# Diagnostic and differential diagnostic aspects of multiple sclerosis

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# Disclosures

- Professor Sten Fredrikson has during recent years received honoraria for lectures, educational activities and/or consultancy from Allergan, Bayer, Biogen, Genzyme, Merck, Novartis, Roche, Sanofi, Teva.

*”Multiple sclerosis is what a good clinician would call multiple sclerosis”*

John Kurtzke, 1970

*”Nothing shuts off critical neurological thought processes faster than a diagnosis of multiple sclerosis”*

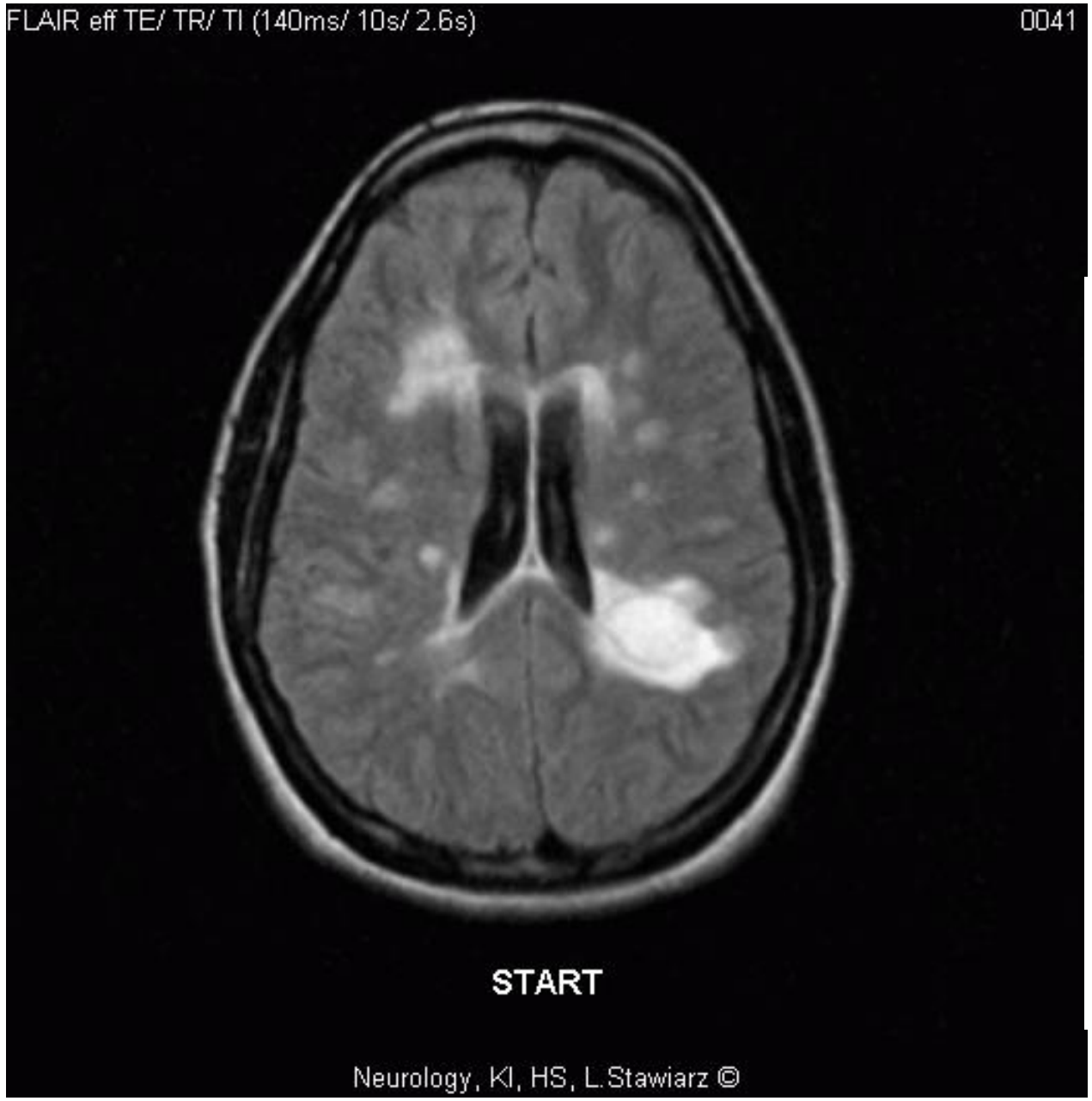
Semin Neurol 1985:5:94-98

# Some possible pitfalls and problems

- There is no definitive diagnostic test for MS
- Misdiagnosis estimated to be 5-10% (or higher?, up to 35% reported)
- Diagnosis is based on (changing) criteria – what is the interrater reliability of the criteria for atypical cases?
- The occurence of ”preclinical” diagnosis based on MRI findings
- A broad spectrum of (treatable) differential diagnoses
- Coincidence of MS and psychiatric/psychological problems (and the latter symptoms constitute the major part of the functional disability)

# Key Steps in the Diagnostic Process

- **History:**
  - → **Previous episodes**
  - → **Other diseases**
  - → **Family history**
- **Comprehensive physical examination:**
  - → **‘Objective evidence’**
  - → **Other lesions**
- **Additional tests:**
  - → **MRI**
  - → **CSF**



