ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

31ST CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS
7–10 OCTOBER 2015, BARCELONA, SPAIN

Medical University of Graz

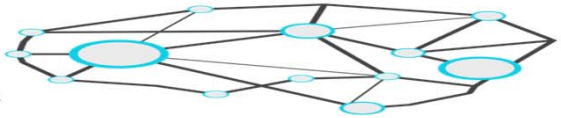
Teaching Course 3 **MAGNIMS**

MRI in monitoring disease activity & progression

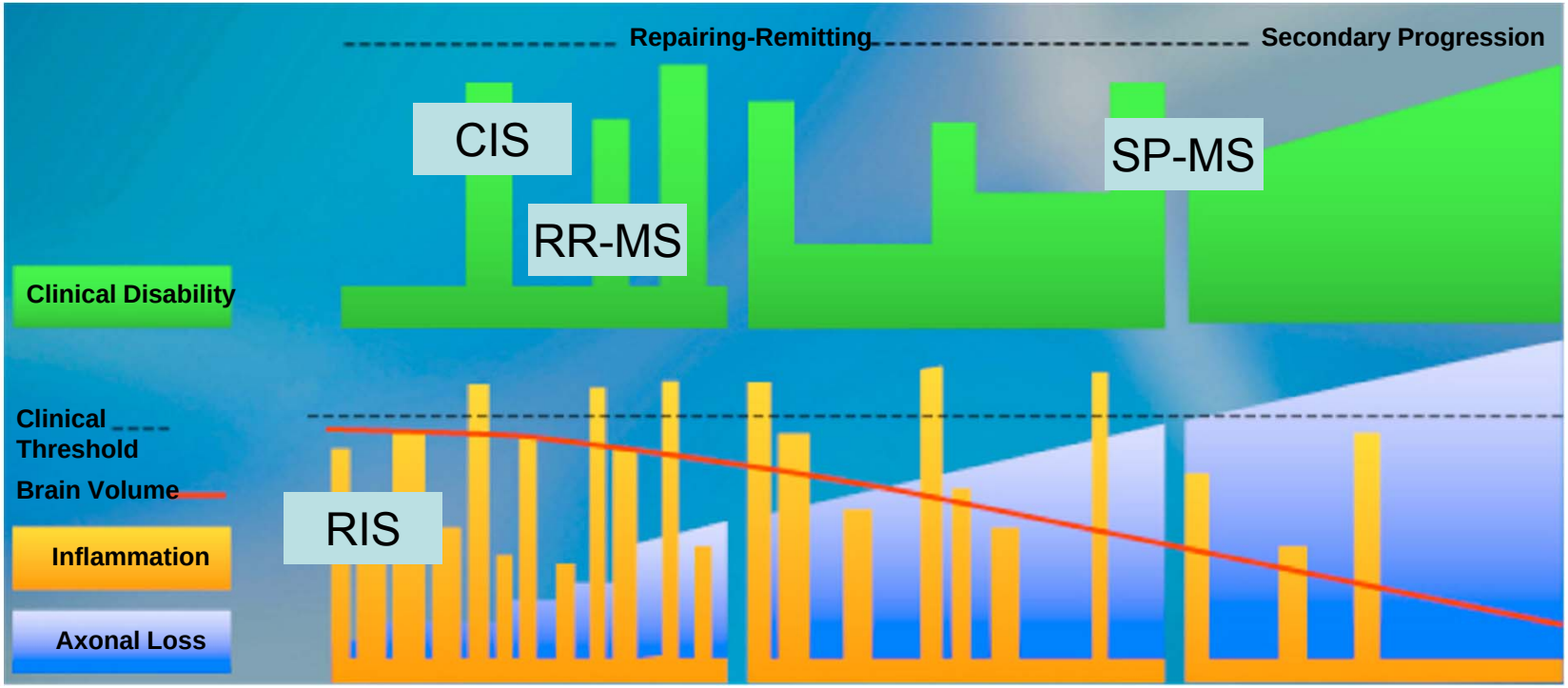
S &

C. Enzinger (Graz, AT)

Magnims
Magnetic Resonance Imaging in Multiple Sclerosis



Model of the evolution of MS



MRI

Inflammation, demyelination, axonal transection, plasticity, remyelination

Inflammation, persistent demyelination

Reduced inflammation, chronic axonal degeneration, gliosis

Compston A, Coles A. *Lancet*. 2002;359:1221-1231.

Chances & Challenges – Heterogeneity of MS

MRI „phenotypes“ of patients after a first clinical episode suggestive of MS

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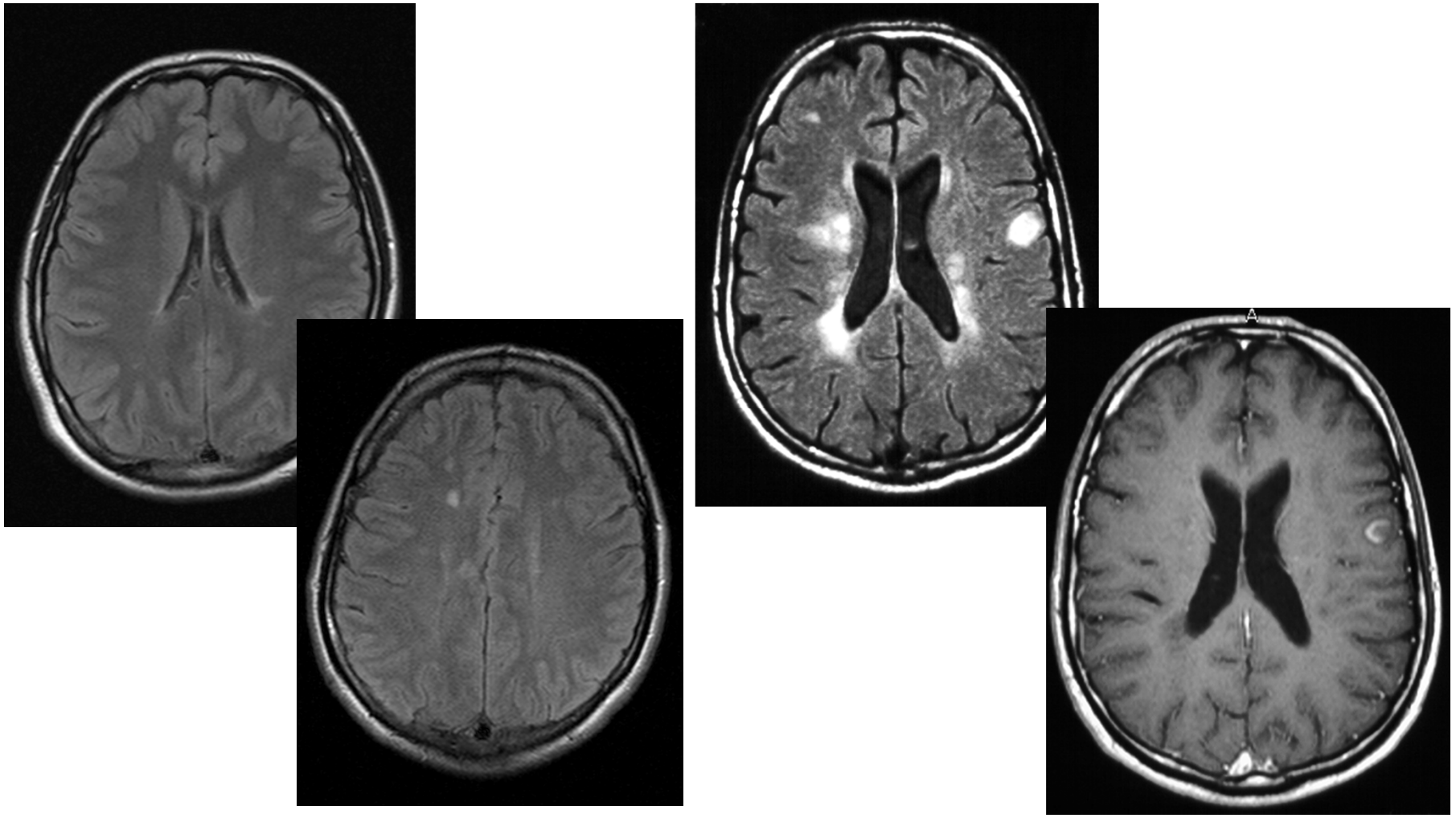

EVIDENCE-BASED GUIDELINES

MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients

Mike P. Wattjes, Àlex Rovira, David Miller, Tarek A. Yousry, Maria P. Sormani, Nicola de Stefano, Mar Tintoré, Cristina Auger, Carmen Tur, Massimo Filippi, Maria A. Rocca, Franz Fazekas, Ludwig Kappos, Chris Polman, Frederik Barkhof and Xavier Montalban; on behalf of the MAGNIMS study group

NATURE REVIEWS | NEUROLOGY

- **Monitoring „natural“ disease course**
- Judging treatment effect / response
- Detecting “side effects“ of treatment

N de Stefano

T Yousry

What can/should we monitor?

