Diagnosis of MS

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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
Jean-Martin Charcot, Leçons du mardi, 1868

« 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 »

Schumacher, 1965

Background
2010 McDonald Revised criteria

DIS

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

DIT

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
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


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


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.
### Revised 2010 McDonald and MAGNIMS 2016

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>aHR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td><strong>DIS + DIT (36 months)</strong></td>
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<tr>
<td>Revised McDonald 2010</td>
<td>2.52 (1.78-3.58)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Inclusion of symptomatic lesions</td>
<td>2.54 (1.77-3.65)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Inclusion of 3 PV lesions</td>
<td>2.54 (1.80-3.58)</td>
<td>&lt;0.0001</td>
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<td>Inclusion of CL</td>
<td>2.60 (1.83-3.71)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Inclusion of ON</td>
<td>2.58 (1.81-3.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>MAGNIMS 2016</strong></td>
<td>2.95 (2.04-4.26)</td>
<td>&lt;0.0001</td>
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</table>

Filippi et al., Lancet Neurol 2018

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**DIS + DIT**

![Graph showing survival analysis](image-url)
**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

<table>
<thead>
<tr>
<th>DIS</th>
<th>DIT</th>
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| ≥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

<p>| | |</p>
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| **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
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
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
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
Is this MS (McDonald 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**
Is this MS (McDonald 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
<table>
<thead>
<tr>
<th>Lesion category</th>
<th>Green flags</th>
<th>Red flags</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Periventricular</strong></td>
<td>- <strong>Location:</strong> abutting the lateral ventricles without intervening white matter</td>
<td>- <em>Periependymal lesions</em> surrounding the lateral ventricles (NMOSD)</td>
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<td></td>
<td>- <em>Infarcts or microbleeds</em> (amyloid angiopathy, cerebrovascular disease)</td>
<td>- <em>Extensive symmetric</em> white matter lesions (leukoedystrophy)</td>
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<td>- <em>Rounded lesions centrally located in the corpus callosum</em> (<em>snowball</em>-like lesion) (Susac syndrome)</td>
<td>- <em>Infarcts or microbleeds</em></td>
</tr>
<tr>
<td><strong>Juxtacortical/cortical</strong></td>
<td>- <strong>Location:</strong> touching or within the cortex</td>
<td>- <em>Infarcts or microbleeds</em> (amyloid angiopathy, cerebrovascular disease)</td>
</tr>
<tr>
<td><strong>Infratentorial</strong></td>
<td>- <strong>Location:</strong> 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</td>
<td>- <em>Infarcts or microbleeds</em> (amyloid angiopathy, cerebrovascular disease)</td>
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<td>- <em>Symmetric lesions</em> in the central pons (amyloid angiopathy, cerebrovascular disease)</td>
<td>- <em>Periaqueductal lesions</em> (NMOSD)</td>
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<td>- <em>Area postrema lesions</em> (NMOSD)</td>
<td>- Medullary lesions <em>contiguous to cord lesions</em> (NMOSD)</td>
</tr>
<tr>
<td><strong>Spinal cord</strong></td>
<td>Multiple discrete <em>(focal)</em> lesions</td>
<td>- Longitudinal extensive transverse myelitis affecting ≥ 3 vertebral segments (NMOSD)</td>
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<td>- <strong>Shape:</strong> sagittal: cigar-like; axial: wedge-shaped</td>
<td>- <em>Cavities</em> (syringohydromyelia)</td>
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<td>- <strong>Size:</strong> small; ≤ 2 vertebral segments; &lt; half of the cord</td>
<td>- <em>Micro/macrolbeeds and ischemic lesions</em> (arteriovenous fistula, ischemic myelopathy)</td>
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<tr>
<td></td>
<td>- <strong>Location:</strong> cervical&gt;thoracic; peripheral region; lateral and posterior columns, but central gray matter not spared</td>
<td>- <em>Indistinct/diffuse/increasing</em> (malignancy)</td>
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<tr>
<td></td>
<td>- <strong>Signal characteristics:</strong> T1-hypointensity (&gt; at higher field strengths)</td>
<td>- Lesion involving only the gray matter (NMOSD, infections, ischemia)</td>
</tr>
<tr>
<td><strong>Gadolinium-enhancing lesions</strong></td>
<td>- <strong>Shape:</strong> nodular; open-ring; closed-ring</td>
<td>- Large or multiple <em>closed-ring enhancement</em> (ADEM, malignancy, infection)</td>
</tr>
<tr>
<td></td>
<td>- <strong>Location:</strong> brain&gt;spinal cord</td>
<td>- <em>(Lepto)meningeal/root enhancement</em> (neurosarcoidosis)</td>
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<td>- <em>Trident sign</em> (neurosarcoidosis)</td>
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<td>- <em>Pancake sign</em> (spondioliothic myelopathy)</td>
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<td></td>
<td>- <em>Punctate or miliary enhancement</em> (CLIPPIERS, vasculitis, PML, Susac syndrome)</td>
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<td>- <em>Band-like enhancement</em> (Baló’s concentric sclerosis)</td>
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<td></td>
<td>- <em>Cloud-like enhancement</em> (NMOSD)</td>
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<td></td>
<td></td>
<td>- <em>Purely cortical enhancement</em> (vasculitis, ischemic lesion)</td>
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<tr>
<td></td>
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<td>- Persistence of enhancement &gt;3 months (malignancy)</td>
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</tbody>
</table>
Practical guidelines (MS vs NMOSD)

<table>
<thead>
<tr>
<th>Multivariate logistic regression</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>JC/C</td>
<td>28.97** (4.47-187.76)</td>
<td>0.0004</td>
</tr>
<tr>
<td>LTM</td>
<td>23.62* (2.85-195.56)</td>
<td>0.003</td>
</tr>
<tr>
<td>Periependymal lateral ventricles</td>
<td>10.21* (1.59-65.81)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dawson’s fingers</td>
<td>7.57** (1.47-38.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>PV</td>
<td>6.37** (0.89-45.41)</td>
<td>0.06</td>
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NMOSD vs MS

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
- Pons

Surface, cisterns/floor of the IV ventricle, trigeminal root-entry
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
• Multiple, small and short
• Cervical portion is more frequently involved
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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- No previous neurological history
- Sudden onset of paraparesis and sensory ataxia

One (probably) symptomatic spinal cord enhancing lesion

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Atypical features: Leptomeningeal and pial enhancement  →  Neurosarcoidosis
Future MRI criteria

Central vein sign

Iron rim

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

Maggi et al., Ann Neurol 2018

Clarke et al., ECTRIMS 2019
Future MRI criteria

Leptomeningal enhancement

Subpial demyelination

Absinta et al., Neurology 2017
Mainero et al., Brain 2015

Depth from pial surface
- Lateral
- Left
- Medial
- Lateral
- Right

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds ratio compared to healthy volunteers</th>
</tr>
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<tbody>
<tr>
<td>CIND</td>
<td></td>
</tr>
<tr>
<td>HTLV</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td>NIND</td>
<td></td>
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<tr>
<td>MS</td>
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</tbody>
</table>
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
References

- **Polman** et al., Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria, Ann Neurol 2011
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