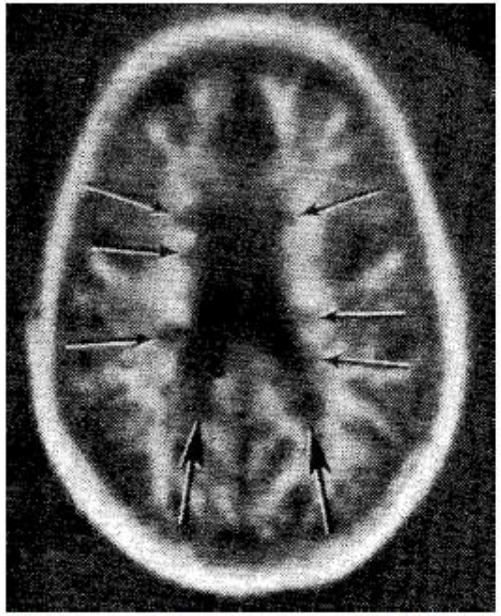
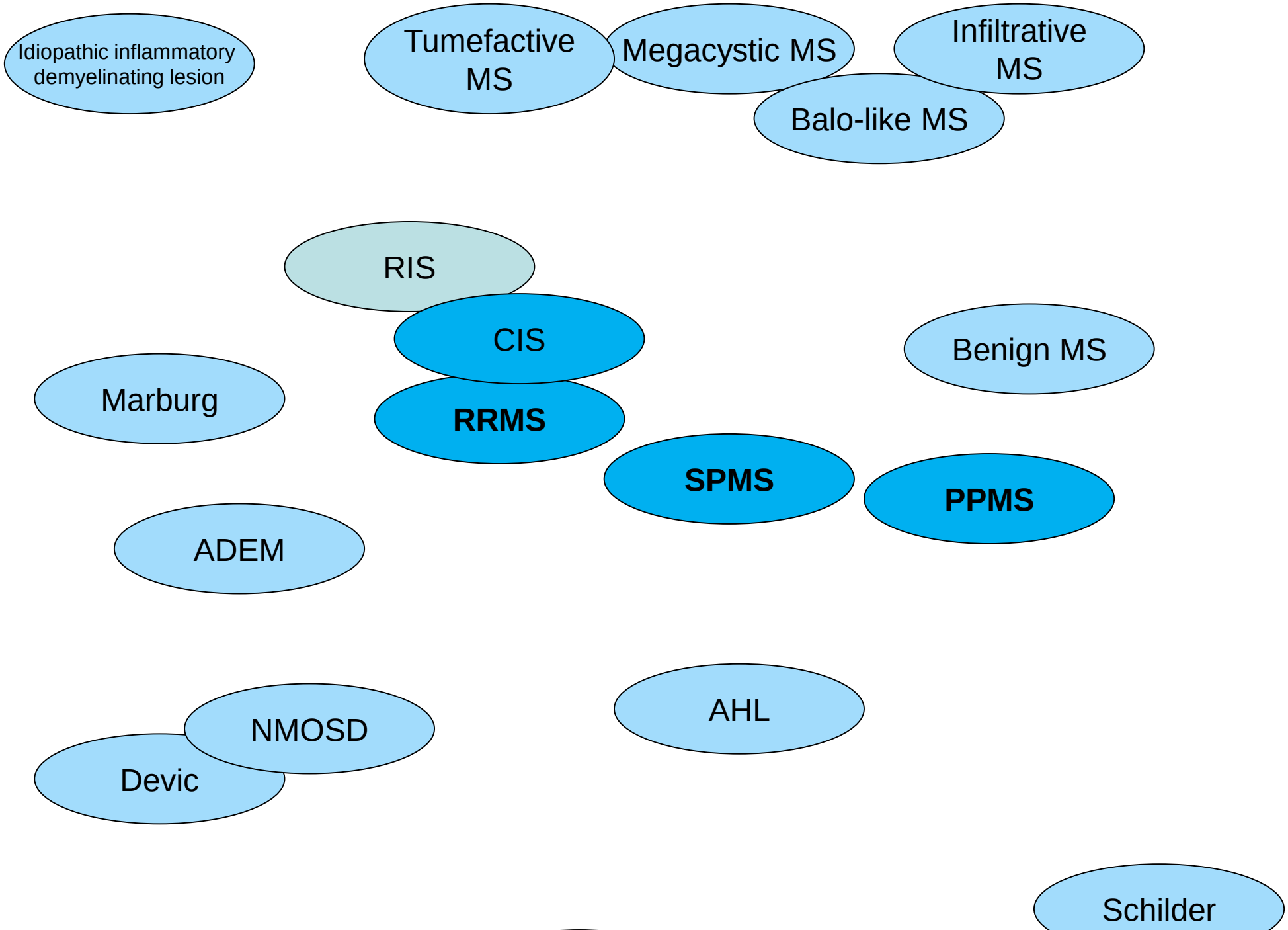



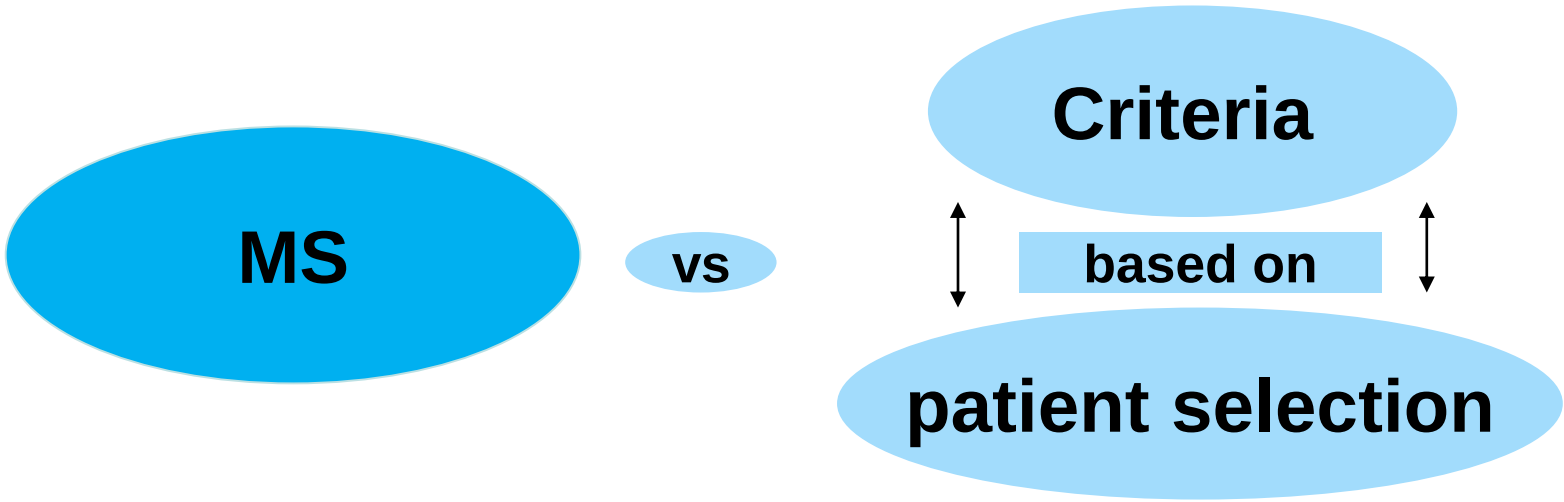
***Figure 5.*** *The first published brain MRI in MS visualizing multiple lesions (arrows) in an 18-year-old female with MS.*[56]