In what manner?

How frequently?

Wattjes, M. P. *et al. Nat. Rev. Neurol.* advance online publication 15 September 2015; doi:10.1038/nrneurol.2015.157

General recommendations for MS disease monitoring

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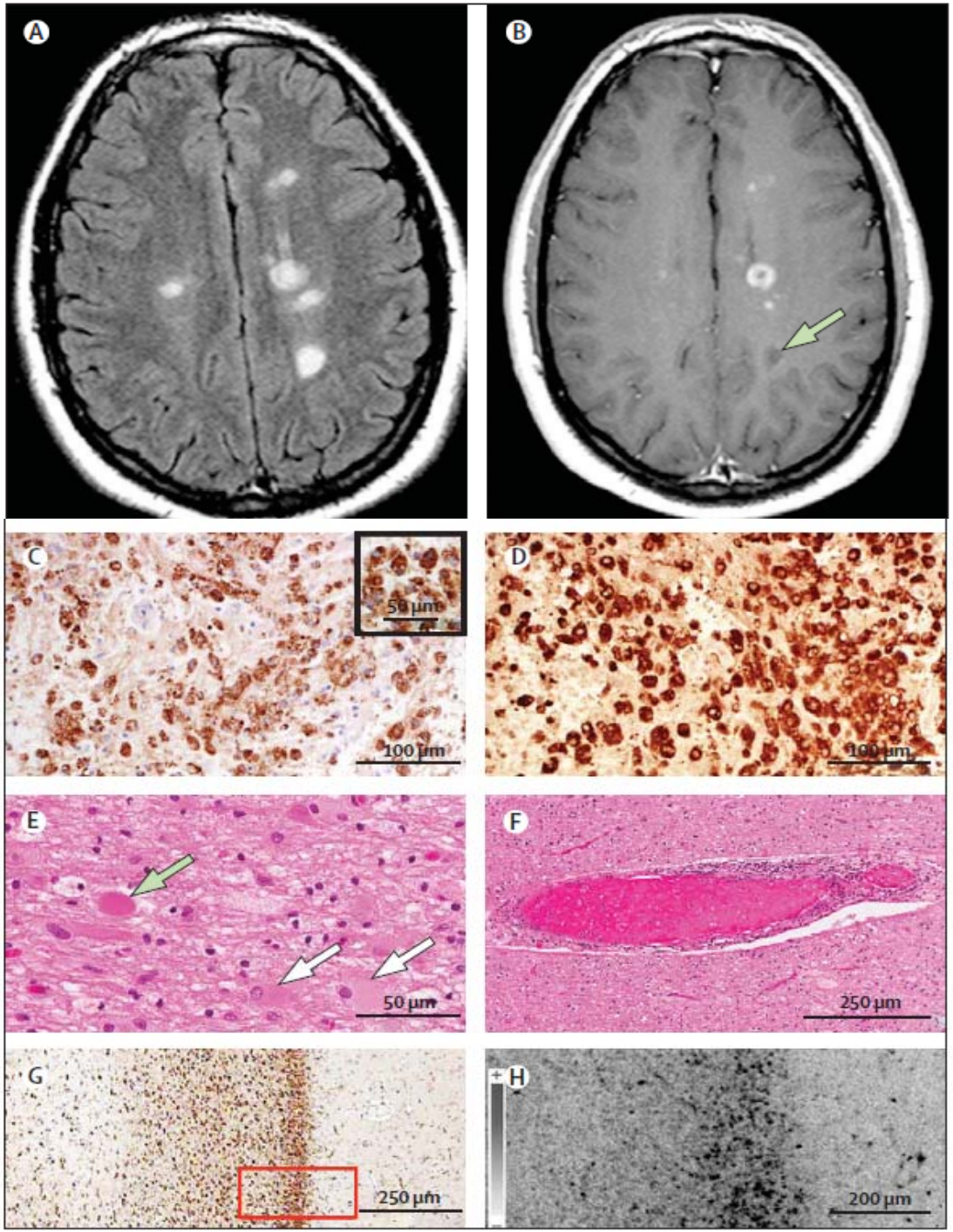
- ✓ MRI protocols for disease monitoring should be identical with MRI scans for diagnostic purposes.
- ✓ Brain MRI is the modality of choice for MS disease monitoring.
  - Contrast-enhanced T1-weighed sequences: acute inflammation
  - FLAIR/T2-weighted sequences: clinically silent disease progression (e.g., active T2 lesions)
- ✓ The recommended frequency of serial MRI during disease monitoring is strongly related to the specific clinical setting (e.g., treatment efficacy, drug safety).
- ✓ In contrast to diagnosis, spinal cord MRI is not recommended for disease monitoring on a regular basis.

Wattjes, M. P. *et al. Nat. Rev. Neurol.* advance online publication 15 September 2015; doi:10.1038/nrneurol.2015.157



Association between pathological and MRI findings in multiple sclerosis

Massimo Filippi, Maria A Rocca, Frederik Barkhof, Wolfgang Brück, Jacqueline T Chen, Giancarlo Comi, Gabriele DeLuca, Nicola De Stefano, Bradley J Erickson, Nikos Evangelou, Franz Fazekas, Jeroen J G Geurts, Claudia Lucchinetti, David H Miller, Daniel Pelletier, Bogdan F Gh Popescu, Hans Lassmann, for the Attendees of the Correlation between Pathological and MRI findings in MS workshop*

Lancet Neurol 2012; 11: 349–60

C–F: ACTIVE LESION:

C: Active demyelinating lesion evidenced by particles positive for myelin proteolipid protein within macrophages

D: Sea of macrophages

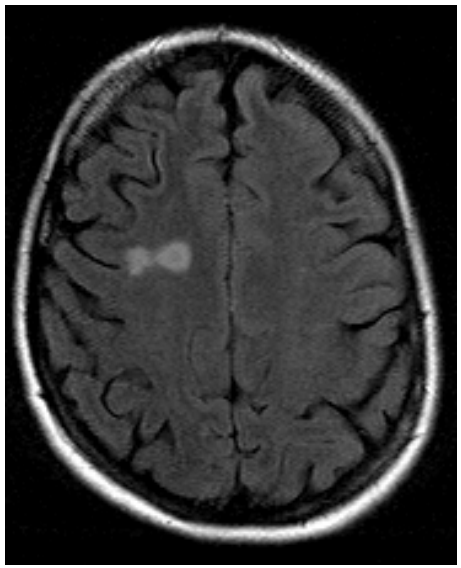
E: Reactive astrocytes (white arrows) and axonal swellings (green arrow)

F: Perivascular inflammation

G,H: CHRONIC ACTIVE LESION:

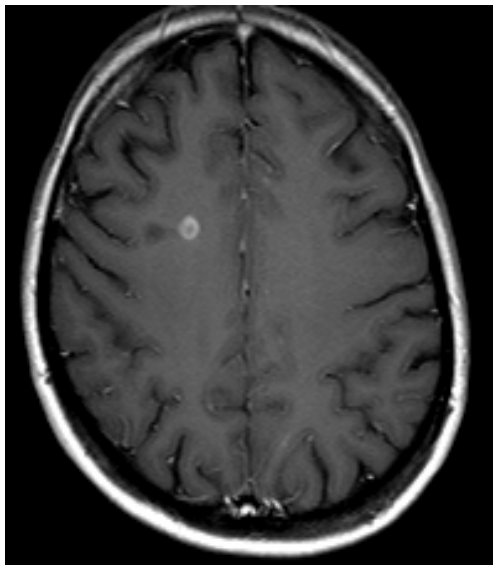
G: Active macrophages at plaque edge

H: Iron map of area boxed in G: most iron within macrophages



Contrast enhancing lesion on T1-weighted scan: Inflammation / active lesion

Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)
8 unpaired electrons in outer layer
strongly paramagnetic, toxic (chelate)
shortening of T1- and T2



