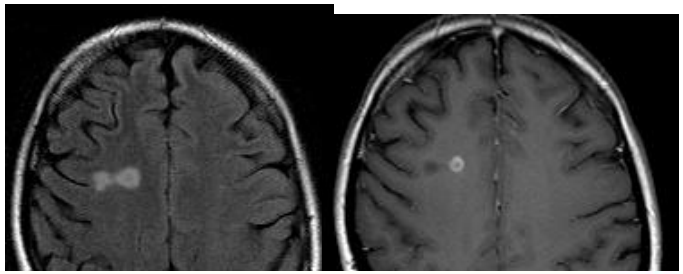
Medical University of Graz

Teaching Course 19

NEUROIMAGING



Multiple Sclerosis & allied white matter conditions

Christian Enzinger

Disclosures

Medical University of Graz

- C. Enzinger has received travel grants and speaker honoraria from Biogen-Idec, Teva-Aventis, Merck-Serono, Bayer-Schering and Teva Pharmaceutical Industries Ltd.
- He has served as consultant or on scientific advisory boards for Biogen-Idec, Teva-Aventis, Novartis and Bayer-Schering.
- He has received unrestricted research grants from Teva-Aventis, Biogen-Idec and Merck-Serono.

Learning objectives

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At the end of this presentation, participants of the teaching course will be familiar with the following topics:

- Typical imaging features of MS
- Current diagnostic criteria of MS and their use in clinical practice
- Imaging features of allied disorders (ADEM, NMO, atypical idiopathic inflammatory demyelinating lesions)
- Red flags in the imaging differential diagnosis of MS

Which patient is suffering from MS?

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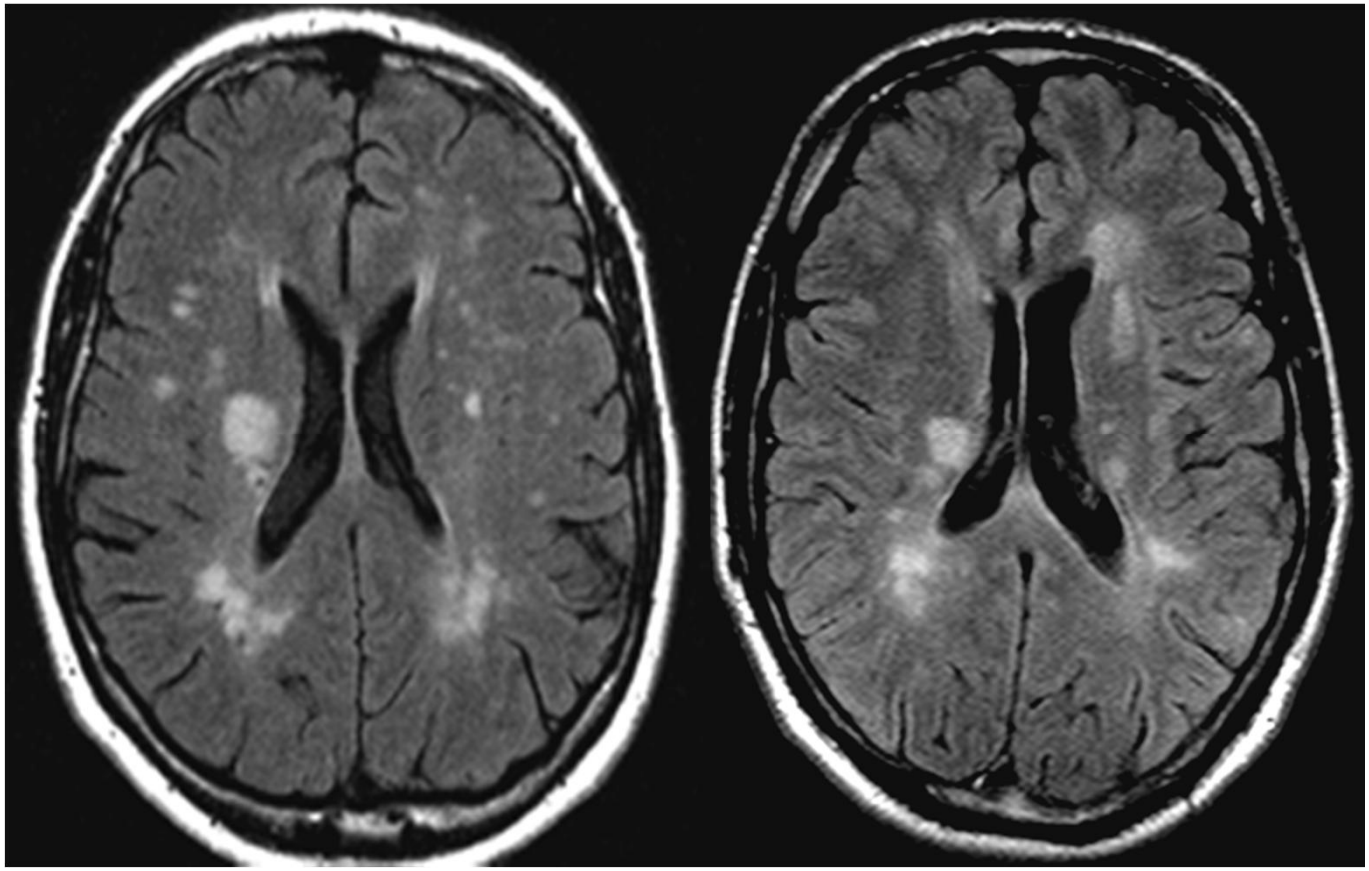

