Diagnosis of MS

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Disclosures

Prof. Massimo Filippi

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Learning objectives

- To understand the theoretical background of the current diagnostic criteria
- To become familiar with 2017 McDonald diagnostic criteria
- To recognize MRI red flags of MS
- To have a look on possible future MRI criteria

Outline of the presentation

- Background
- 2017 Revised McDonald criteria
- MRI red flags of MS
- Future MRI criteria
- Key messages

Background

« de l'**altération scléreuse** en plaques **disséminées**, est surtout relative à la **substance blanche**, niais elle peut s'appliquer également, d'une manière générale au moins, à la **substance grise** »

Jean-Martin Charcot, Leçons du mardi, 1868

Schumacher, 1965

Clinically definite multiple sclerosis

1

2

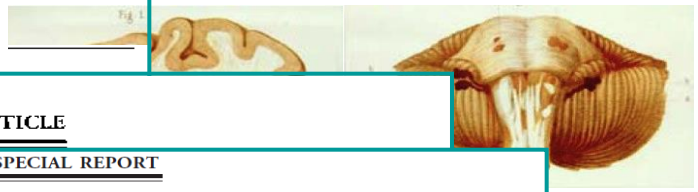
3

4

5

6

No path
been dis



SPECIAL ARTICLE

Charles
Floyd A

SPECIAL REPORT

Hans-

William S

New diagno
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Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald Criteria"

Chris
Han

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]

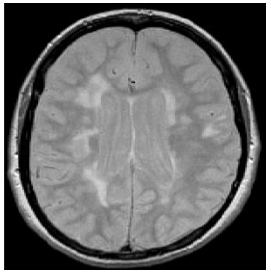
New evidence and consensus has led to further revision of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination of central nervous system lesions in space and time has been simplified, and in some circumstances dissemination in space and time 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

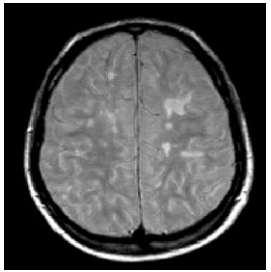
2010 McDonald Revised criteria

DIS

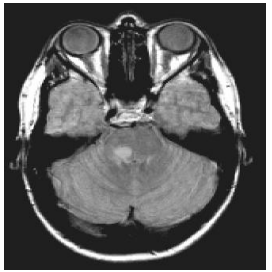
≥1 T2 asymptomatic lesion in at least 2 of 4 CNS areas:



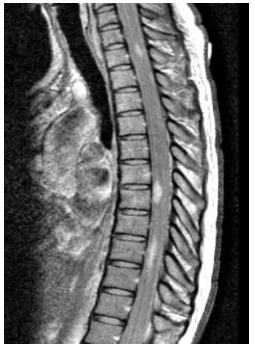
PERIVENTRICULAR



JUXTACORTICAL

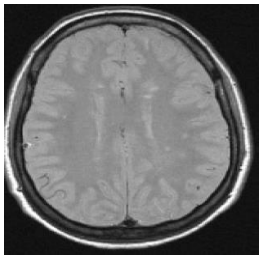


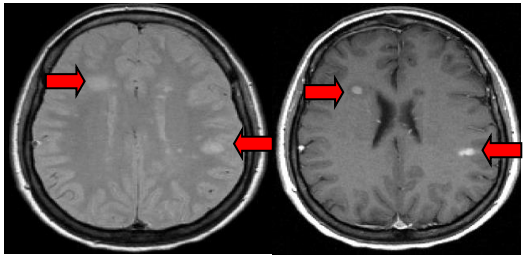
INFRATENTORIAL



SPINAL CORD

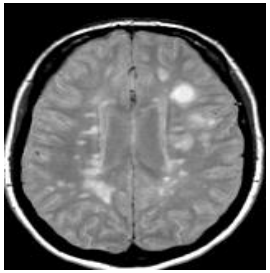
DIT

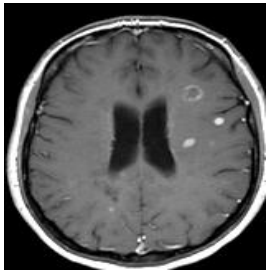




BASELINE FOLLOW-UP

1) A **new T2 and/or GD-enhancing lesion** on follow-up MRI, irrespective of the timing of the baseline MRI





2) Simultaneous presence of **asymptomatic Gd-enhancing and non-enhancing lesions** at any time

Polman et al., Ann Neurol 2011

2016 MAGNIMS MRI criteria

MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines

*Massimo Filippi, Maria A Rocca, Olga Ciccarelli, Nicola De Stefano, Nikos Evangelou, Ludwig Kappos, Alex Rovira, Jaume Sastre-Garriga, Mar Tintorè, Jette L Frederiksen, Claudio Gasperini, Jacqueline Palace, Daniel S Reich, Brenda Banwell, Xavier Montalban, Frederik Barkhof, on behalf of the MAGNIMS Study Group**

Lancet Neurol 2016; 15: 292–303

Panel 2: Recommended 2016 MAGNIMS MRI criteria to establish disease dissemination in space in multiple sclerosis

Dissemination in space can be shown by involvement* of at least two of five areas of the CNS as follows:

- Three or more periventricular lesions
- One or more infratentorial lesion
- One or more spinal cord lesion
- One or more optic nerve lesion
- One or more cortical or juxtacortical lesion†

*If a patient has a brainstem or spinal cord syndrome, or optic neuritis, the symptomatic lesion (or lesions) are not excluded from the criteria and contribute to the lesion count. †This combined terminology indicates the involvement of the white matter next to the cortex, the involvement of the cortex, or both, thereby expanding the term juxtacortical lesion.