- Gd enhanced MRI indicates **break down of BBB**
- Active lesions enhance for 2 – 6 weeks
- Modification of enhancement by
  - dosage of and delay after contrast material application
  - Imaging parameters
  - Steroid treatment
- Outcome variables
  - Active scans
  - Number of contrast-enhancing lesions / scan or cumulative

MRI contrast uptake in new lesions in relapsing-remitting MS followed at weekly intervals

Francois Cotton, MD; Howard L. Weiner, MD; Ferenc A. Jolesz, MD; and Charles R.G. Guttmann, MD

NEUROLOGY 2003;60:640–646

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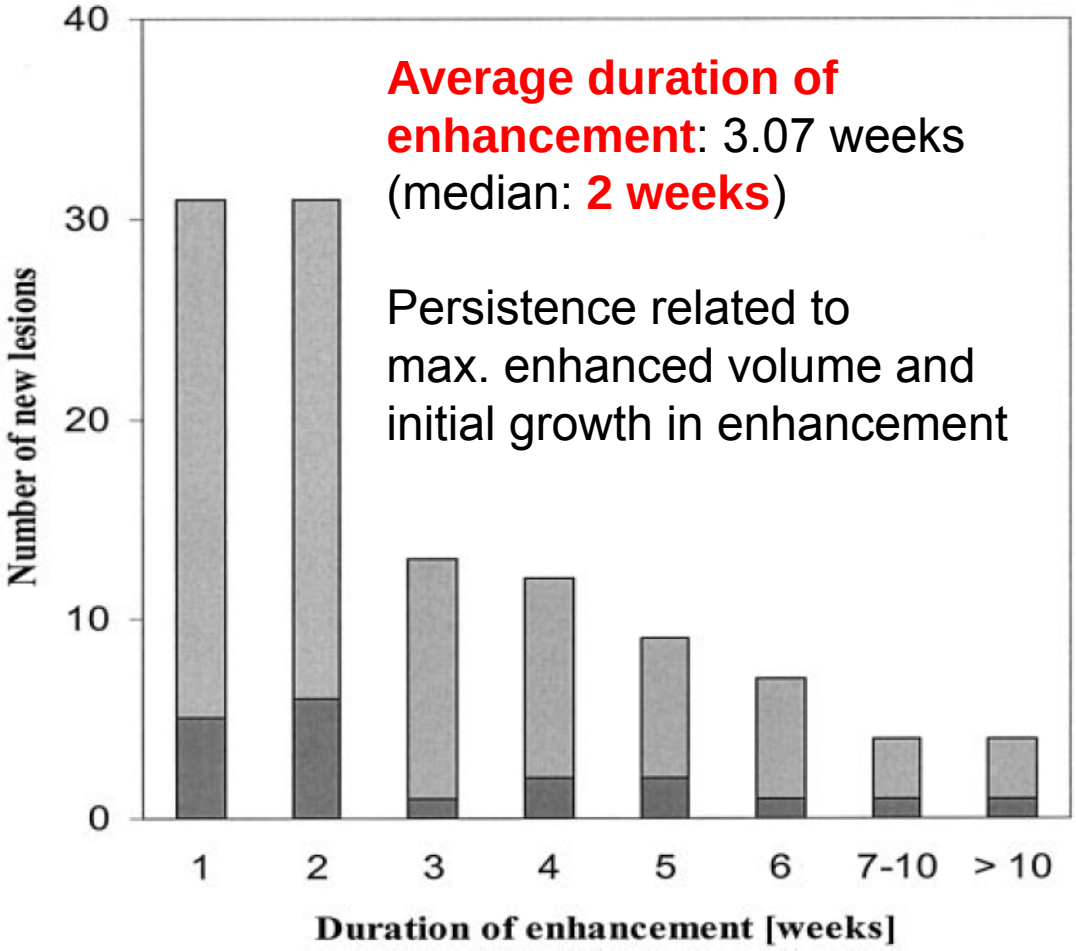

Average duration of enhancement: 3.07 weeks (median: **2 weeks**)

Persistence related to max. enhanced volume and initial growth in enhancement

One year, 26 RRMS, weekly MRI for 8 weeks, e.o.w. for 16 weeks, monthly thereafter: quantitative analysis of each new EL (n 113) during first 6 weeks

Distribution of new ELs according to enhancement duration: non-gaussian, skewed toward enhanc. ≤ 2 weeks (dark gray: 21 lesions potentially affected by corticotherapy, light gray: 92 natural history lesions)

Neuroradiology (1994) 36: 382–387

Neuro radiology

Limited duration of the effect of methylprednisolone on changes on MRI in multiple sclerosis*

F. Barkhof[1], M. W. Tas[1], S. T. F. M. Frequin[2], P. Scheltens[3], O. R. Hommes[2], J. J. P. Nauta[4], J. Valk[1]

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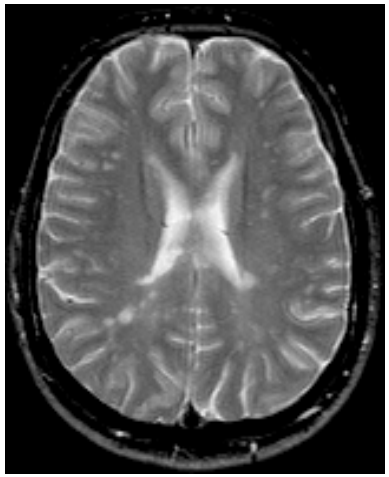
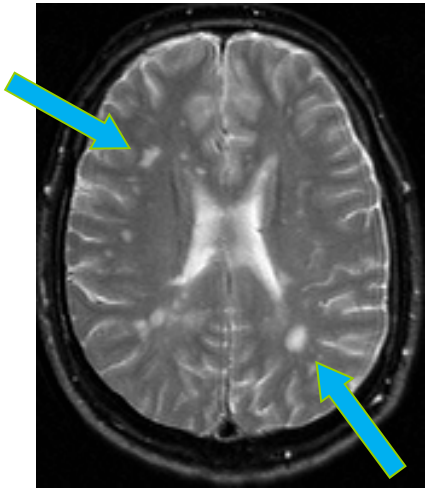
- Serial MRI after MP (31 courses)
- 13 patients with definite MS
- Gd-enhanced MRI before and after MP, then monthly
- 609 active lesions on 195 examinations
- Directly after treatment 78% reduction in number of EL
- No beneficial effect on rate of disappearance of related T2-abnormalities.
- MP effect temporary (on average 9.7 weeks)



New lesion formation (enlarging lesions)



- Occurrence of new (focal) T2 lesions is consistent with **new areas of MS related tissue damage**
- Modifications by
  - Imaging parameters (sequence, slice thickness, etc.)
- Outcome variables
  - Number of new T2 lesions
  - Number of enlarging T2 lesions

Number of newly active lesions
(new and enlarging T2 and new contrast enhancing lesions)

