**Multiple Sclerosis**

- Chronic and persistent inflammatory-demyelinating disease of the CNS, characterized pathologically:
  - Inflammation
  - Demyelination
  - Gliosis
  - Axonal loss

- Most common disabling neurological disease of young adults
- Women affected more than men (2:1)
- Symptoms onset between 20 and 40 years of age
- 1.3 to 2.5 million estimated cases of MS worldwide; 350,000 in Western Europe
Multiple Sclerosis

Most people with MS have a normal or near-normal life expectancy (median survival time from onset is ~10 years shorter)

Brünnum-Hansen et al. Brain 2004

• Up to 60% are no longer fully ambulatory 20 years after onset, with major implications for their quality of life and the financial cost to society

• No curative treatment, although different disease modifying treatments (DMT) significantly decrease the frequency and severity of relapses and delay permanent disability

No single clinical feature or diagnostic test is sufficient for the diagnosis of this disease

Optic neuritis  Mielitis  Brainstem syndrome

Who will develop multiple sclerosis?

Who will develop disability?
Diagnostic criteria
Clinical

Diagnostic Criteria:
- Allison y Millar (1954)
- McAlpine (1965)
- Schumacher (1965)
- Rose (1976)
- Poser et al. (Ann Neurol. 1983)

Dissemination in space and time
Exclusion of other diagnosis

Clinical attack

CDMS

Different CNS topographies

Optic neuritis Brainstem syndrome

CIS  CDMS

Clinical threshold

CIS

RR

SP

Poser criteria (clinical)
Treatment initiated at different stages of MS can affect outcomes

![Diagram showing different stages of MS (Preclinical, CIS, RRMS, SPMS) and treatment outcomes over time]

**MRI revolution in clinical practice**

Ten patients with multiple sclerosis (MS) were scanned by means of cranial X-ray computed tomography (CT) with and without intravenous contrast enhancement, and by nuclear magnetic resonance (NMR) using an inversion-recovery sequence. NMR demonstrates abnormalities in MS on a scale not previously seen except at necropsy.

1981


2012

MORE THAN 30 YEARS OF PROGRESS
Multiple Sclerosis
Conventional MR imaging

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

Tintoré et al. Ann Neurol 2005
Fisniku et al. Brain 2008
MR negative 36\%

38% MRI evidence of MS

Clinical threshold

21 %

Median time to conversion 6.0 years

CIS

20 years CDMS

Brain and spinal cord MRI
Role in the initial diagnosis

- International Panel
- AIMS:
  - Re-assess existing criteria
  - Retain useful features of prior criteria
  - Integrate imaging in diagnostic criteria
  - Clarify definitions; simplify categories
  - Create a scheme useful for practitioners

Tintoré et al. Ann Neurol 2005
Fisniku et al. Brain 2008
McDonald criteria

Dissemination in *time* and *space*
Exclusion of other diagnosis

- Clinical evidence:
  - Historical symptoms
  - Objective signs
- Paraclinical investigations:
  - MRI
  - CSF
  - VEP (PPMS)

Brain hemispheres

Eye/ON

Brain stem/ Cerebellum

Spinal cord

MRI criteria for dissemination in space (DIS) for MS

<table>
<thead>
<tr>
<th>DIS</th>
<th>3 or more of:</th>
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<tbody>
<tr>
<td></td>
<td>9 T2 lesions or 1 Gd-enhancing lesion</td>
</tr>
<tr>
<td></td>
<td>3 or more PV lesions</td>
</tr>
<tr>
<td></td>
<td>1 or more JC lesions</td>
</tr>
<tr>
<td></td>
<td>1 or more PF lesions</td>
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<tr>
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<td>1 cord lesion can replace 1 brain lesion</td>
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Barkhof-Tintore criteria

Gd = gadolinium enhancing lesion; PV = periventricular; JC = juxtacortical; PF = posterior fossa; BS = brainstem; SC = spinal cord
**MRI criteria for dissemination in space (DIS) for MS**

**McDonald 2001**
(McDonald et al. Ann Neurol 2001)

**McDonald 2005**
(Polman et al. Ann Neurol 2005)

**DIS**
3 or more of:
- 9 T2 lesions or 1 Gd-enhancing lesion
- 3 or more PV lesions
- 1 or more JC lesions
- 1 or more PF lesions
- 1 cord lesion can replace 1 brain lesion

**McDonald 2001**
(McDonald et al. Ann Neurol 2001)

**McDonald 2005**
(Polman et al. Ann Neurol 2005)

**DIS**
3 or more of:
- 9 T2 lesions or 1 Gd-enhancing lesion
- 3 or more PV lesions
- 1 or more JC lesions
- 1 or more PF lesions
- 1 cord lesion can replace 1 brain lesion