Filippi et al., Lancet Neurol 2016

Revised 2010 McDonald and MAGNIMS 2016

Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study

Massimo Filippi, Paolo Preziosa, Alessandro Meani, Olga Ciccarelli, Sarlota Mesaros, Alex Rovira, Jette Frederiksen, Christian Enzinger, Frederik Barkhof, Claudio Gasperini, Wallace Brownlee, Jelena Drulovic, Xavier Montalban, Stig P Cramer, Alexander Pichler, Marloes Hagens, Serena Ruggieri, Vittorio Martinelli, Katherine Miszkiel, Mar Tintorè, Giancarlo Comi, Iris Dekker, Bernard Uitdehaag, Irena Dujmovic-Basuroski, Maria A Rocca

Background In 2016, the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network proposed modifications to the MRI criteria to define dissemination in space (DIS) and time (DIT) for the diagnosis of multiple sclerosis in patients with clinically isolated syndrome (CIS). Changes to the DIS definition included removal of the distinction between symptomatic and asymptomatic lesions, increasing the number of lesions needed to define periventricular involvement to three, combining cortical and juxtacortical lesions, and inclusion of optic nerve evaluation. For DIT, removal of the distinction between symptomatic and asymptomatic lesions was suggested. We compared the performance of the 2010 McDonald and 2016 MAGNIMS criteria for multiple sclerosis diagnosis in a large multicentre cohort of patients with CIS to provide evidence to guide revisions of multiple sclerosis diagnostic criteria.

Interpretation The 2016 MAGNIMS criteria showed similar accuracy to the 2010 McDonald criteria in predicting the development of clinically definite multiple sclerosis. Inclusion of symptomatic lesions is expected to simplify the clinical use of MRI criteria without reducing accuracy, and our findings suggest that needing three lesions to define periventricular involvement might slightly increase specificity, suggesting that these two factors could be considered during further revisions of multiple sclerosis diagnostic criteria.

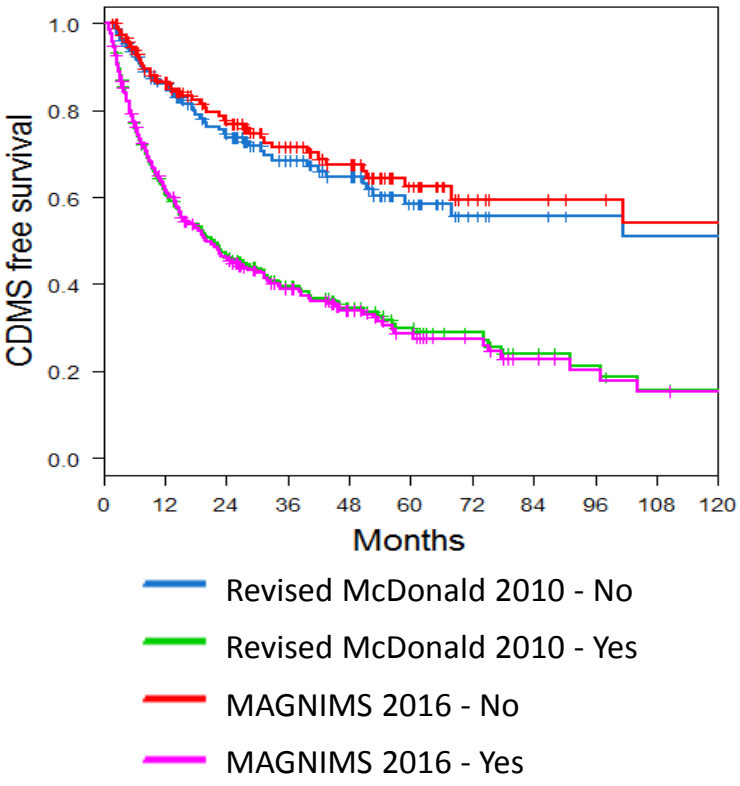
Filippi et al., Lancet Neurol 2018

Revised 2010 McDonald and MAGNIMS 2016

	aHR (95% CI)	p value
DIS + DIT (36 months)		
Revised McDonald 2010	**2.52 (1.78-3.58)**	<0.0001
Inclusion of symptomatic lesions	2.54 (1.77-3.65)	<0.0001
Inclusion of 3 PV lesions	2.54 (1.80-3.58)	<0.0001
Inclusion of CL	2.60 (1.83-3.71)	<0.0001
Inclusion of ON	2.58 (1.81-3.67)	<0.0001
MAGNIMS 2016	**2.95 (2.04-4.26)**	<0.0001

Filippi et al., Lancet Neurol 2018

DIS + DIT



MAGNIMS 2016 vs 2017 McDonald Revision

MAGNIMS 2016

- No distinction between symptomatic and asymptomatic lesions

↓

- No reason any more to exclude the optic nerve

↓

- To reduce the risk of FP: increased number of PV required (1→3)

↓

- In addition: cortical lesions (new sequences)

2017 McDonald Revision

CIS

DIS	DIT
≥1 T2 lesion (**both symptomatic and asymptomatic**) in at least 2 of 4 CNS areas: PV, JC/**CL**, spinal cord, infratentorial	Simultaneous presence of Gd+ and Gd- lesions at any time (**both symptomatic and asymptomatic**) OR A new T2 and/or Gd+ lesion on follow-up MRI OR Presence of **CSF-specific OCBs**