Serial MRI: identical protocol and repositioning are essential

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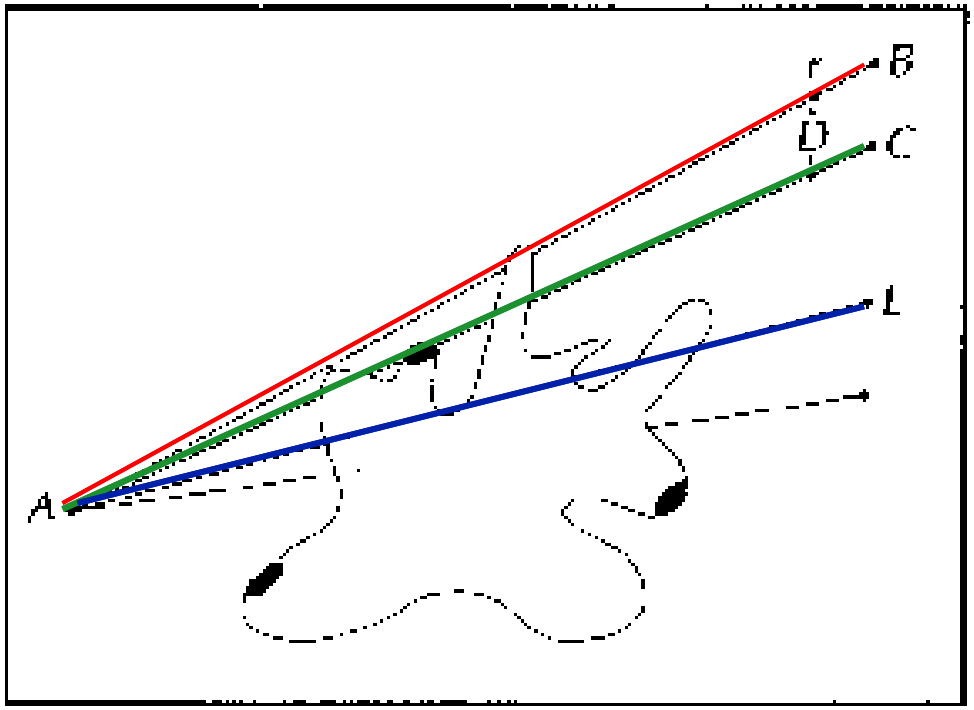
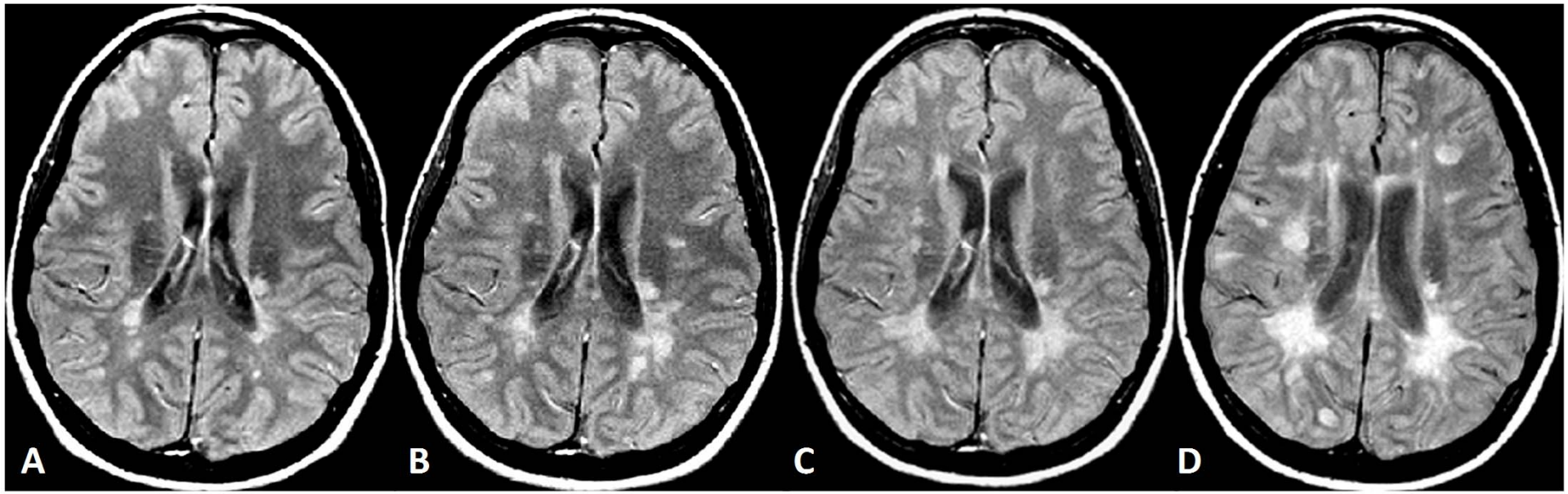


Hypothetical multiple sclerosis plaque measured by serial brain scans. See text of letter for explanation of labeled lines.

- The shaded portions represent discrete areas of enhancement at the lesion border, and the lines represent possible MRI scan sections originating from different angulations.
- D indicates the displacement resulting from the repositioning error in a follow-up scan.
- Thus, the following results would be obtained:
- **Line AB**: Baseline scan, one lesion
- **line AC**: 3 lesions, one of which enhances
- **line AE**: 3 lesions, the first being new or a confluence, the second being an enlargement of a previous one, the third being new; the previously enhanced lesion disappeared

Goodkin DE, Vanderburg-Medendorp S, Ross J. Arch Neurol. 1993 Jun;50(6):569-71

Serial MRI obtained in a patient with relapsing-remitting multiple sclerosis.



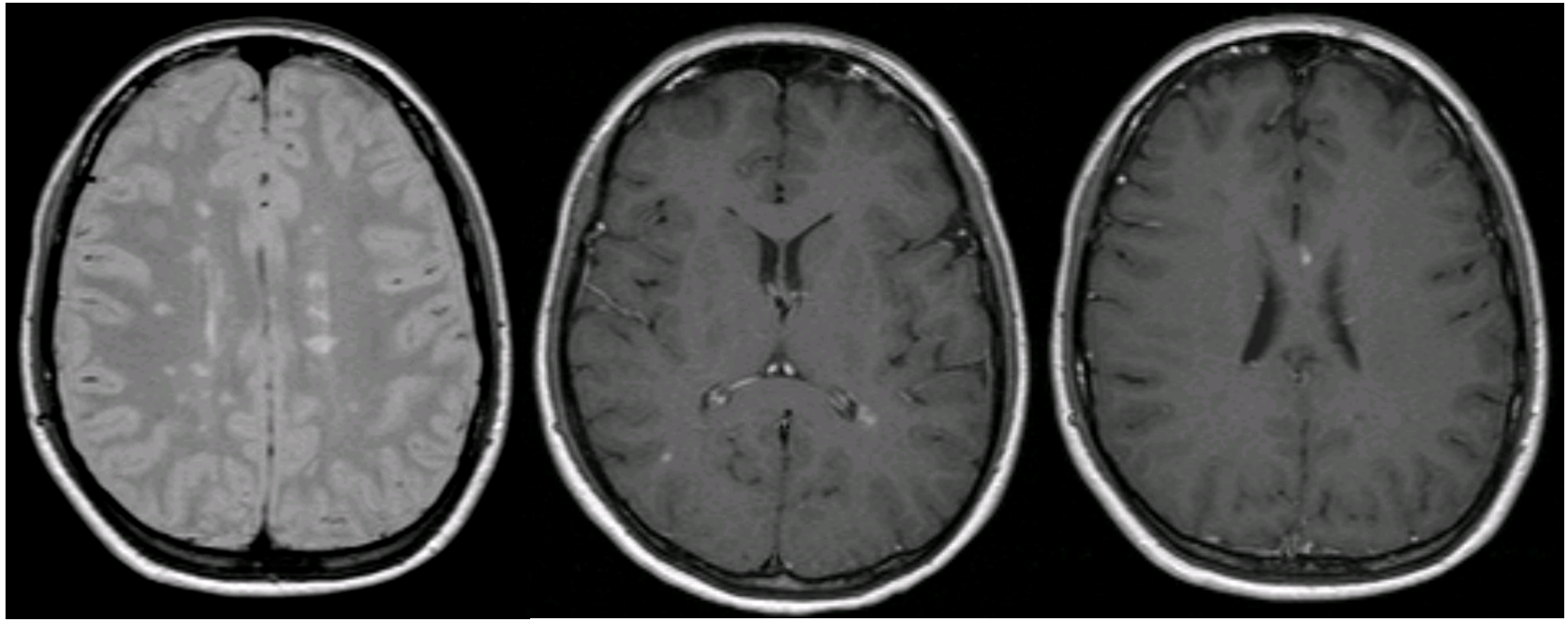
Proton-density (PD)-weighted MR images obtained at baseline (A), and one (B), two (C), and three (D) years after. Please note the disease progression with new and enlarging focal lesions over time.