- A SC lesion can replace an infratentorial lesion
- An enhancing SC lesion is equivalent to an enhancing brain lesion
- Any number of SC lesions can be included in total lesion count

**Barkhof-Tintore criteria + SC**

**Gd** = gadolinium enhancing lesion; **PV** = periventricular; **JC** = juxtacortical; **PF** = posterior fossa; **BS** = brainstem; **SC** = spinal cord

**Conversion to CDMS**

**Baseline MRI**

Cumulative probability developing CDMS

- 0 Barkhof criteria
- 1-2 Barkhof criteria
- 3-4 Barkhof criteria

Time since first attack (months)

Tintore et al. Neurology 2006
Time to reach EDSS 3.0

Baseline MRI

EDSS at 5 years correlates with number of Barkhof criteria at baseline (r=0.46, p<0.0001)

MRI criteria for dissemination in time (DIT) for MS

<table>
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<th>McDonald 2001</th>
<th>McDonald 2005</th>
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(i) A Gd-enhancing lesion at least 3 months after CIS onset
(ii) A new T2 lesion with reference to a baseline scan obtained at least 30 days after CIS onset

Gd = gadolinium enhancing lesion; PV = periventricular; JC = juxtacortical; PF = posterior fossa; BS = brainstem; SC = spinal cord
MRI criteria for dissemination in time (DIT) for MS

McDonald 2001
(McDonald et al. Ann Neurol 2001)

McDonald 2005
(Polman et al. Ann Neurol 2005)

<table>
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<th>DIT</th>
<th>Timing of Scanning</th>
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<td>(i) A Gd-enhancing lesion at least 3 months after CIS onset</td>
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Gd = gadolinium enhancing lesion; PV = periventricular; JC = juxtacortical; PF = posterior fossa; BS = brainstem; SC = spinal cord

Optic neuritis
CIS
> 3 months

Clinical threshold
CIS
RR
SP

Clinical events
Subclinical events

McDonald criteria 2005
Clinical threshold

April 2004

Brain MR

McDonald 2001/5 criteria

December 2005

Brain MR

Poser criteria

139 patients with CIS

80% CDMS at 3 years

CDMS

1y 11%

2y 24%

3y 44%

McDonald

1y 37%

Tintoré et al. Neurology 2003
Criticism to McDonald 2005 criteria

- Too complicated for demonstration DIS and DIT
- Difficult to remember
- Too restrictive: DIS/DIT
- Require two MRI examinations in most cases

New version required

- Based in new evidences
- Keep specificity, increase sensibility
- Simplify current definitions
- Create useful schemes for daily practice

New proposal: Dissemination in space

≥ 1 lesion in each of ≥2 characteristic locations:

- Periventricular
- Juxtacortical
- Posterior fossa
- Spinal cord

Symptomatic lesions excluded in BS and SC syndromes

Swanton et al. JNNP 2006
New proposal: Dissemination in time

A new T2 lesion on follow up MRI irrespective of timing of baseline scan

No gadolinium required
Minimum of **two** scans needed

Multicenter validation of the new criteria for DIS (Swanton): conversion to CDMS
217 patients

<table>
<thead>
<tr>
<th>DIS y DIT</th>
<th>Sensitivity (95% C.I.)</th>
<th>Specificity (95% C.I.)</th>
<th>Accuracy (95% C.I.)</th>
<th>PPV (95% C.I.)</th>
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<tbody>
<tr>
<td>McDonald 2001</td>
<td>47.1% (36-58%)</td>
<td>91.1% (85-95%)</td>
<td>73.1% (67-79%)</td>
<td>78.4% (65-85%)</td>
</tr>
<tr>
<td>McDonald 2005</td>
<td>60.0% (49-70%)</td>
<td>87.8% (81-93%)</td>
<td>76.4% (70-82%)</td>
<td>77.3% (65-87%)</td>
</tr>
<tr>
<td>Swanton 2006</td>
<td>71.8% (61-81%)</td>
<td>87.0% (80-92%)</td>
<td>80.8% (75-86%)</td>
<td>79.2% (68-88%)</td>
</tr>
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MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study

*Josephine K Swanton, Alex Rowa, Max Theuret, Dalli Kallio, Petri Hiltunen, Marcus Ilmarinen, Kari Konttinen, Alastair Thompson, Xavier Kastorfer, Dominik Miller*