**Young IR et al, Lancet 1981:2:1063-66**


Idiopathic inflammatory demyelinating lesion
Tumefactive MS
Megacystic MS
Infiltrative MS
Balo-like MS
RIS
CIS
Benign MS
Marburg
RRMS
SPMS
PPMS
ADEM
AHL
NMOSD
Devic
Schilder

# What is in a name?

- Intention tremor, nystagmus and slurred speech  (1870´s)
- Temporal pallor of the optic disc, absence of abdominal reflexes and ”spastic” reflexes in the legs (1915)
- McDonald 2001, 2005, 2011
- Next???




Applicability to ”atypical” cases?

# Issues related to the diagnosis

## Evaluation of multiple sclerosis diagnostic criteria in Suzhou, China – risk of under-diagnosis in a low prevalence area

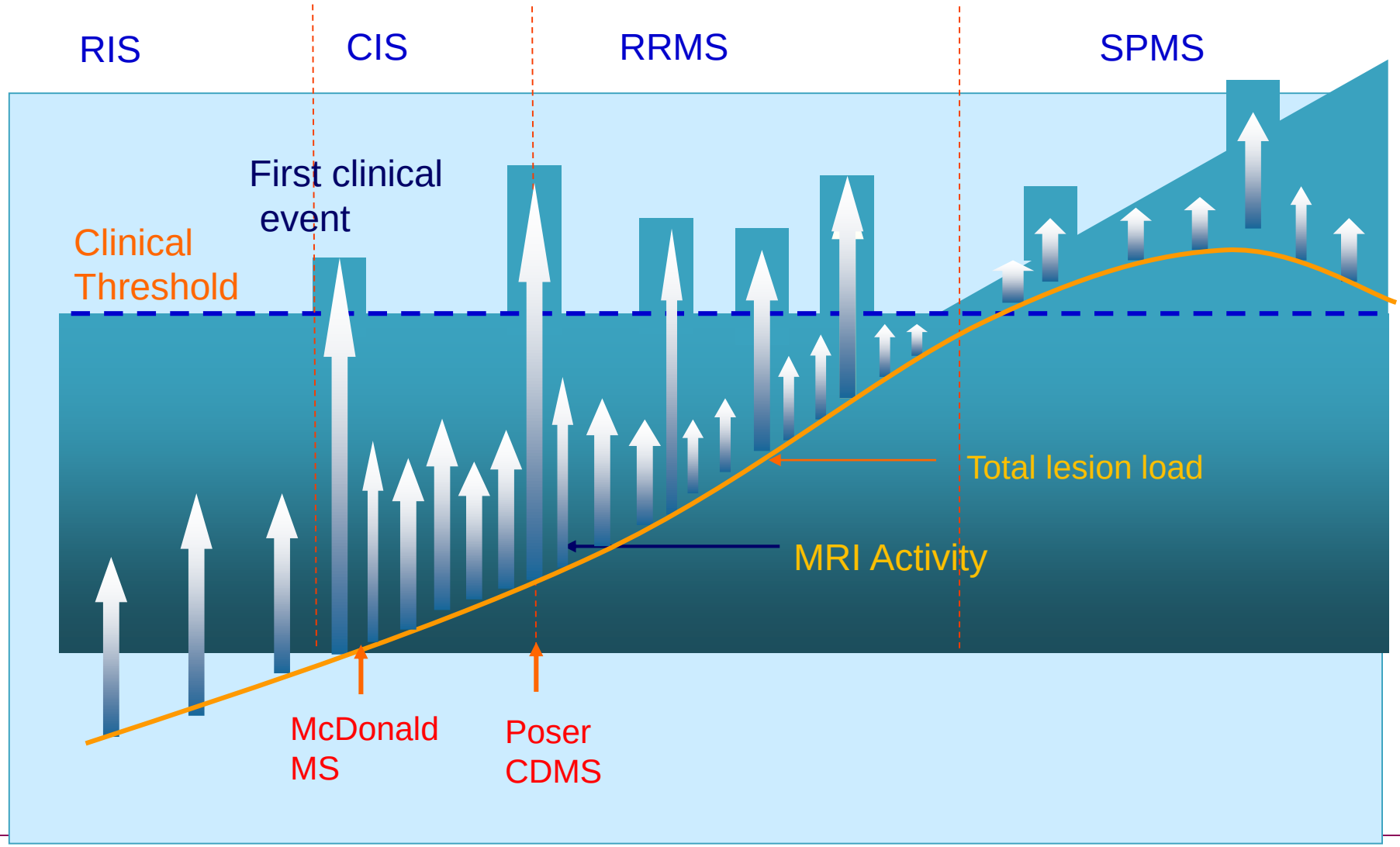
Cheng X-J, Cheng Q, Xu L-Z, Zhao H-Q, Zhao Z, Wang W, Jiang G-X, Fredrikson S. Evaluation of multiple sclerosis diagnostic criteria in Suzhou, China – risk of under-diagnosis in a low prevalence area. Acta Neurol Scand: 2010: 121: 24–29.