Wattjes M. et al. Nat Rev Neurol. 2015 Sep 15. doi: 10.1038/nrneurol.2015.157. [Epub ahead of print]

1

2

1



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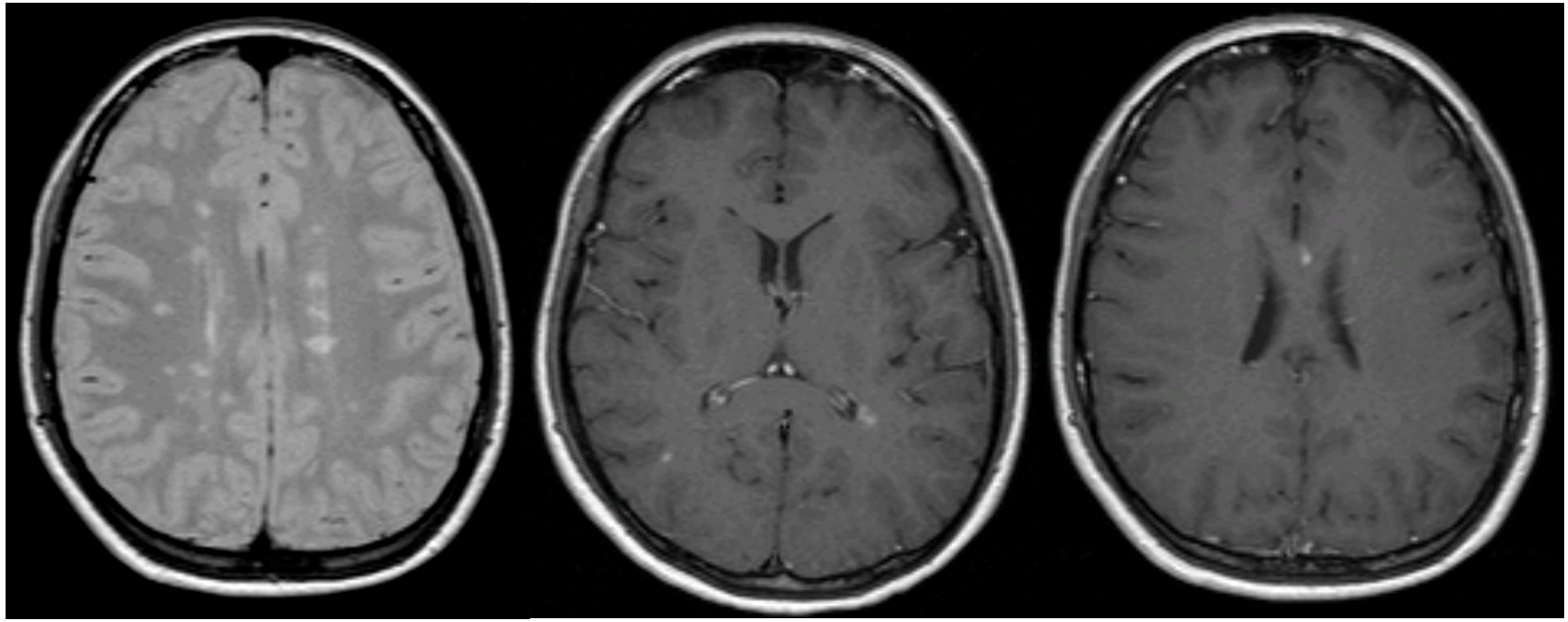

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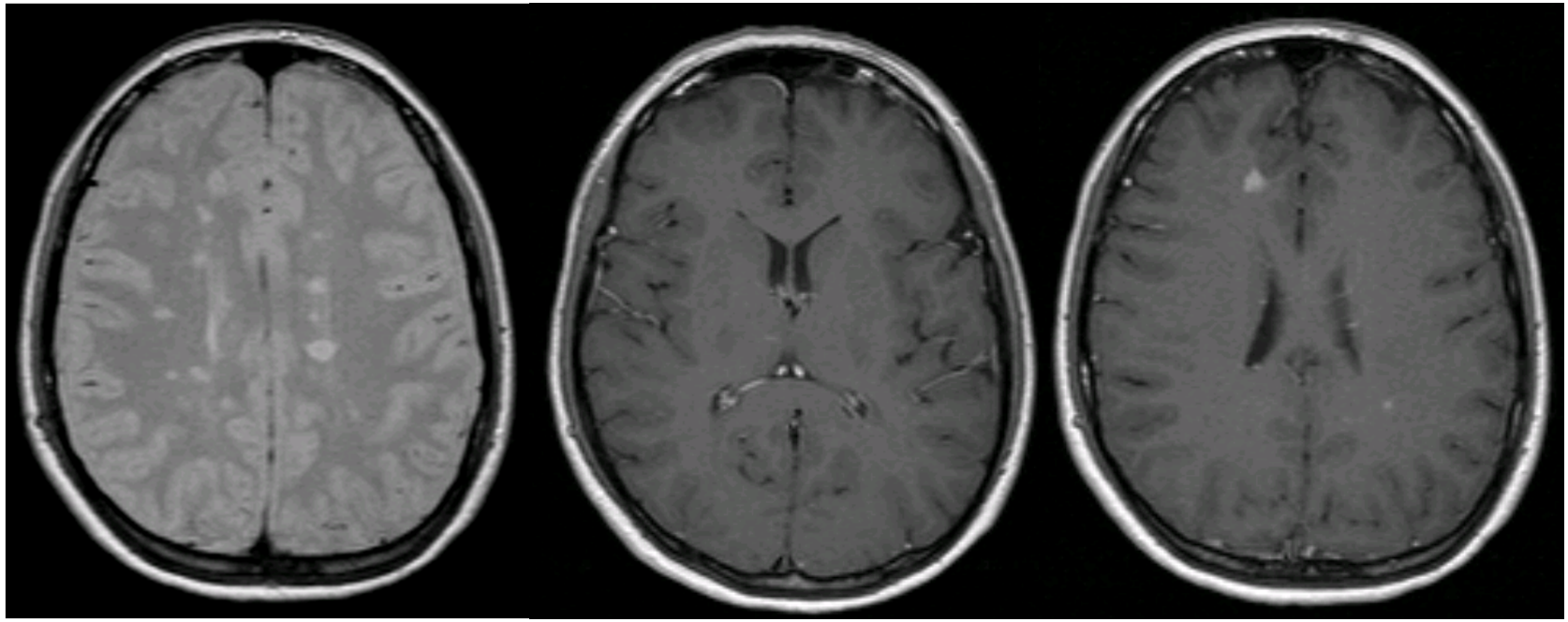
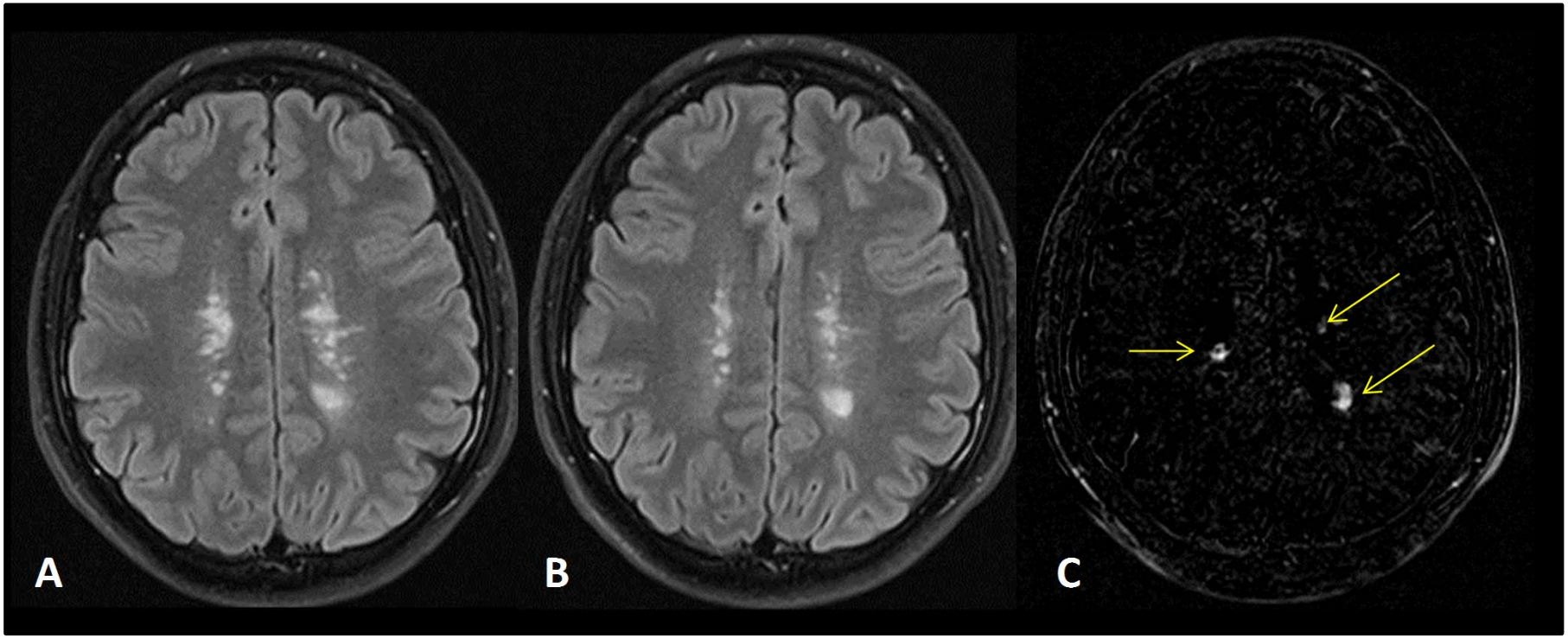


Subtraction analysis of repeated MRI to identify new / enlarging lesions



Example of subtraction MRI in a patient with relapsing-remitting MS.
FLAIR T2-weighted images at year 0 (y0) (A) and at year 1 (y1) (B), and subtracted images (y1-y0) (C).
The arrows indicate the new and enlarging lesions (C).

