesions	+/-	+/-
Enhancement focal lesions	1/3	constant in new lesions
Diffusion restriction	yes (acute lesions)	rare (acute lesions)
Leptomeningeal enhancement	10-15%	rare, focal
Concentric vessel wall enhancement	+/-	absent
Segmental arterial stenosis	+/-	absent
Hemorrhage: brain and SAH	+/-	absent
Spinal cord lesions	+/-	frequent

Salvarani et al. Lancet 2012; Obusez et al. Am J Neuroradiol 2014; Campi et al. Am J Neuroradiol 2001

Susceptibility-weighted MR imaging

Intralesional susceptibility signal (ISS) in MS (3T)



Intralesional susceptibility signal (ISS)
48% of non-enhancing MS lesions
58% of enhancing MS lesions

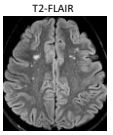
Rovira et al. Multiple Sclerosis Journal 2015; 21 (S11):209

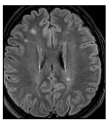
Likely represents iron-rich macrophages / microglia
Myelin loss also contributes

Hagemeier et al. J Magn Reson Imaging 2012;36:73-83; Bian et al. Mult Scler 2013;19:69-75

Migraine-related WMLs vs Multiple Sclerosis (3T)

T2-FLAIR

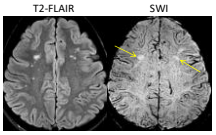




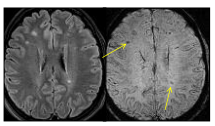
Rovira et al. Multiple Sclerosis Journal 2015; 21 (S11):209

Migraine-related WMLs vs Multiple Sclerosis (3T)

T2-FLAIR SWI



Migraine

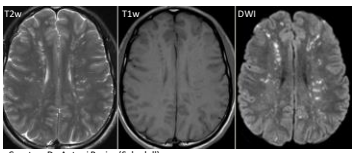


MS

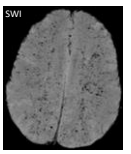
Areas of intralesional signal loss on SWI increases diagnostic specificity and accuracy

Rovira et al. Multiple Sclerosis Journal 2015; 21 (S11):209

25 year old man. Dyspnea, skin rash, encephalopathy



Courtesy Dr. Antoni Rovira (Sabadell)



Diagnosis?

1. Multiple sclerosis
2. Watershed infarcts
3. Fat embolism
4. ADEM

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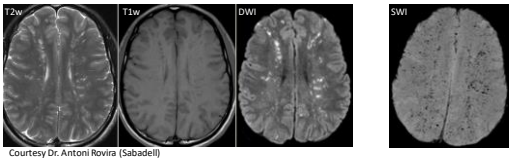

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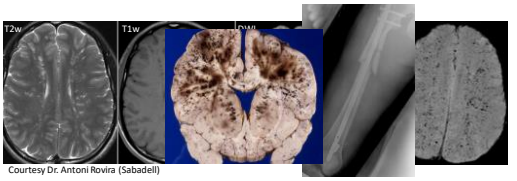

Courtesy Dr. Antoni Rovira (Sabadell)

- associated with displaced long bone fracture of the lower extremities
- characterized by: respiratory disability, petechial skin rash, and neurologic symptoms typically seen between 12 and 72 hours after the injury.
- Incidence of 0.9%–2.2%.
- although usually self-limiting, it may be fatal.

Kuo et al. Am J Neuroradiol 2013

Mimickers of Multiple Sclerosis

Disorders/conditions	Prevalence
Incidental nonspecific MRI abnormalities	high
Dilated Virchow-Robin spaces	high
Migraine	high
Cerebrovascular disoders: small vessel diseases (CADASIL)	rare
Inflammatory: SUSAC, vasculitis, sarcoidosis	medium
Infections: Lyme disease, HTLV, Whipple	rare
Other: DAI, fat embolism	medium

Summary

- Wide variety of causes may present with multifocal WM lesions
- MRI is the preferred imaging technique for diagnostic workup
- Radiological interpretation with demographic, clinical history, and lab findings
- Standardized brain (spinal cord) MRI protocol
- Comprehensive checklist for evaluation of WM spots is crucial

Sánchez Aliaga E, Barkhof F. Handb Clin Neurol 2014;122:291-316; Charil et al. Lancet Neurol 2006;5:841-52; Rovira et al. Nat Rev Neurol 2015;11:471-82