AGENDA - The role of MRI in the…

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- Dx of MS
- Dx of allied disorders
- Differential Dx

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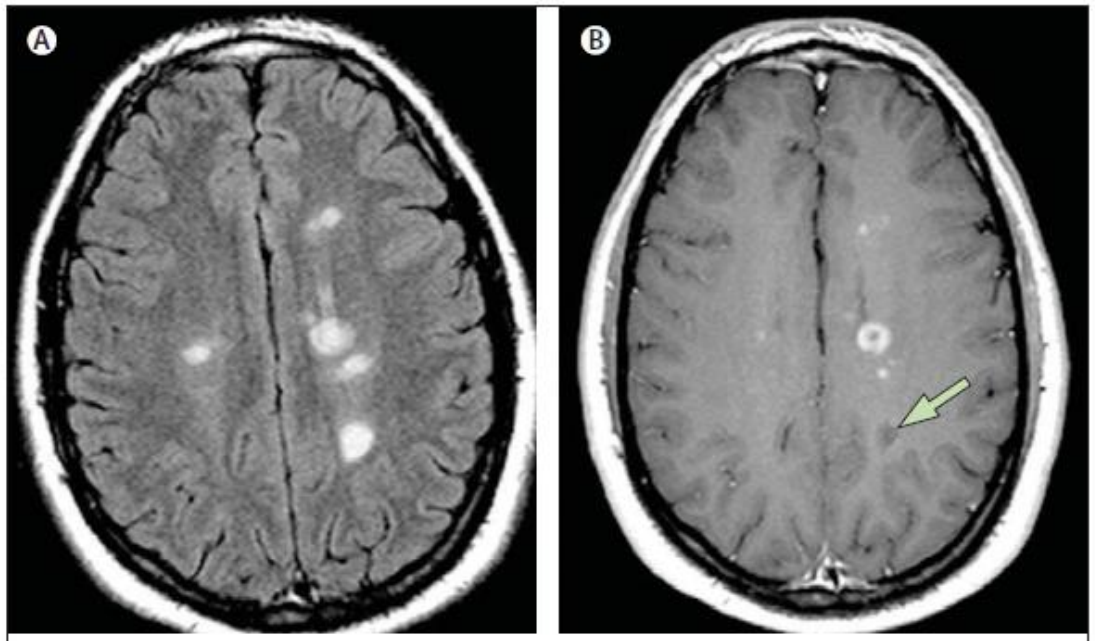
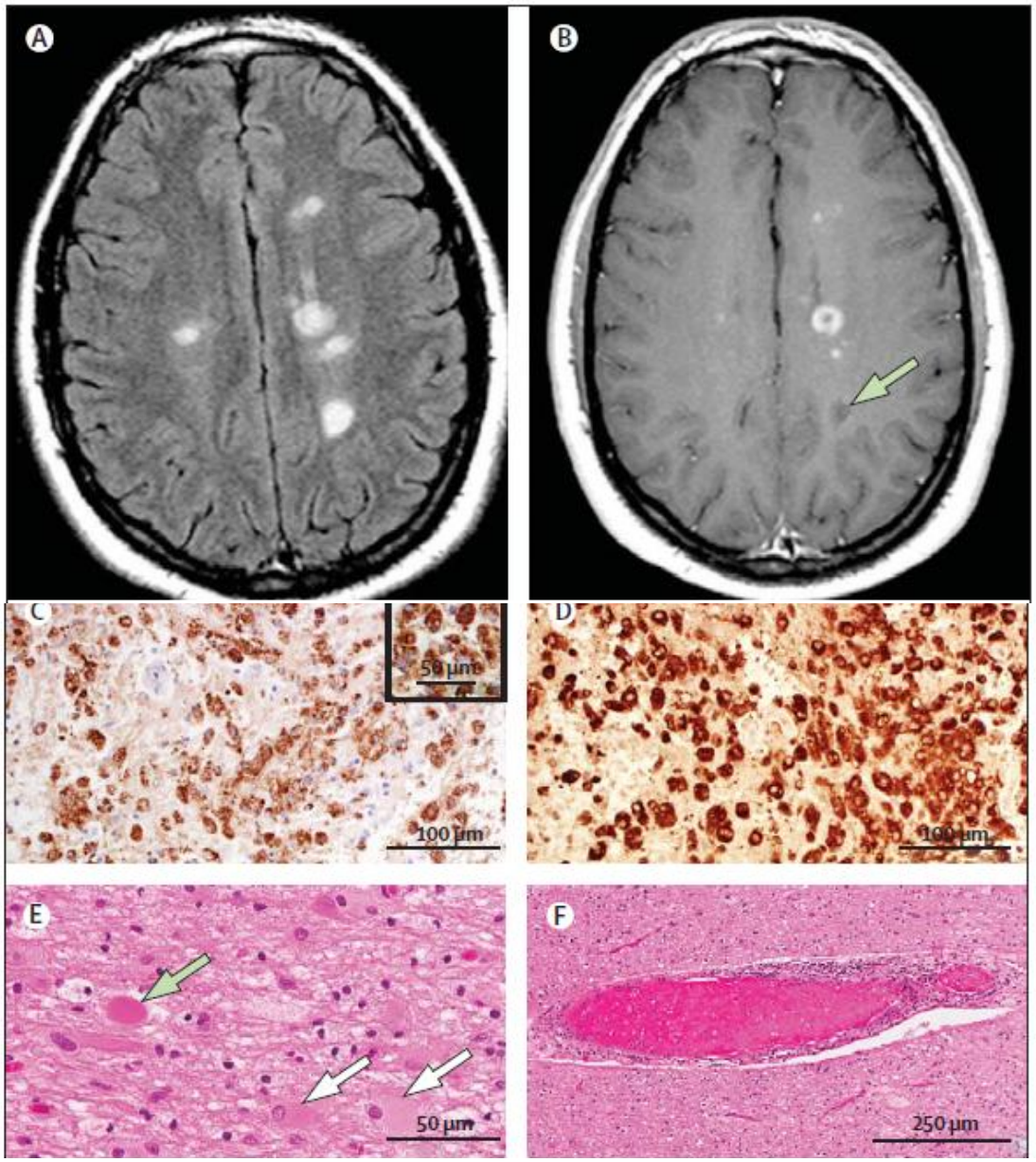