X.-J. Cheng[1,2], Q. Cheng[1,2], L.-Z. Xu[3], H.-Q. Zhao[4], Z. Zhao[5], W. Wang[6], G.-X. Jiang[2,7], S. Fredrikson[8]

[1]Department of Neurology, Ruijin Hospital, Medical

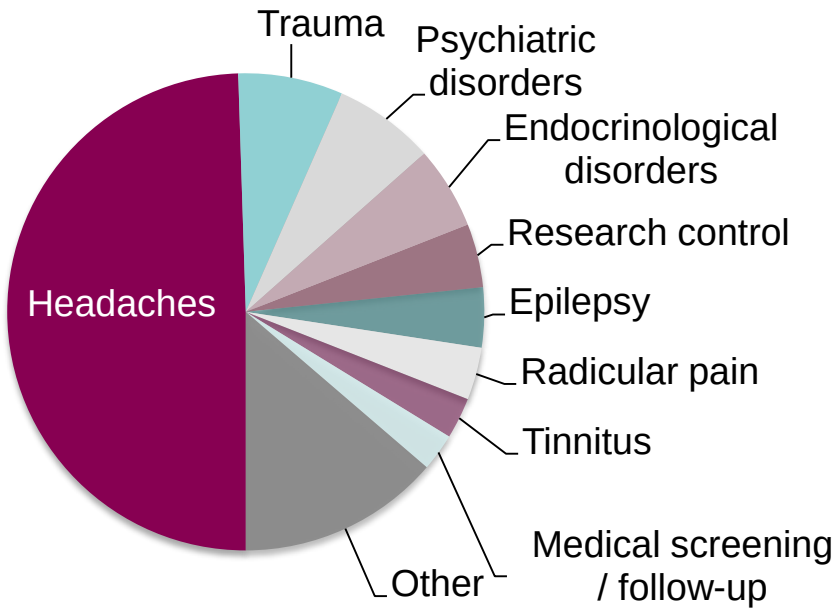
*If you don´t expect MS, you will not give the diagnosis*

# The evolution of MS

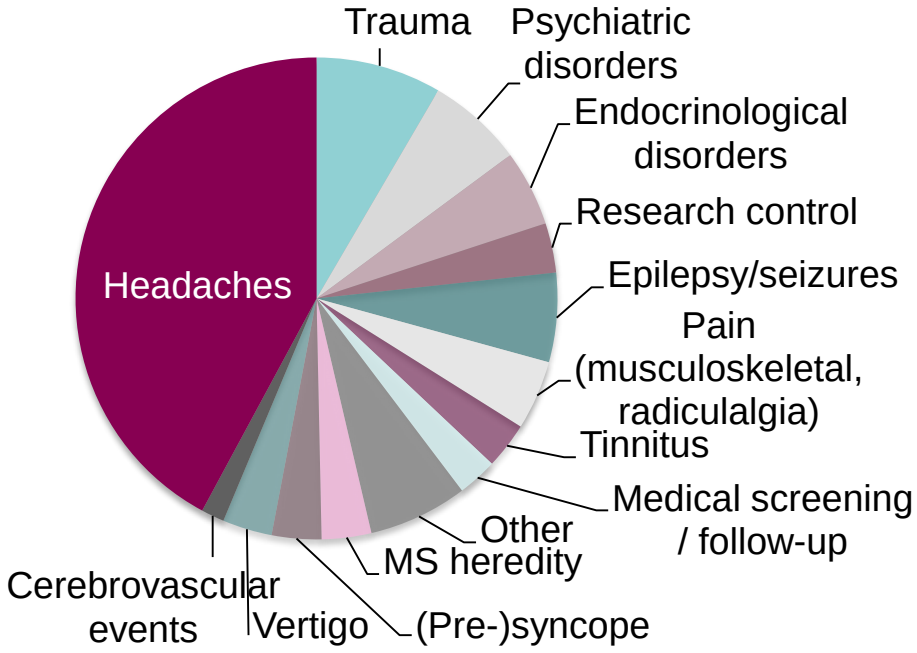



Adapted from Trapp BD et al. Neuroscientist. 1999;5(1):48-57

# RIS




Granberg T et al. Mult Scler 2012;19:271-280




Okuda DT, et al. *PLoS ONE.* 2014;9(3):e90509.

# Current RIS criteria

| | |
|---|---|
| **A** | Incidental white matter anomalies in the CNS meeting the following MRI criteria:<br>1. Ovoid, well-circumscribed and homogeneous foci with or without involvement of the corpus callosum<br>2. T2 hyperintensities measuring >3mm and fulfilling Barkhof criteria (≥3 out of 4) for dissemination in space.[27]<br>3. CNS white matter anomalies not consistent with a vascular pattern |
| **B** | No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction |
| **C** | The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of functioning |
| **D** | The MRI anomalies are not due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure) or a medical condition |
| **E** | Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum |
| **F** | The CNS MRI anomalies are not better accounted for by another disease process |

Okuda DT, et al. *Neurology*. 2009;72(9):800–805.

# Future aspects

## Proposition for new RIS criteria

| | |
|---|---|
| **A** | MRI findings fulfilling the current diagnostic MRI criteria for DIS.* |
| **B** | No symptoms or neurological findings typical for MS.** |
| **C** | The findings should not be more likely or better explained by another disease process, comorbidities or substances*** |

**Currently the 2010 McDonald criteria.*[25]
***Symptoms should be interpreted with the consultation of an experienced MS neurologist. Only symptoms that do not render a CIS or MS diagnosis, following a thorough physical neurological examination, are accepted.*
****The concept of "no better explanation" has been thoroughly discussed by Charil et al.*[26]