Wattjes M. et al. Nat Rev Neurol. 2015 Sep 15. doi: 10.1038/nrneurol.2015.157. [Epub ahead of print]

Monitoring „natural history“ of MS

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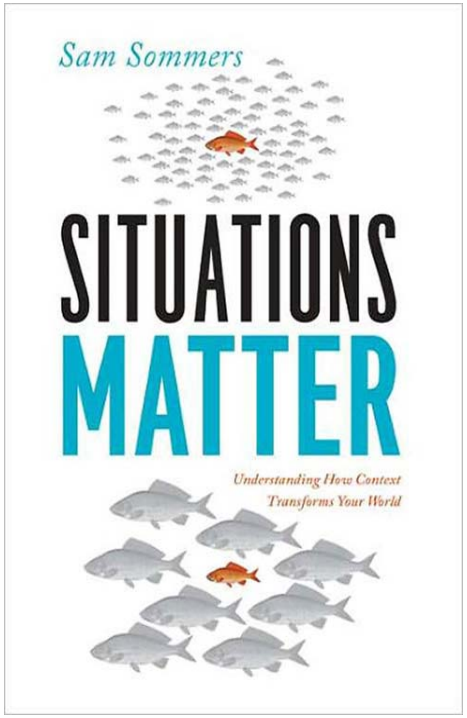
- Which situations?
  - Radiologically isolated syndrome (RIS)
  - Clinically isolated syndrome (CIS)
  - MS without disease modifying treatment
- Which MRI parameters?
  - Gadolinium-enhancing lesions
  - New T2-lesions
- When?
  - One repeated MRI 6-12 months after initial work-up
  - Further scans depending on clinical situation / symptoms



Following-up the „natural course“ of disease

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- Follow-up brain imaging after 3-6 months is recommended in CIS patients with an abnormal baseline MRI, not fulfilling the 2010 McDonald diagnostic criteria.
- If not conclusive, a third brain MR scan might be acquired 6-12 months later.
- In RIS subjects, a follow-up brain MR after 3-6 months is also recommended.
- Spinal cord follow-up MR imaging in CIS patients in order to demonstrate DIS and DIT has limited value and should not be routinely performed.

Wattjes, M. P. *et al. Nat. Rev. Neurol.* advance online publication 15 September 2015; doi:10.1038/nrneurol.2015.157

Judging treatment efficacy

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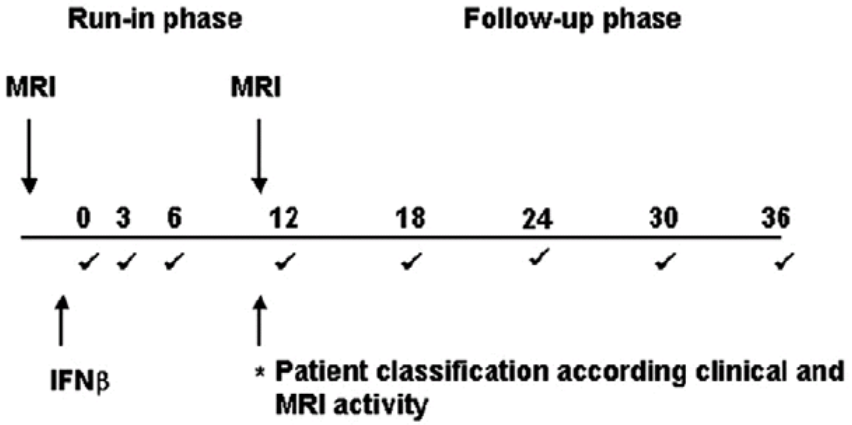
- In which patients and when?
  - Clinical suspicion of treatment failure / inadequate response
  - Routinely after the first year of treatment?
- Which MRI parameters to consider?
  - Gadolinium-enhancing lesions
  - New T2-lesions
  - Atrophy estimation not yet ready for clinical use!

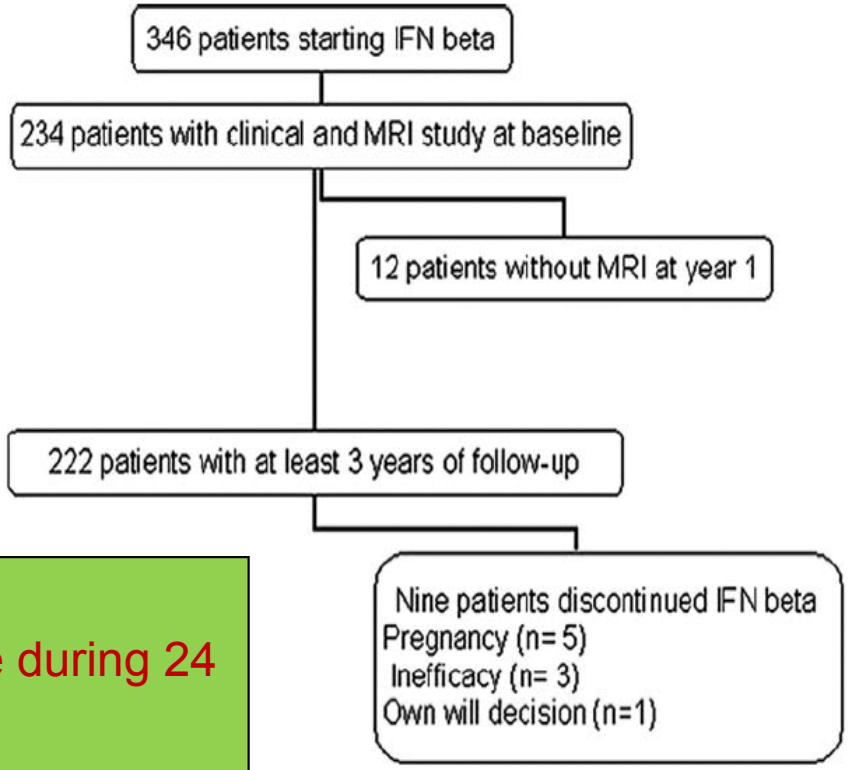
RESEARCH PAPER

Multiple Sclerosis 2009; 15: 848–853

Measures in the first year of therapy predict the response to interferon β in MS

J Río[1], J Castilló[1], A Rovira[2], M Tintoré[1], J Sastre-Garriga[1], A Horga[1], C Nos[1], M Comabella[1], X Aymerich[2] and X Montalbán[1]





Outcome variables

Definition of inadequate treatment response during 24 months of follow-up

- Presence of relapses
- Disease progression (increase EDSS ≥ 1 for ≥ 6 months)

Predictor variables

R+ = ≥ 1 relapse within first year

P+ = increase of ≥ 1 EDSS point within first year

MRI+ = > 2 active lesions (new or enlarging T2 or Gd+ lesions)

Table 2 Risk of activity during the period of follow-up (months 12–36) according the positivity for the different variables after 12 months of therapy

	Odds ratio (CI)	Significance
One positive variable	1.4 (0.7–2.6)	0.3
Two positive variables	5.9 (2.5–15.6)	<0.0001
Three positive variables	13.2 (2.9–125.7)	0.0003

Table 3 Risk of new relapses and increase of disability during the period of follow-up (months 12– 36) according the positivity for the different variables after 12 months of therapy