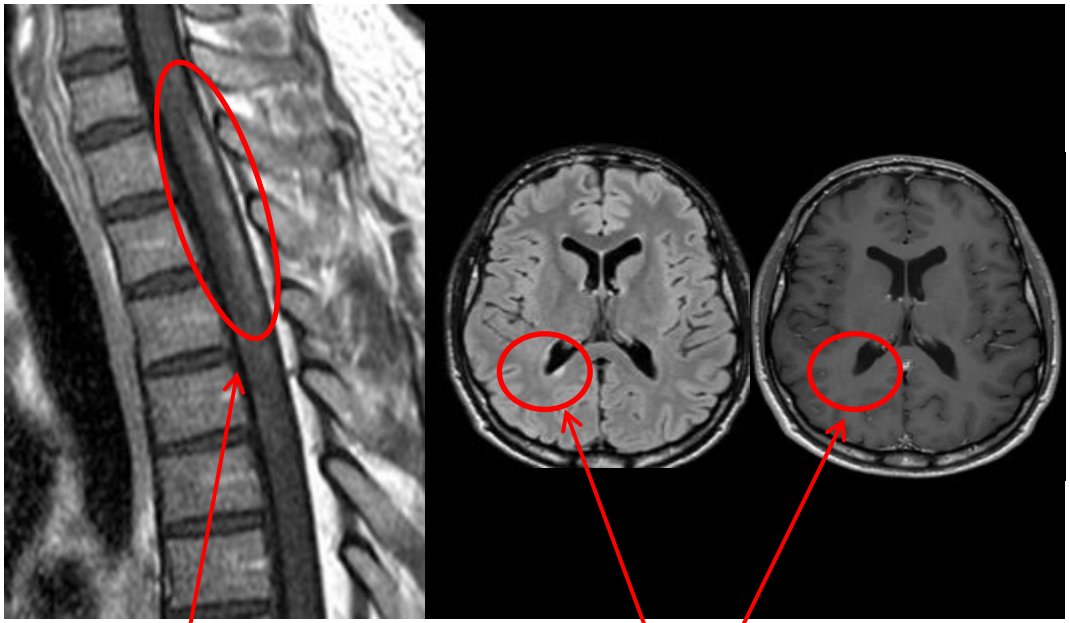
PPMS

One year of disability progression (retrospectively or prospectively determined) independent of clinical relapse + **> 2/3 of:**	• ≥1 T2 lesion (**symptomatic and asymptomatic**) both in ≥1 areas in the brain characteristic of MS (PV, JC/CL or infratentorial) • ≥2 T2-hyperintense lesions in the **spinal cord** • Presence of **CSF-specific OCBs**

Thompson et al., Lancet Neurol 2018

Clinical case 1

- 37 year-old woman
- No previous neurological history
- Sudden onset of paraparesis and sensory ataxia



One (probably) symptomatic spinal cord enhancing lesion

One non-enhancing PV lesion

Is this MS (Mc Donald 2017 criteria)?

1) The patient satisfies both criteria for DIS and DIT

2) The patient satisfies criteria for DIS, but not DIT

3) The patient does not satisfy criteria for DIS, but satisfies criteria for DIT

4) The patient does not satisfy neither criteria for DIS nor DIT

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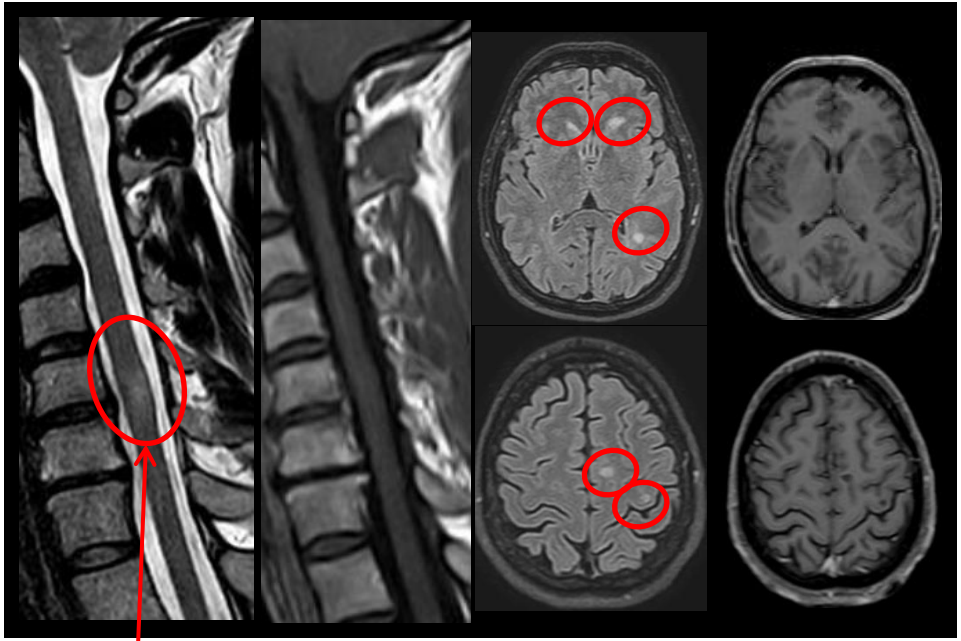
Clinical case 2

- 29 year-old man
- No previous neurological history
- Bilateral hand paresthesias started almost one month ago

→ **Positive OCBs**



One symptomatic spinal cord non-enhancing lesion

≥ 3 PV and JC non-enhancing lesions

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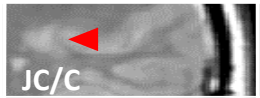
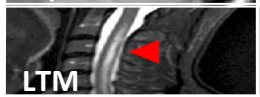
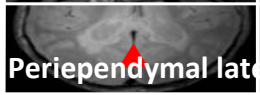
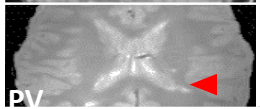
Practical guidelines (MS)

Lesion category	Green flags	Red flags
Periventricular	- Location: **abutting the lateral ventricles without intervening white matter**	- **Periependymal lesions** surrounding the lateral ventricles (NMOSD) - **Infarcts or microbleeds** (amyloid angliopathy, cerebrovascular disease) - **Extensive symmetric** white matter lesions (leukodystrophy) - Rounded lesions centrally located in the corpus callosum **("snowball"-like** lesion) (Susac syndrome)
Juxtacortical/cortical	- Location: **touching or within the cortex**	- **Infarcts or microbleeds**
Infratentorial	- Location: brainstem, cerebellar peduncles and cerebellar hemispheres; contiguous to cisterns or the floor of the fourth ventricle; surface of the pons and the pontine trigeminal root entry zone; lining of CSF border zones; cerebral peduncles and close to the periaqueductal gray matter; uni- or bilateral paramedian location in medulla oblongata	- **Infarcts or microbleeds** (amyloid angliopathy, cerebrovascular disease) - **Symmetric lesions** in the central pons (amyloid angliopathy, cerebrovascular disease) - **Periaqueductal lesions** (NMOSD) - **Area postrema** lesions (NMOSD) - Medullary lesions **contiguous to cord lesions** (NMOSD)
Spinal cord	Multiple discrete (**focal**) lesions - Shape: sagittal: cigar-like; axial: wedge-shaped - Size: small; ≤ 2 vertebral segments; < half of the cord - Location: cervical>thoracic; peripheral region; lateral and posterior columns, but central gray matter not spared - Signal characteristics: T1-hypointensity (> at higher field strengths)	- Longitudinal extensive transverse myelitis affecting **≥ 3 vertebral segments** (NMOSD) - **Cavities** (syringohydromyelia) - **Micro/macrobleeds and ischemic lesions** (arteriovenous fistula, ischemic myelopathy) - **Indistinct/diffuse/increasing** (malignancy) - Lesion involving **only the gray matter** (NMOSD, infections, ischemia)
Gadolinium-enhancing lesions	- Shape: nodular; open-ring; closed-ring - Location: brain>spinal cord	- Large or multiple **closed-ring enhancement** (ADEM, malignancy, infection) - **(Lepto)meningeal/root enhancement** (neurosarcoidosis) - **Trident sign** (neurosarcoidosis) - **Pancake sign** (spondilothic myelopathy) - **Punctate or miliary** enhancement (CLIPPERS, vasculitis, PML, Susac syndrome) - **Band-like** enhancement (Balò's concentric sclerosis) - **Cloud-like** enhancement (NMOSD) - **Purely cortical** enhancement (vasculitis, ischemic lesion) - Persistence of enhancement **>3 months** (malignancy)