25. Polman CH, et al. *Ann. Neurol.* 2011;69(2):292–302.
26. Charil A, et al. *Lancet Neurol*. 2006;5(10):841–852.

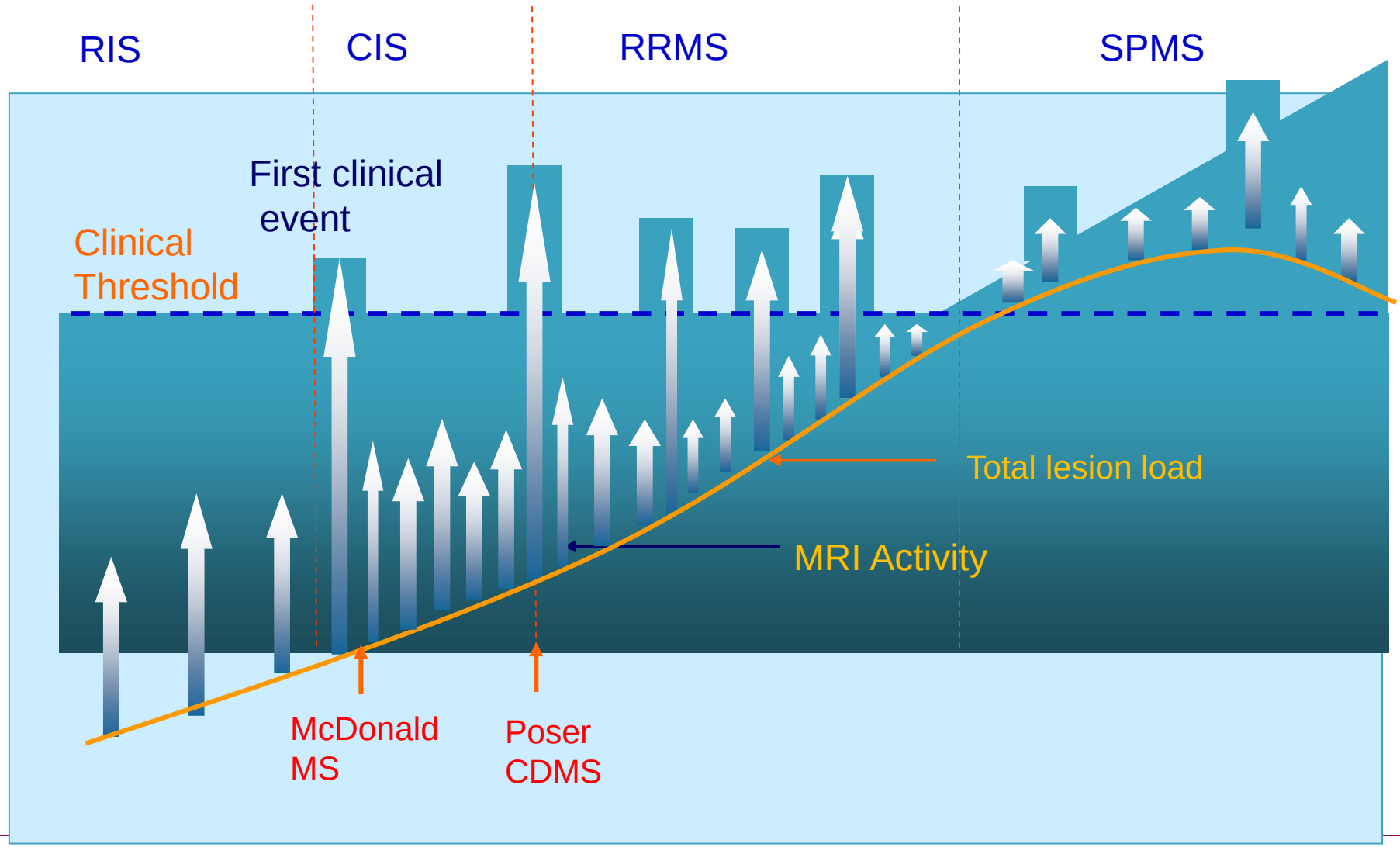
# RIS
# Radiologically isolated syndrome

- *Approximately two-thirds of persons with RIS show radiological progression and one-third develop neurological symptoms during mean follow-up times of up to five years. Cervical cord lesions are important predictors of clinical conversion.*

Mult Scler Jour 2013 Mar;19(3):271-80.

**Radiologically isolated syndrome--incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review.**

# The evolution of MS




Adapted from Trapp BD et al. Neuroscientist. 1999;5(1):48-57

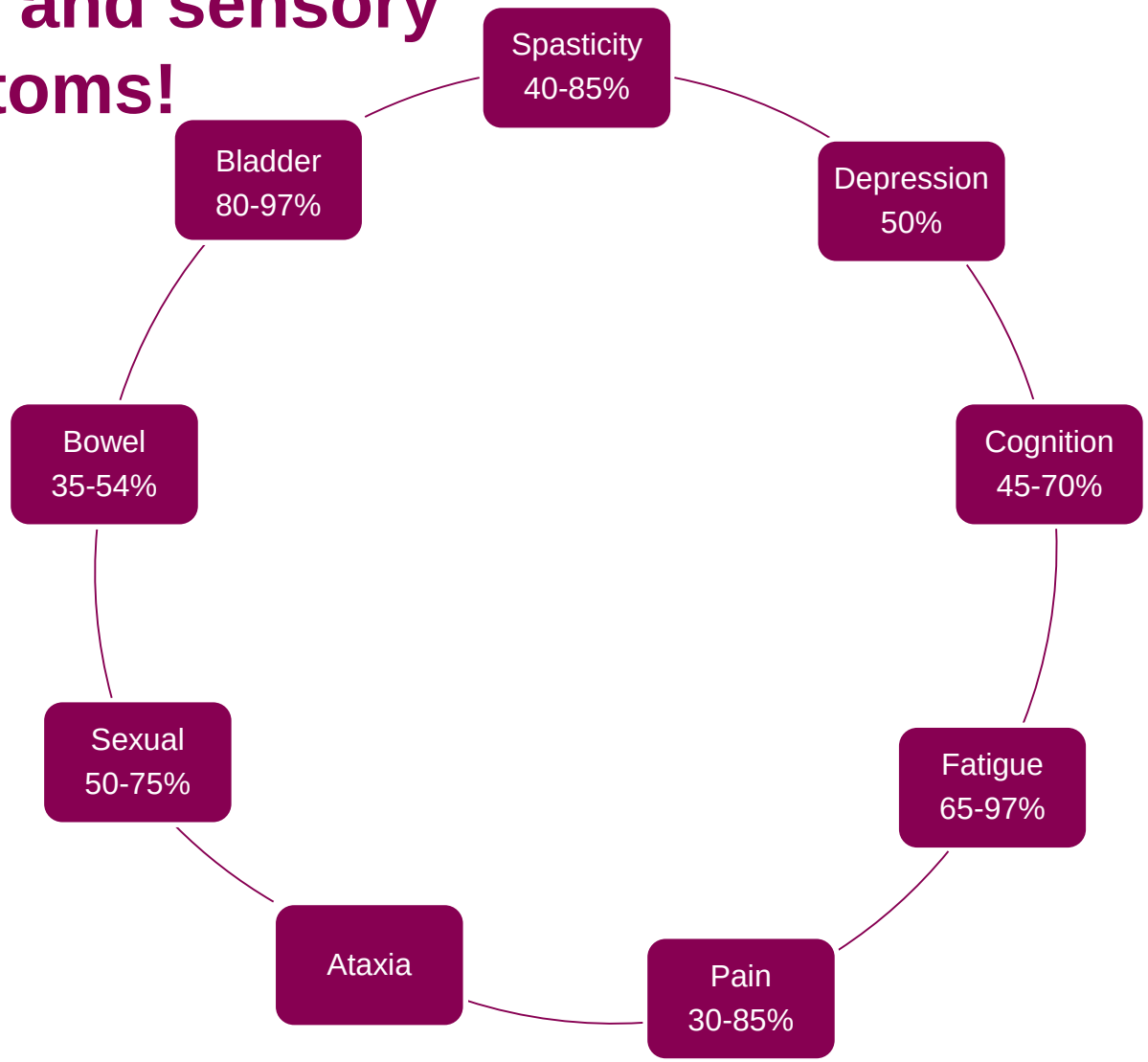
# What is a Clinically Isolated Syndrome?