	N	Relapses		Progression	
		Odds ratio (CI)	Significance	Odds ratio (CI)	Significance
R+/P+/MRI+	11	9.8 (2.6–53.4)	0.0005	6.5 (1.9–23.4)	0.004
R+/P−/MRI+	18	8.3 (2.9–28.9)	<0.0001	4.4 (1.6–12.5)	0.004
R−/P+/MRI+	7	3.3 (0.8–15.6)	0.1	7.1 (1.6–33.9)	0.011
R+/P+/MRI−	5	1.8 (0.3–9.9)	0.5	3.9 (0.6–21.6)	0.1
R−/P+/MRI−	10	1.2 (0.3–4.3)	0.8	0.3 (0–2.1)	0.3
R+/P−/MRI−	17	1.1 (0.4–3.2)	0.8	0.5 (0.1–2.2)	0.4
R−/P−/MRI+	35	1.5 (0.7–3.4)	0.3	2.3 (0.9–4.4)	0.07
R−/P−/MRI−	119	1*		1*	

*Reference category

Different MR criteria proposed for predicting treatment response based on observational studies

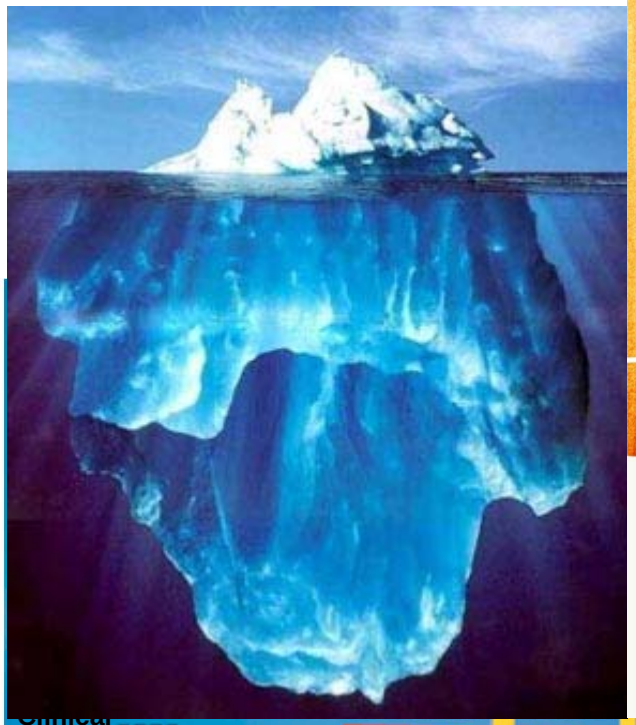
Table 1 | MRI criteria for predicting treatment response

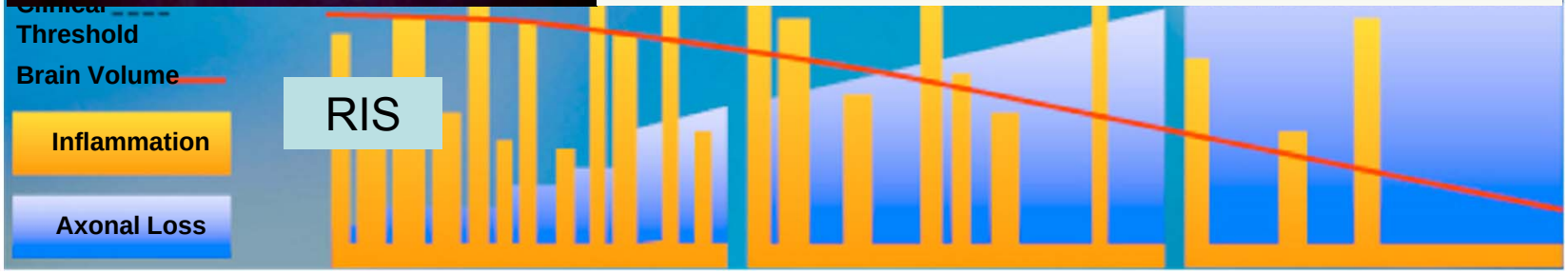
Criteria	Outcome measure	Results
Three or more active lesions in 1 year[134]	Disability progression over 3 years	OR 8.3 71% sensitivity 71% specificity
Three or more active lesions plus one or more relapse or ≥1 point confirmed EDSS score increase in 1 year[67]	Relapse rates and/or disability progression over 3 years	OR 3.3–9.8 for relapses OR 6.5–7.1 for progression
Modified Rio Score ≥2 and more than five new T2 lesions plus one relapse; or more than one relapse[79]	Relapse rates and/or disability progression over 4 years	24% sensitivity 97% specificity
One or more relapse and nine or more T2 lesions or a minimum of one CEL[80]	Relapse rates and/or disability progression over 4 years	34% sensitivity 90% specificity
One or more relapse, or at least one CEL[80]	Relapse rates and/or disability progression over 4 years	68% sensitivity 80% specificity
One or more CELs, or at least two new T2 lesions[80]	Relapse rates and/or disability progression over 4 years	61% sensitivity 83% specificity

All patients in these observational studies had relapsing–remitting multiple sclerosis treated with a formulation of IFN-β. Odds ratios refer to the probability that patients meeting the criteria will demonstrate the outcome measure, relative to patients who do not meet the criteria. Abbreviations: CEL, contrast-enhancing lesion; EDSS, Expanded Disability Status Scale.

Wattjes M. et al. Nat Rev Neurol. 2015 Sep 15. doi: 10.1038/nrneurol.2015.157. [Epub ahead of print]

Increased vigilance vs. premature conclusions drawn from MRI





MRI

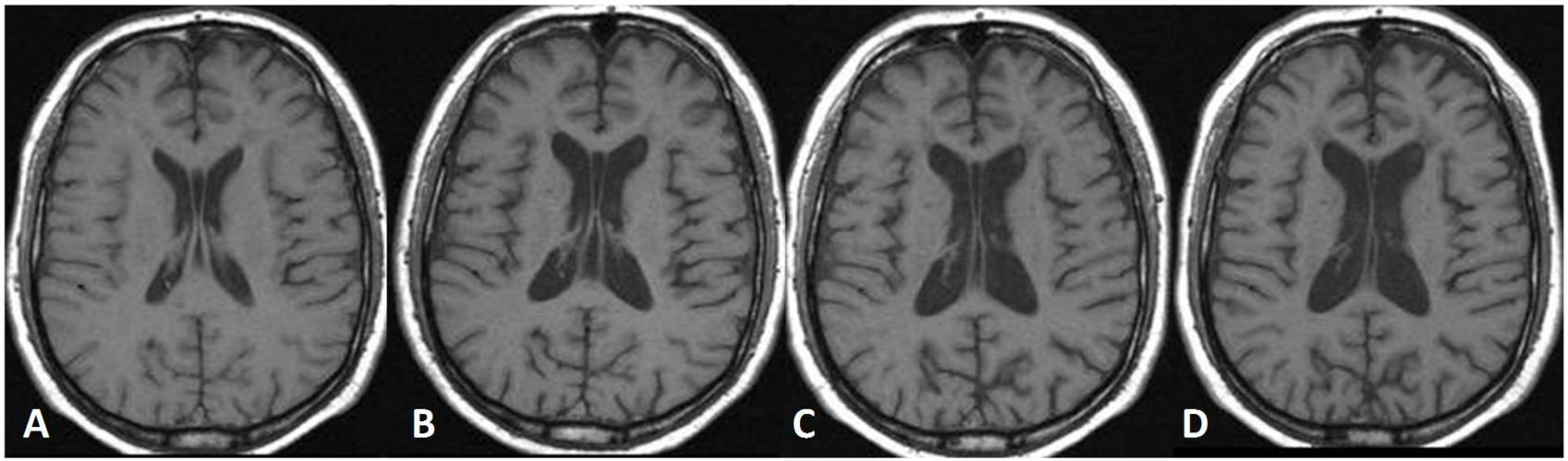
Inflammation, demyelination, axonal transection, plasticity, remyelination

Inflammation, persistent demyelination

Reduced inflammation, chronic axonal degeneration, gliosis

Compston A, Coles A. *Lancet*. 2002;359:1221-1231.

Problems regarding individual assessment of „atrophy“



Evolution of brain volume over 6 years in RR-MS patient

- Strong interindividual variability of brain volume and volume changes
- Multiple factors affecting brain volume (Noxa, hydration, drugs, etc.)
- Variability of estimation dependent on MRI technique and analysis
- Brain volume ≠ brain atrophy

Follow-up MRI for monitoring treatment effects in MS

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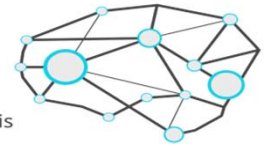
- Routine follow-up brain MRI, including T2-weighted and contrast-enhanced T1-weighted sequences, recommended 6-12 months after the onset of treatment effect.
- New T2 lesions count requires high quality comparable MRI scans and interpretation by highly qualified individuals.
- There is still not enough data supporting the use of brain volume changes for predicting treatment response in individual patients.