Filippi et al., Brain 2019

Practical guidelines (MS *vs* NMOSD)

Multivariate logistic regression	OR (95% CI)	p
 JC/C	28.97** (4.47-187.76)	0.0004
 LTM	23.62* (2.85-195.56)	0.003
 Periependymal lateral ventricles	10.21* (1.59-65.81)	0.01
 Dawson's fingers	7.57** (1.47-38.8)	0.01
 PV	6.37** (0.89-45.41)	0.06

NMOSD MS

* Presence ** Absence

At least 2/5:

- Training sample: **Sensitivity 0.92, Specificity 0.91**
- Validation sample: **Sensitivity 0.82, Specificity 0.91**

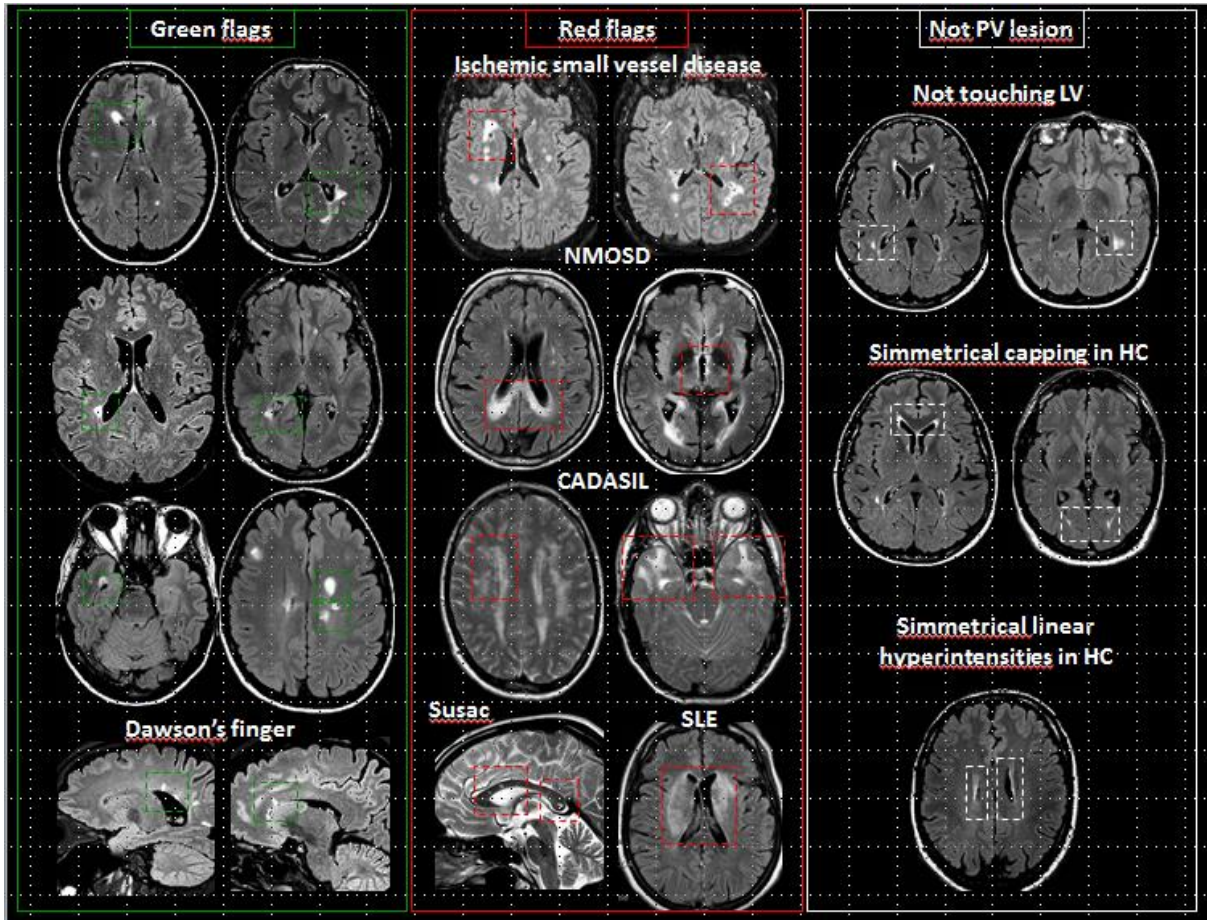
Cacciaguerra et al., Ann Neurol 2019

Periventricular lesions

- **Direct contact** with the lateral ventricles, without intervening white matter

- Lesions abutting (**touching**) the ventricles and located in the corpus callosum are included