- A clinically isolated syndrome (CIS) is a first acute or subacute episode of neurological dysfunction with a high suspicion of development of multiple sclerosis
- A CIS is usually the first clinical event in an MS patient
- Magnetic resonance imaging (MRI) findings compatible with:
  - → No or minimal oedema/mass effect
  - → T2-hyperintense lesions
  - → Contrast enhancing lesions
  - → Location of lesion
- Spontaneous or steroid responsive remissions

*To exclude other pathologies that may underly the same syndrome*

*(Always look for RED FLAGS, Miller DH, Mult Scler 2008:14:1157-74)*

# MS symptoms – more than motor and sensory symptoms!



# Multiple sclerosis and diagnosis

- The main principle: **dissemination in time (DIT) and space (DIS)**
  - Schumacher 1965[5]
  - Poser 1983[6]
  - McDonald 2001[7]
  - Revised McDonald 2005 (Polman)[8]
  - Revised McDonald 2011 (Polman)[9]
  - *New revision 2017-2018*

- Demonstration of DIS and DIT with MRI:
  - Paty 1988[10]
  - Barkhof 1997[11]
  - Revised Barkhof (Tintoré) 2000[12]
  - Swanton 2006[13]


5. Schumacher GA, et al. Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. Ann N Y Acad Sci. 1965;122(1):552–68.
6. Poser CM, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Ann Neurol. 1983;13(3):227–31.
7. McDonald WI, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol. 2001;50(1):121–7.
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9. Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Ann Neurol. 2011;69(2):292–302.
10. Paty DW, et al. MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. Neurology. 1988;38(2):180–5.
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12. Tintoré M, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. Am J Neuroradiol. 2000;21(4):702–6.
13. Swanton JK, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2006;77(7):830–3.

# Recent radiological classifications for MS lesions

| MS criteria | McDonald 2005[29] | McDonald 2010[25] |
|---|---|---|
| Radiological classification | Barkhof-Tintoré[81] | Swanton[71] |
| Demonstration of DIS | At least 3 out of:<br>≥3 periventricular lesions<br>≥1 juxtacortical lesion<br>≥1 infratentoriell or spinal lesion<br>≥1 contrast-enhancing or ≥9 lesions | At least 2 out of:<br>≥1 periventricular lesion<br>≥1 juxtacortical lesion<br>≥1 infratentoriell lesion<br>≥1 spinal lesion |
| Demonstration of DIT | - New lesion(s) ≥1 month after the initial clinical event<br>- Contrast-enhancing lesion(s) ≥3 months after the initial clinical event | - New/contrast-enhancing lesion(s) on follow-up *and/or*<br>- Concomitant asymptomatic contrast-enhancing lesion(s) |
| Sensitivity, specificity[82] | 60%, 88% | 72%, 87% |

Tintoré M, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. Am J Neuroradiol. 2000;21(4):702–6.

Swanton JK, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. J Neurol Neurosurg Psychiatry. 2006;77(7):830–3.

# Table 2. Comparison of the 2005 and 2010 McDonald DIS criteria.

**Table 2.** Comparison of the 2005 and 2010 McDonald DIS criteria.

| | | 2010 McDonald DIS criteria | | |
|---|---|---|---|---|
| | | Met | Not met | Total |
| **2005 McDonald DIS criteria** | Met | 63 | 2 | 65 (59.6%) |
| | Not met | 13 | 31 | 44 (40.4%) |
| | Total | 76 (69.7%) | 33 (30.3%) | *N* = 109 |

DIS: dissemination in space.

***Using 2010 McDonald criteria, 30% of the CIS patients could be diagnosed with MS using a single MRI scan***

Previous CIS patients will be MS patients according to the new criteria.
Thus, the average disease severity will be lower in both groups.
How will this switch influence clinical trials?

**Kang H et al. Mult Scler 2013;1352458513501230**



MULTIPLE SCLEROSIS JOURNAL
Formerly Multiple Sclerosis

| Clinical Presentation | Additional Data Needed for MS Diagnosis |
|---|---|
| ≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b] | None[c] |
| ≥2 attacks[a]; objective clinical evidence of 1 lesion | Dissemination in space, demonstrated by:<br>≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or<br>Await a further clinical attack[a] implicating a different CNS site |
| 1 attack[a]; objective clinical evidence of ≥2 lesions | Dissemination in time, demonstrated by:<br>Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or<br>A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or<br>Await a second clinical attack[a] |
| 1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome) | Dissemination in space and time, demonstrated by:<br>For DIS:<br>≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or<br>Await a second clinical attack[a] implicating a different CNS site; and<br>For DIT:<br>Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or<br>A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or<br>Await a second clinical attack[a] |
| Insidious neurological progression suggestive of MS (PPMS) | 1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria[d]:<br>1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions<br>2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord<br>3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) |