Wattjes M. et al. Nat Rev Neurol. 2015 Sep 15. doi: 10.1038/nrneurol.2015.157. [Epub ahead of print]

MRI in the detection of treatment related adverse effects

Magnims
Magnetic Resonance Imaging in Multiple Sclerosis



- Important findings are:
  - ✓ opportunistic infections (e.g., PML, herpes infection)
  - ✓ unexpected disease activity including paradoxical reactions (e.g., tumefactive demyelination)
  - ✓ comorbidities (e.g., vascular, neoplastic)
- MRI protocol and frequency of imaging strongly depend on the specific drug and the patients risk profile (e.g., treatment duration, serostatus for JCV, previous treatment with other immunosuppressive drugs).
- T2-weighted, FLAIR and diffusion weighted images are useful screening sequences for PML lesion detection.

Wattjes M. et al. Nat Rev Neurol. 2015 Sep 15. doi: 10.1038/nrneurol.2015.157. [Epub ahead of print]

MRI „phenotyping“ of MS

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VIEWS & REVIEWS

Defining the clinical course of multiple sclerosis

The 2013 revisions

OPEN

Fred D. Lublin, MD
Stephen C. Reingold, PhD
Jeffrey A. Cohen, MD
Gary R. Cutter, PhD
Per Soelberg Sørensen, MD, DMSc
Alan J. Thompson, MD
Jerry S. Wolinsky, MD
Laura J. Balcer, MD, MSCE
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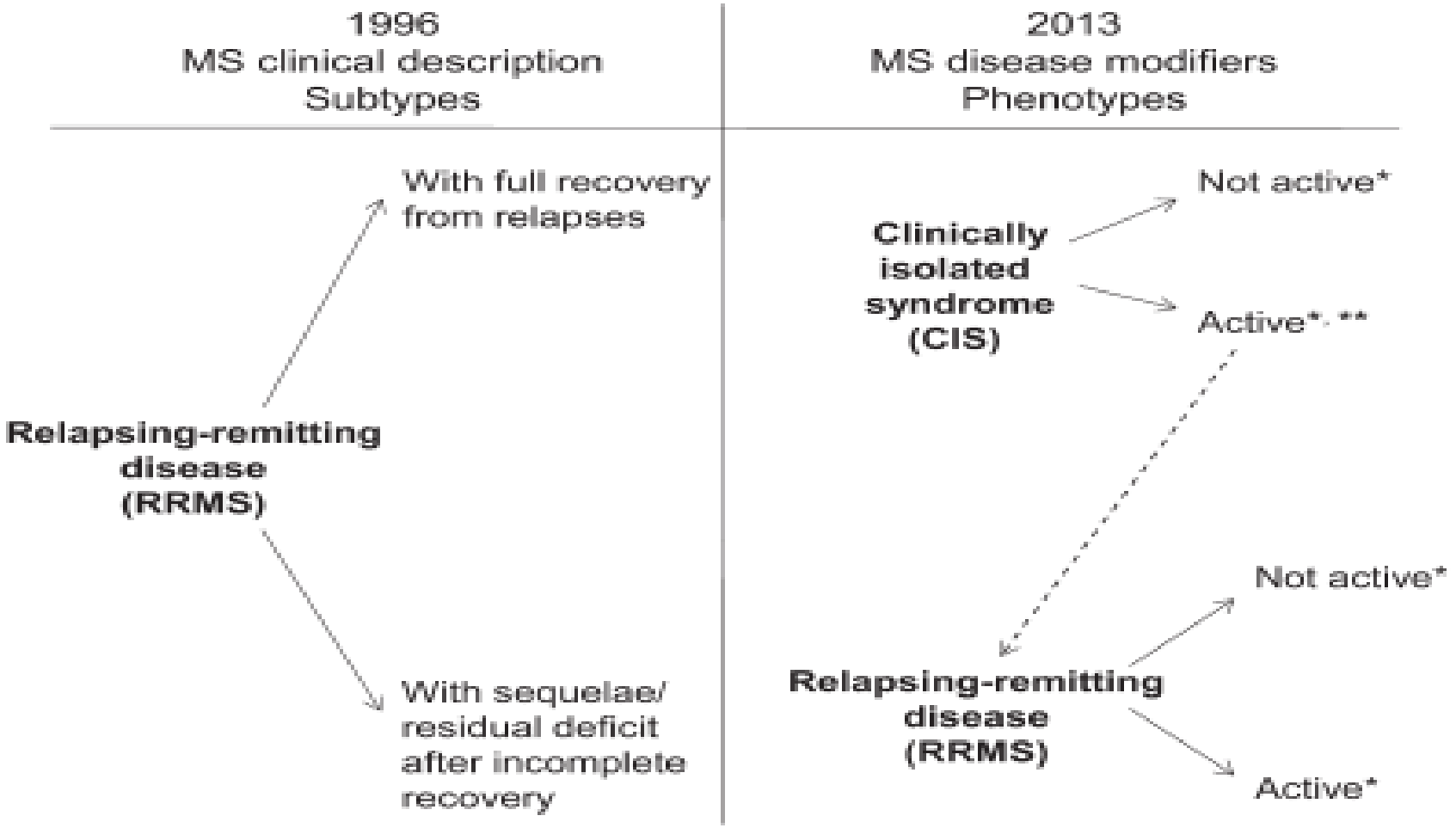
Bruce Bebo, Jr., PhD

ABSTRACT

Accurate clinical course descriptions (phenotypes) of multiple sclerosis (MS) are important for communication, prognostication, design and recruitment of clinical trials, and treatment decision-making. Standardized descriptions published in 1996 based on a survey of international MS experts provided purely clinical phenotypes based on data and consensus at that time, but imaging and biological correlates were lacking. Increased understanding of MS and its pathology, coupled with general concern that the original descriptors may not adequately reflect more recently identified clinical aspects of the disease, prompted a re-examination of MS disease phenotypes by the International Advisory Committee on Clinical Trials of MS. While imaging and biological markers that might provide objective criteria for separating clinical phenotypes are lacking, we propose refined descriptors that include consideration of disease activity (based on clinical relapse rate and imaging findings) and disease progression. Strategies for future research to better define phenotypes are also outlined.

Neurology® 2014;83:278-286

Figure 1 **The 1996 vs 2013 multiple sclerosis phenotype descriptions for relapsing disease**



*Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually); if assessments are not available, activity is "indeterminate." **CIS, if subsequently clinically active and fulfilling current multiple sclerosis (MS) diagnostic criteria, becomes relapsing-remitting MS (RRMS).

Conclusions

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- Besides its merits in diagnosing MS, MRI is helpful in the assessment of the clinical course of the disease.
- „Routine“ MRI controls without exact clinical motivation and indication are not justified.
- Akquisition and interpretation of MRI data have to follow high quality standards
- MRI may provide pertinent ancillary information in these situations:
  - Disease activity after first clinical manifestation / diagnosis without disease modifying treatment
  - Identifying inadequate treatment response / treatment failure
  - Unclear clinical evolution (e.g. relapses yes / no; progression?)
  - Monitoring of potential adverse treatment-related side effects

Selected References (alphabetical)

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- ***Rovira À*** et al. MAGNIMS study group. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat Rev Neurol. 2015 Aug;11(8):471-82. Epub 2015 Jul 7.
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www.ectrims.eu/ectrims-magnims-fellowship-programme/

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Magnetic Resonance Imaging in Multiple Sclerosis

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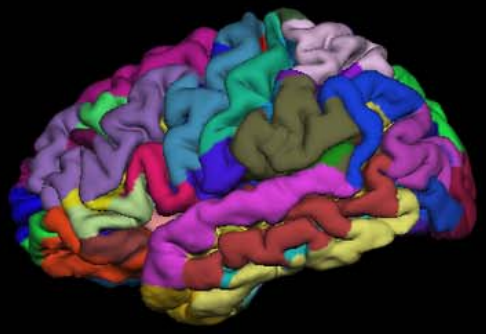
MAGNIMS

2016 ECTRIMS-MAGNIMS Research Fellowship



Applications are now open

The deadline for application is 01 / February / 2016

MAGNIMS (Magnetic Resonance Imaging in MS) is a European network of academics that share a common interest in the study of multiple sclerosis using magnetic resonance imaging techniques.