Filippi et al., Brain 2019



Infratentorial lesions

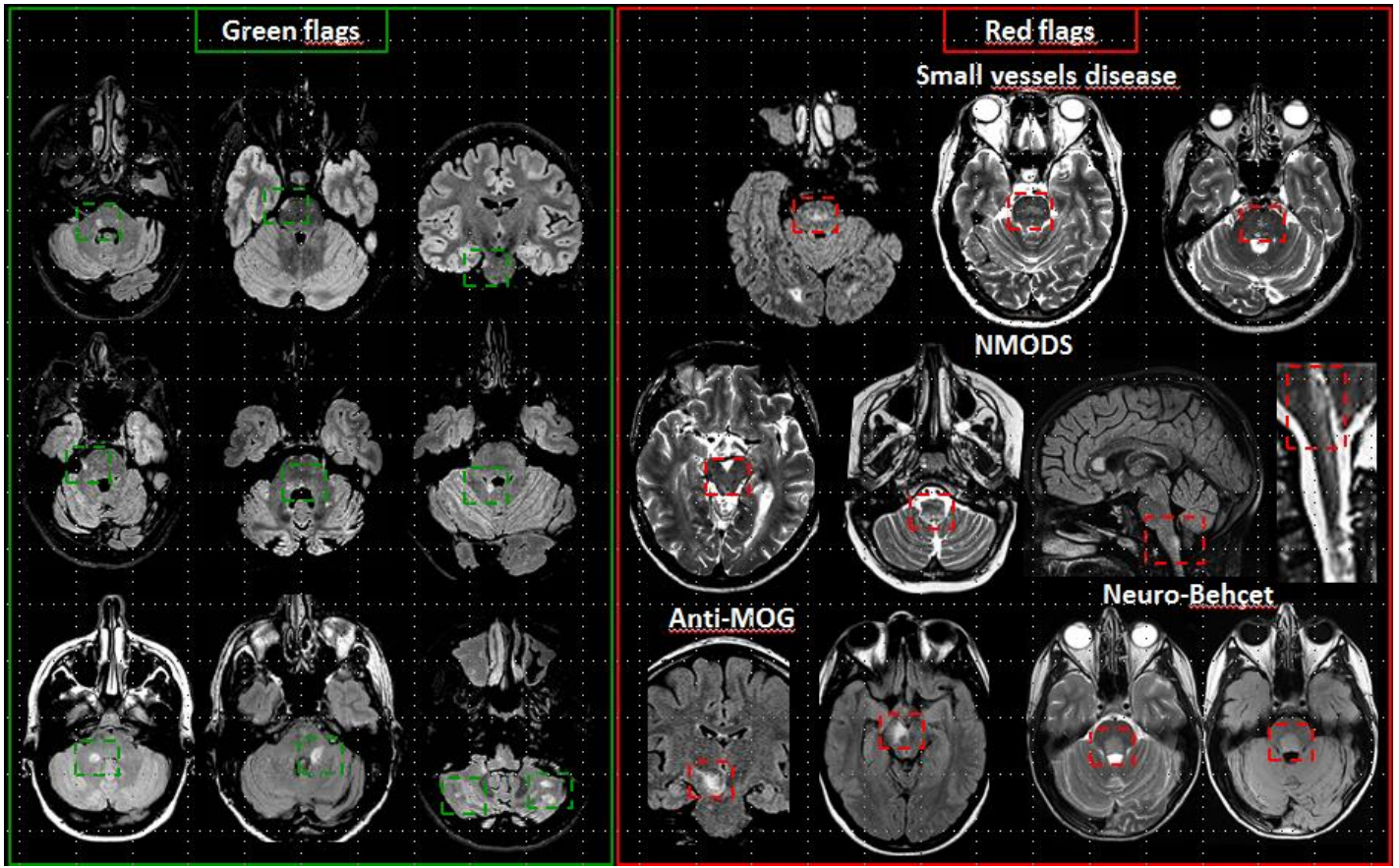
- **Brainstem**
- **Cerebellum**

} Surface

- **Pons**

↓

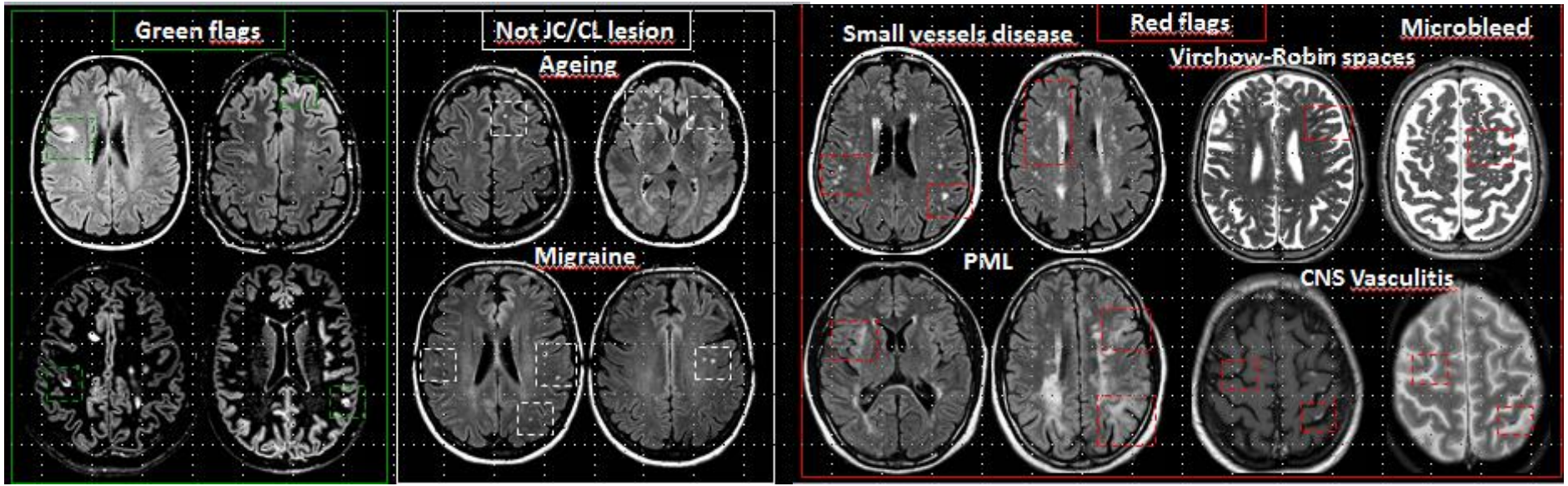
Surface, cisterns/floor of the IV ventricle, trigeminal root-entry