**Ann Neurol 2011:69:292-**

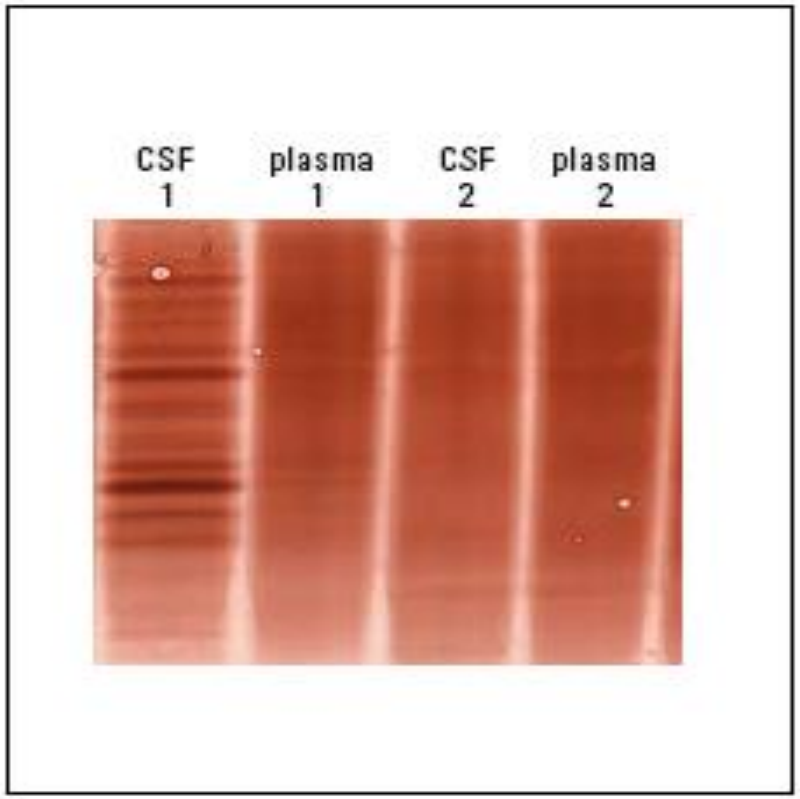
# Diagnostic criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Ann Neurol 2011:69:292-302

| PPMS May Be Diagnosed in Subjects With: |
| --- |
| 1. One year of disease progression (retrospectively or prospectively determined) |
| 2. Plus 2 of the 3 following criteria[a]: |
| A. Evidence for DIS in the brain based on ≥1 T2[b] lesions in at least 1 area characteristic for MS (periventricular, juxtacortical, or infratentorial) |
| B. Evidence for DIS in the spinal cord based on ≥2 T2[b] lesions in the cord |
| C. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) |

[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.
[b]Gadolinium enhancement of lesions is not required.
MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

# Oligoclonal bands




Nature Rev Neurol 2013:9:267-276

REVIEWS

**The utility of cerebrospinal fluid analysis in patients with multiple sclerosis**

*Martin Stangel, Sten Fredrikson, Edgar Meinl, Axel Petzold, Olaf Stüve and Hayrettin Tumani*

## Frequencies of abnormal CSF variables in clinically definite MS

| | |
|---|---|
| **Oligoclonal IgG in CSF** | **>95%** |
| **Increased IgG index** | **70-80%** |
| **Increased cell count** | **50%** |
| **Abnormal albumin ratio** | **12%** |

Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report
J Neurol Neurosurg Psych 1994:57:897-902

**Andersson M, Alvarez-Cermeno J, Bernardi G, Cogato I, Fredman P, Frederiksen J, Fredrikson S, Gallo P, Grimaldi LM, Gronning M, Keir G, Lamers K, Link H, Magalhaes A, Massaro AR, Ohman S, Reiber H, Rönnbäck L, Schluep M, Schuller E, Sindic CJM, Thompson EJ, Trojano M, Wurster W.**

***CSF is of particular value in patients:***
***-older than 50 years***
***-with vascular risk factors***
***-with migraine***
***-with non-specific neurologic symptoms***

# Differential diagnoses

# Some differential diagnoses to MS

- **ADEM, NMO, AHL, PML, Balo**
- ***Systemic*: Sarcoidosis, SLE, Behcet, Sjögren, Wegener**
- ***Vascular*: Stroke, Vasculitis, CADASIL, anti-phospholipid syndrome, AV-malformations, hemangioma**
- ***Metabolic*: Leukodystrophies (metachromatic/adreno-), mitochondrial disorders (MERFF, MELAS, Leber), B12-deficiency, CPM**
- ***Genetic*: SCAs, Friedreich, HSP**
- ***Neoplastic*: Lymphomas, paraneoplastic syndromes**
- ***Infection*: HIV, syphilis, Borrelia, herpes, Whipple**
- ***Psychiatric***
- ***Others (toxic, compression, neuromuscular (MG) etc)***

# RED FLAGS

- Lung involvement
- Multiple cranial neuropathies or polyradiculopathy
- Peripheral neuropathy
- Tendon xanthomas
- Cerebral venous sinus thrombosis
- Cardiac disease
- Myopathy
- Renal involvement
- Cortical infarcts
- Haemorrhages/microhaemorrhages
- Extrapyramidal features/ Movement disorders
- Livedo reticularis
- Retinopathy
- Calcifications on CT scans
- Bone lesions
- Diabetes insipidus
- Increase serum lactate level
- Selective involvement of the anterior temporal and inferior frontal lobe
- Hematological manifestations
- Lacunar infarcts
- Mucosal ulcers
- Myorhythmia
- Hypothalamic disturbance
- Recurrent spontaneous abortion or thrombotic events
- Simultaneous enhancement of all lesions
- Rash
- Arthritis, polyarthalgias, myalgias
- Amyotrophy
- Headache or meningismus

## REMEMBER:

- **Age?**
- **Abrupt onset?**
- **Short duration or poor recovery?**
- **Lack of typical symptoms?**
- **Nonspecific symptoms?**
- **Family history?**
- **Normal examination?**
- **Normal MRI/CSF?**