Association between pathological and MRI findings in multiple sclerosis

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

Pathological “specificity“ of MRI in MS



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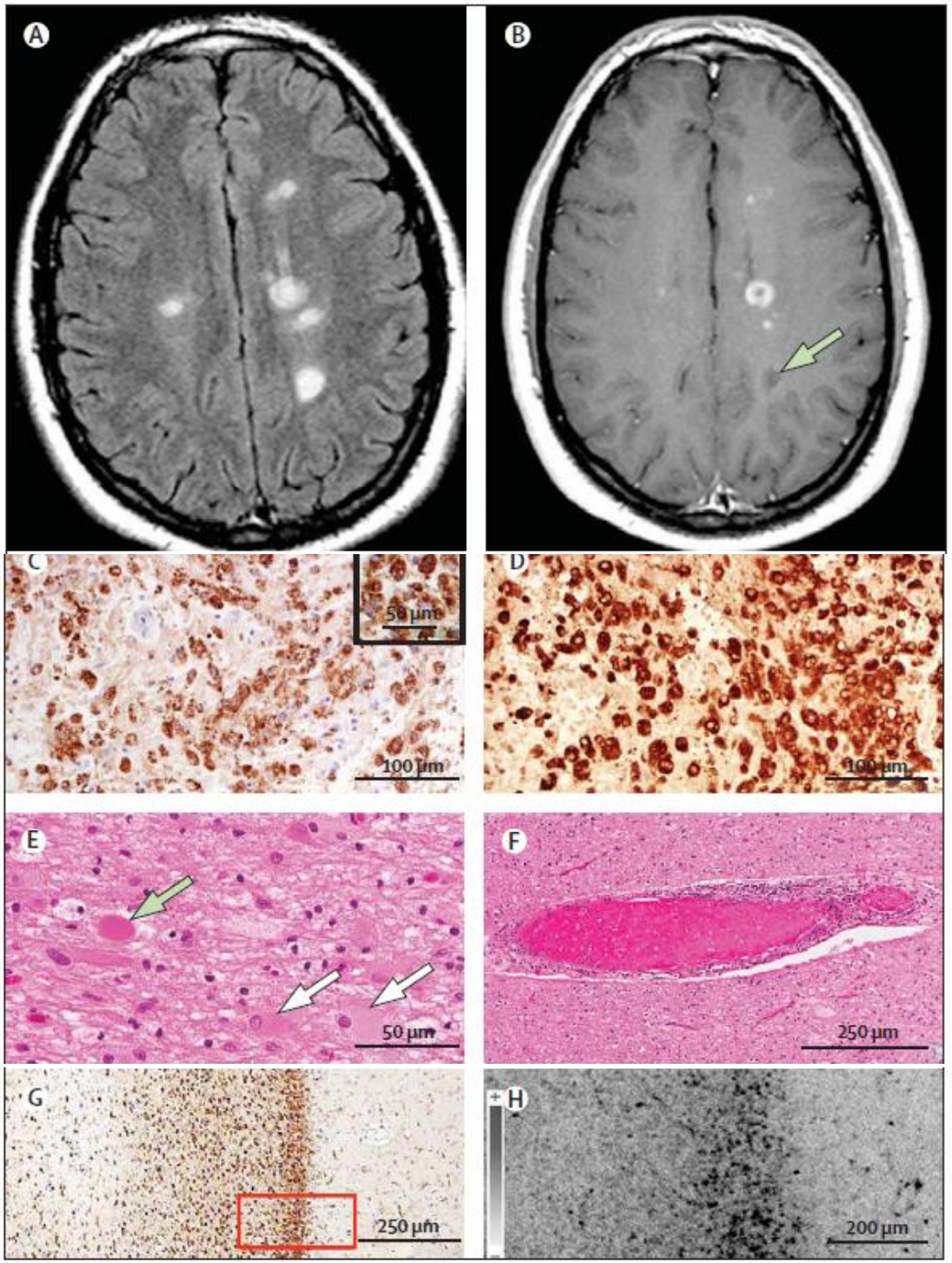
C–F: ACTIVE LESION:

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



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D: Sea of macrophages

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

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G,H: CHRONIC ACTIVE LESION:

G: Active macrophages at plaque edge

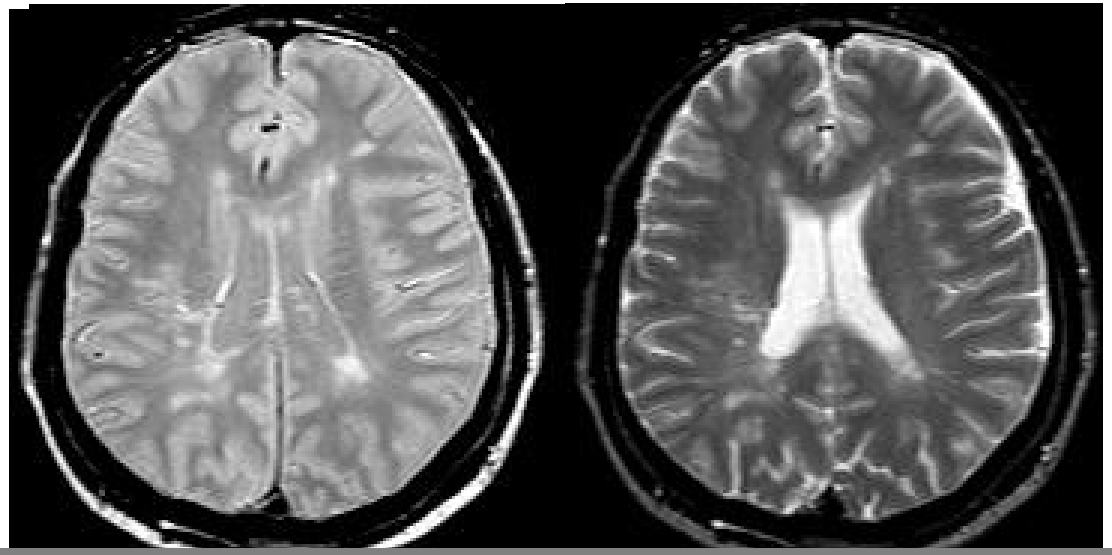
H: Iron map of area boxed in G: most iron within macrophages

MS brain lesion characteristics

Graz

Lesion configuration	ovoid (round shape)
Size of lesions	> punctate
Typical lesion location	periventricular, juxtacortical, infratentorial
Lesion pattern	random, asymmetric
Tissue destruction	variable
Contrast enhancement	frequent