*Lancet Neurology 2007*
New proposal: Dissemination in time

Multicenter European study on 250 CIS patients: conversion to CDMS

Any time (concomitant enhancing / non enhancing lesion)
21-30% of CIS patients

32 year-old woman with brainstem syndrome

Rovira et al. Arch Neurol 2009

New proposal: Dissemination in time

Multicenter European study on 250 CIS patients: conversion to CDMS

Rovira et al. Arch Neurol 2009
Brain MRI ± spinal cord (any time) 
DS + and DT +

Multiple Sclerosis

DS: Swanton criteria (Lancet Neurol 2007) 
DT: Swanton, Rovira criteria (Lancet Neurol 2007; Arch Neurol 2009)

Montalban et al. Neurology 2010
Multiple Sclerosis

DS: Swanton criteria (Lancet Neurol 2007)
DT: Swanton, Rovira criteria (Lancet Neurol 2007; Arch Neurol 2009)

Montalban et al. Neurology 2010

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

Chris H. Polman, MD, PhD,1 Stephen C. Reingold, PhD,1 Brenda Banwell, MD,3 Michel Clenet, MD, Jeffrey L. Cohen, MD,3 Massimo Filippi, MD,7 Kazuo Fujihara, MD,7 Eva Havrdova, MD, PhD,8 Michael Hutchinson, MD,9 Ludwig Kappos, MD,10 Fred D. Lublin, MD,10 Xavier Montalban, MD,11 Paul O’Connor, MD,11 Magnhild Sandberg-Wollheim, MD, PhD,11 Alan J. Thompson, MD,11 Emmanuel Waubant, MD,11,12,14 Brian Wieser, MD,11,12 and Jerry J. Wolinsky, MD,11

New evidence and consensus has led to further revisions of the McDonald Criteria for diagnosis of multiple sclerosis. The use of imaging for demonstration of dissemination 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 interpretation.

DIS Can Be Demonstrated by ≥1 T2 lesion in at least 2 of 3 Areas of the CNS:
- Periventricular
- Juxtacortical
- Infratentorial
- Spinal cord

Based on Swanton et al. 2006; 2007; 2007;
*Gadolinium enhancement of lesions is not required for DIS.
*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.

DTI Can Be Demonstrated by:
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
2. Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time
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 scan.

These revisions...
...simplify the Criteria,
...preserve their diagnostic sensitivity and specificity
...address their applicability across populations (pediatric, Latino-America, Asian)
...may allow earlier diagnosis
...more uniform and widespread use

Polman et al., Ann Neurol 2011; 69:292-302
2010 Diagnostic criteria: key points

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

“In applying the McDonald Criteria, it remains imperative that alternative diagnoses are considered and excluded.”

Differential diagnosis of suspected multiple sclerosis: a consensus approach

DH Miller1, BG Weinshenker2, M Filippi2, BL Banwell3, JA Cohen3, MS Freedman3, SL Galetta3, M Hutchinson4, RT Johnson4, L Kappos15, J Kira11, FD Lublin5, HF McFarland16, X Montalban17, H Panitch18, JR Richert19, SC Reingold10,12 and CH Polman19

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 and shape of lesions
  - Involvement:
    - callososeptal interface
    - U-fibers
    - brainstem
    - spinal cord
Causes of MRI focal white matter lesions
Young patients (<50 years)

Incidental finding:
- normal population
- migraine

Hipoxic-ischemic vasculopathies
- small-vessel disease
- hyperhomocysthenimia
- CADASIL

Multiple sclerosis and variants

Vasculitis:
- primary
- systemic: lupus, Behçet, APLAS

Metabolic:
- inherited: Fabry, Leber, xantomatosis, adult forms of leukodystrophy
- acquired: B12 def, copper def

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 and shape of lesions
- Involvement:
  - callososeptal interface
  - U-fibers
  - brainstem
  - spinal cord

Ovoid lesions
Juxtacortical lesions
Spinal cord lesions
FLAIR
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 and shape of lesions
  - Involvement:
    - callososeptal interface
    - U-fibers
    - brainstem
    - spinal cord

Sensorineural hearing loss, branch retinal artery occlusions
**Multiple Sclerosis**

**MS diagnosis is a subjective and objective process**

- **Subjective: best made by experts**
  - Clinical features, differential diagnosis
  - Interpretation of paraclinical test (MRI, CSF analysis, EP)

- **Objective: diagnostic criteria**
  - Based on demonstration of lesions disseminated in space and time
  - Minimize false positive/negative diagnosis
  - Facilitate a prompt and accurate diagnosis and early treatment with DMTs