# Differential diagnosis based on presenting symptoms from the brainstem, spinal cord, optic nerves or cerebrum.

Mult Scler 2008:14:1157-74

# Brain stem presentation

| *MS* | *Less common* | *Atypical* |
|---|---|---|
| Internuclear ophthalmoplegia | Facial palsy, facial myokymia | |
| Ataxia and multidirectional nystagmus | Deafness | Vascular territory syndrome, e.g., lateral medullary |
| Sixth nerve palsy | One-and-a-half syndrome | Third nerve palsy |
| Facial numbness | Trigeminal neuralgia | Progressive trigeminal sensory neuropathy |
| | Paroxysmal tonic spasms | Focal dystonia, torticollis |

# Optic nerve presentation

| *MS* | *Less common* | *Atypical* |
|---|---|---|
| Unilateral optic neuritis | Bilateral simultaneous optic neuritis | Progressive optic neuropathy |
| Pain on eye movement | No pain | Severe, continuous orbital pain |
| Partial and mainly central visual blurring | No light perception | Persistent complete loss of vision |
| Normal disc or mild disc swelling | Severe disc swelling | Neuroretinitis (optic disc swelling with macular star) |
| | Uveitis (mild, posterior) | Uveitis (severe, anterior) |

# Spinal cord presentation

| *MS* | *Less common* | *Atypical* |
|---|---|---|
| Partial myelopathy | Complete transverse myelitis | Anterior spinal artery territory lesion (sparing posterior columns only) |
| Lhermitte's symptom | Radiculopathy, areflexia | Cauda equina syndrome |
| Deafferented hand | Segmental loss of pain and temperature sensation | Sharp sensory level to all modalities & localised spinal pain |
| Numbness | Partial Brown-Sequard syndrome (sparing posterior columns) | Complete Brown-Sequard syndrome |
| Urinary urgency, incontinence, erectile dysfunction | Faecal incontinence | Acute urinary retention |
| Progressive spastic paraplegia (asymmetrical) | Progressive spastic paraplegia (symmetrical) | Progressive sensory ataxia (posterior columns) |

## Cerebral presentation

| *MS* | *Less common* | *Atypical* |
|---|---|---|
| Mild subcortical cognitive impairment | Epilepsy | Encephalopathy (obtundation, confusion, drowsiness) |
| | Hemianopia | Cortical blindness |
| Hemiparesis | Chorea, myoclonus | Generalized movement disorder or Parkinsonian syndrome |

# Typical presentation of MS

- Internuclear ophthalmoplegia
- Ataxia and multidirectional nystagmus
- Sixth nerve palsy
- Facial numbness
- Unilateral optic neuritis with pain on eye movement
- Partial and mainly central visual blurring
- Normal disc or mild disc swelling
- Partial myelopathy
- Lhermitte’s symptom
- Deafferented hand
- Numbness
- Urinary urgency, incontinence, erectile dysfunction
- Progressive spastic paraplegia (asymmetrical)
- Mild subcortical cognitive impairment
- Hemiparesis

# Atypical presentation of MS

- Vascular territory syndrome, e.g., lateral medullary
- Third nerve palsy
- Progressive trigeminal sensory neuropathy
- Focal dystonia, torticollis
- Progressive optic neuropathy
- Severe, continuous orbital pain
- Persistent complete loss of vision
- Neuroretinitis (optic disc swelling with macular star)
- Uveitis (severe, anterior)
- Anterior spinal artery territory lesion (sparing posterior columns only)
- Cauda equina syndrome
- Sharp sensory level to all modalities & localised spinal pain
- Complete Brown-Sequard syndrome
- Acute urinary retention
- Progressive sensory ataxia (posterior columns)
- Encephalopathy (obtundation, confusion, drowsiness)
- Cortical blindness
- Generalized movement disorder or Parkinsonian syndrome

# Some comments on MRI

*”The most common reason for falsely attributing a patients´s symptoms to multiple sclerosis is faulty interpretation of the magnetic resonance imaging”*

**Rolak: Neurologist, Vol:13(2) 2007:57-72**

# What differ age related changes on MRI from MS?

| MS lesions | Ischemic-degenerative lesions |
|---|---|
| • Younger patients (15-40 years)<br>• Often female<br>• Periventricular lesions radiating from corpus callosum<br>• Corpus callosal lesions and atrophy<br>• Juxtacortical lesions<br>• Infratentorial lesions often affect the middle cerebellar peduncles<br>• Contrast-enhancing lesions<br>• Dynamic lesions (see above) | • Older patients (>40 years)<br>• Male predominance<br>• Lesions in watershed areas<br>• Lack of lesions in MS predilection areas<br>• Sparing of the U-fibers and corpus callosum<br>• No contrast-enhancing lesions |

# Red flags on MRI

- Persistent Gd-enhancement and continued enlargement of lesions
- Persistently unifocal manifestations
- Large and infiltrating brainstem lesions
- Predominance of lesions at the cortical/subcortical junction
- Meningeal enhancement
- T2-hyperintensity in the dentate nuclei
- No "black holes“
- Large lesions
- Marked asymmetry of WM lesions
- No enhancement

# Laboratory tests in MS diagnosis???

- SR
- ANA titer
- Borrelia serology
- Angiotensin converting enzyme activity
- X-ray chest
- B-12 -folate
- SS-A/Ro and SS-B/La
- Anti-cardiolipin antibodies
- HTLV-1 - HIV - WR
- Paraneoplastic antibodies (Anti-YO - Anti-HU etc)
- Very long chain fatty acids
- Arylsulphatase A

**Only to be used in selected or atypical cases!**

*”Mindless screening these patients with an unvarying battery of tests seldom generates a different diagnosis and more often leads to confusing false-positive results”*

**Rolak: Neurologist, Vol:13(2) 2007:57-72**

# In conclusion…

**MS remains a diagnosis requiring an expert neurologist**

**Differential diagnoses are many, but they can usually be excluded by considering "red flags"**

**Although a disease specific marker does not exist, a robust diagnosis can usually be established early after onset in most cases based on compatible clinical-, CSF- and MRI-data**

**MRI should be interpreted cautiously**

# Thank you!

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