Filippi et al., Brain 2019

Cortical/Juxtacortical lesions

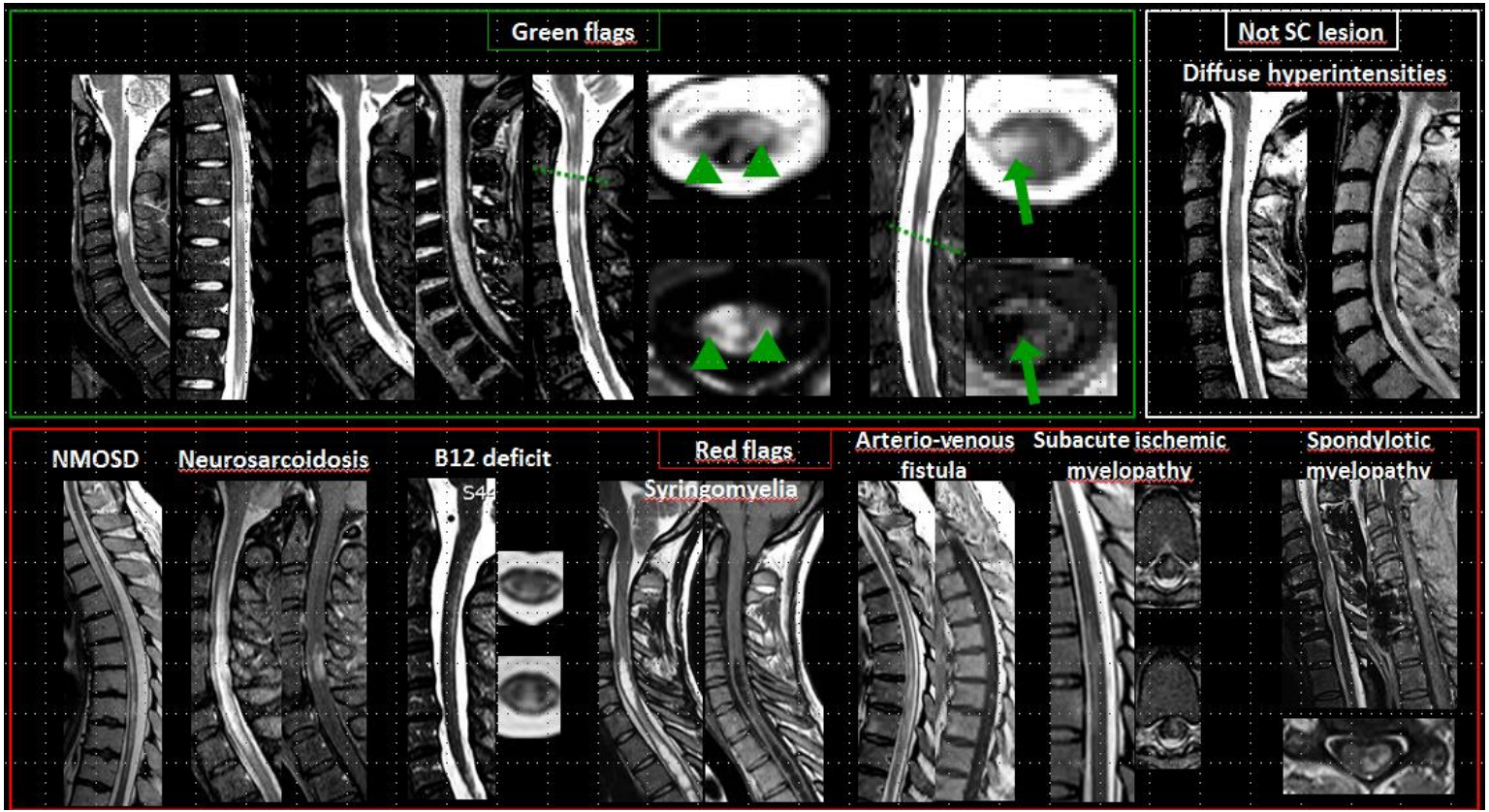
- **Abutting** (in direct contact) with the cortex without intervening normal WM
- **T2-FLAIR** sequence (preferably 3D) or **DIR** (cortical lesions)
- JC lesions typically involve the **U-fibers**



Filippi et al., Brain 2019

Spinal cord lesions

- Multiple, small and **short**
- **Cervical** portion is more frequently involved

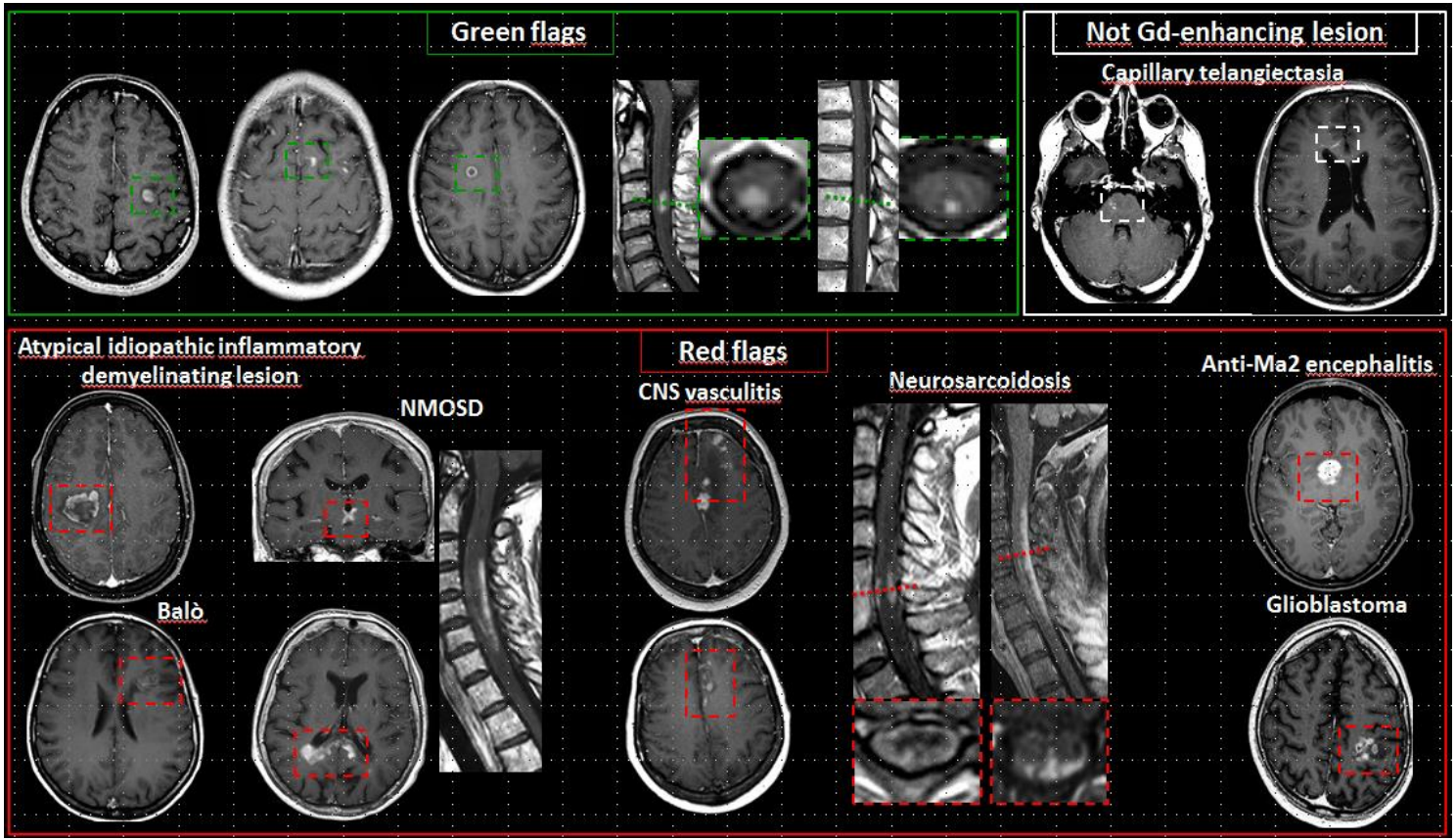


Filippi et al., Brain 2019

Gadolinium-enhancement

Contrast enhancement suggestive of MS:

- **nodular**
- **open-ring**
- **(closed-ring)**



Filippi et al., Brain 2019

Clinical case 1 (Revisited)

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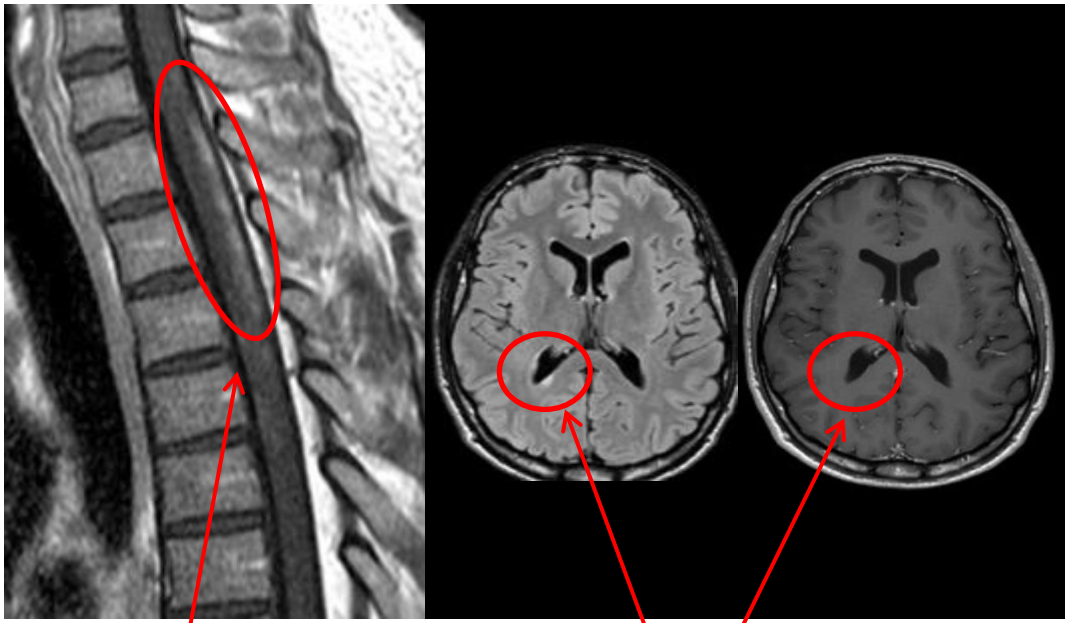

One (probably) symptomatic spinal cord enhancing lesion

One non-enhancing PV lesion

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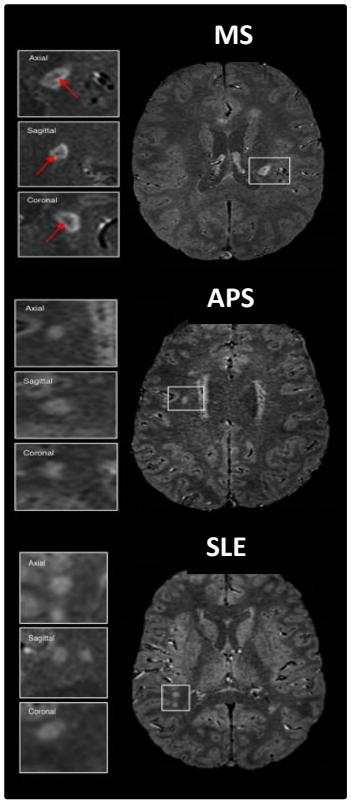
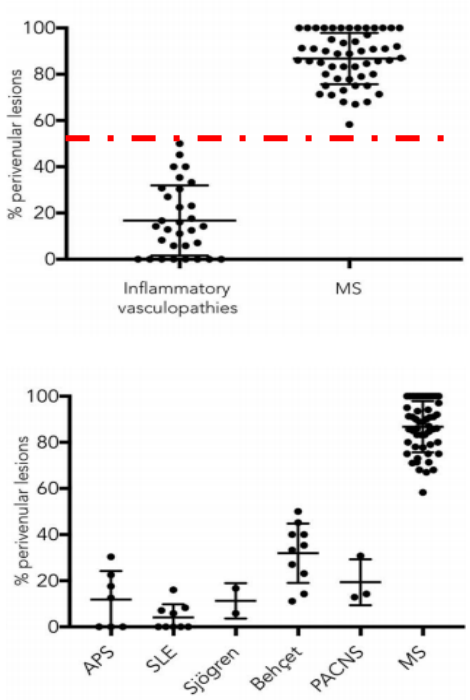
Atypical features: Leptomeningeal and pial enhancement → Neurosarcoidosis

Future MRI criteria

Central vein sign

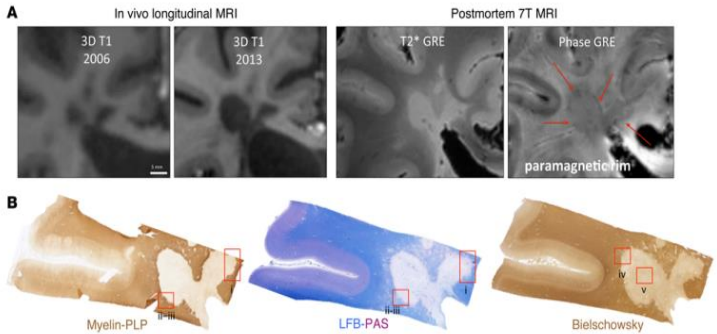




Maggi et al., Ann Neurol 2018

Iron rim

Absinta et al., J Clin Invest 2016



Activated microglia **Myelin degradation** **Iron** **Axonal loss**

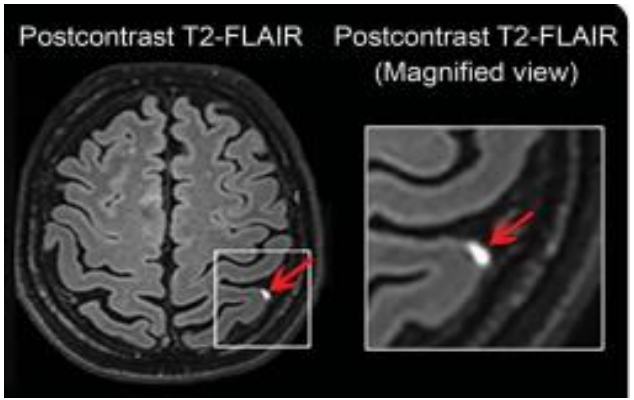
Results: 112 CIS, 103 RR, 49 PMS and 35 non-MS patients were included

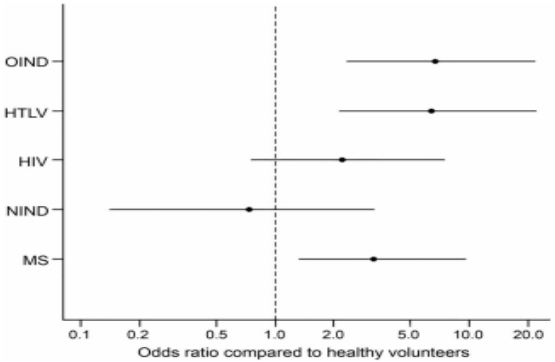
- 48% of CIS, 59% of RR and 39% of PMS patients had at least one iron rim
- **None of the non-MS patients had any iron rims**

Clarke et al., ECTRIMS 2019

Future MRI criteria

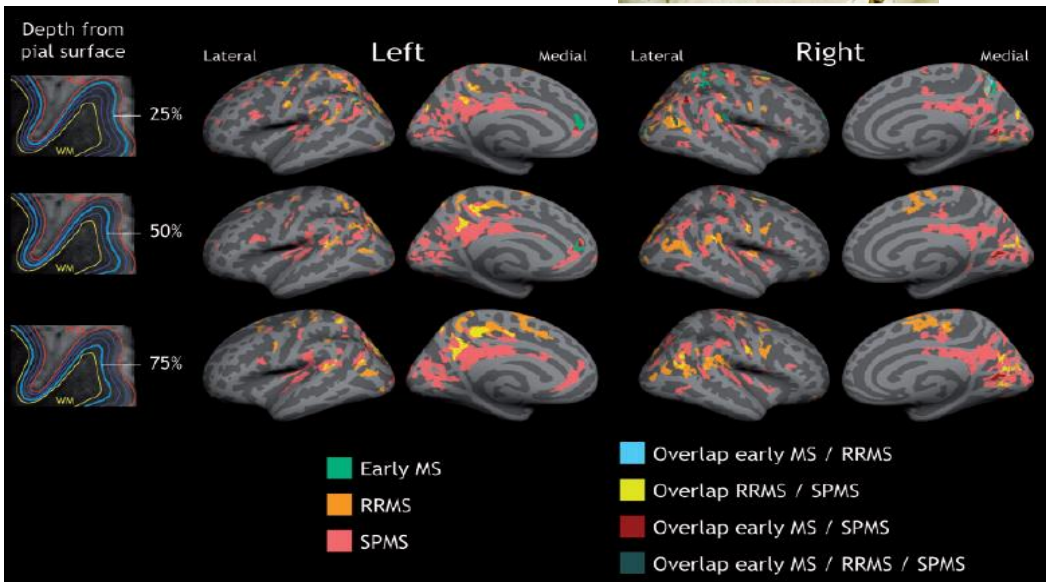
Leptomeningal enhancement





Absinta et al., Neurology 2017

Subpial demyelination



Mainero et al., Brain 2015

Key messages

- **Refinement of MRI criteria to show DIS and DIT in MS patients with a simplified ("unified“) approach**
- **The clinical context remains central**
- **MR quality should be of high standard**
- **Lesion identification and assessment of MRI scans should be done in the appropriate clinical context by qualified personnel**
- **New highly-specific MRI hallmarks of MS are under investigation**

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