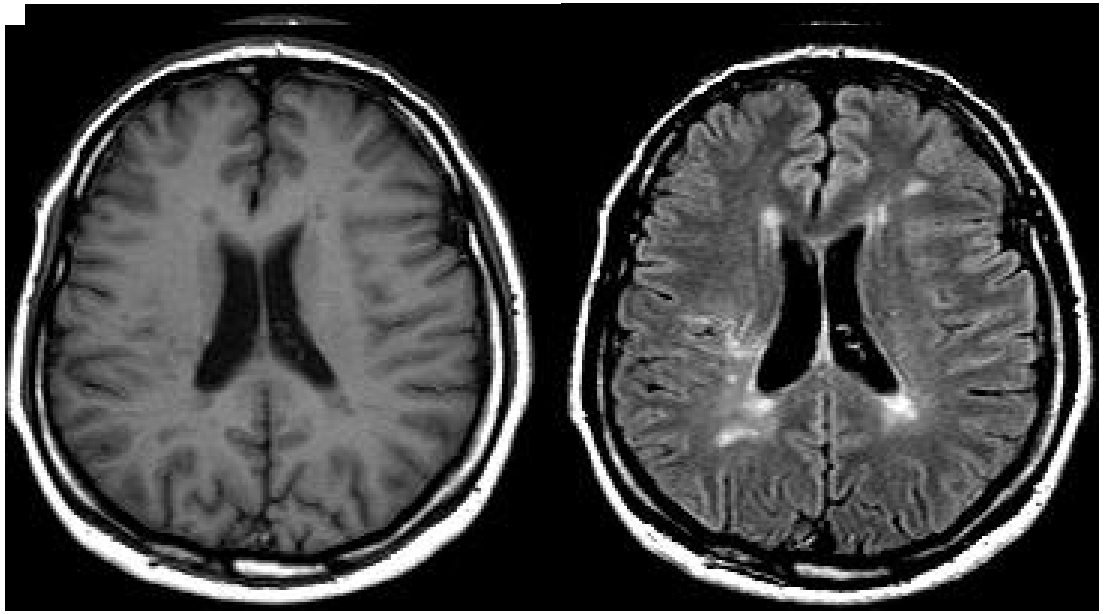
PD



T2

Lesion identification and characterization

T1



FLAIR

Diagnostic criteria for MS

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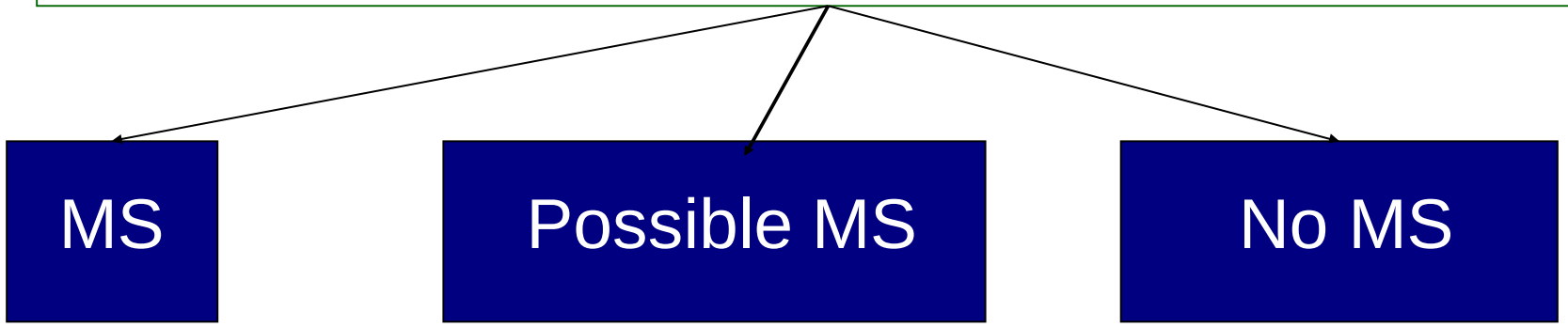
(McDonald WI et al., Ann Neurol 2001, Polman C et al., Ann Neurol 2005, Polman C et al., Ann Neurol 2011)

- Objective evidence for dissemination in **time** and **space** of lesions typical for MS
- After **exclusion** of a better explanation for the clinical symptoms



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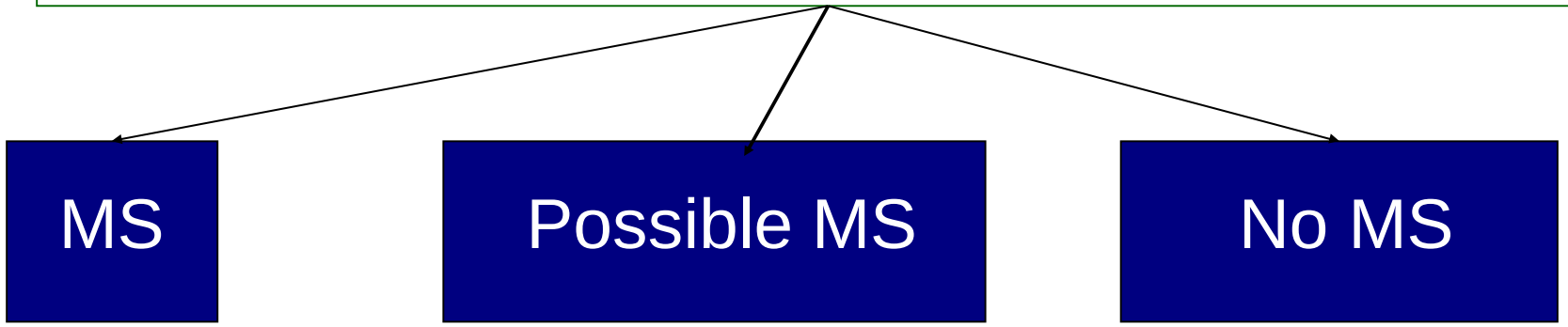


Current diagnostic criteria for MS

(context: 1st clinical episode, consistent with demyelination)

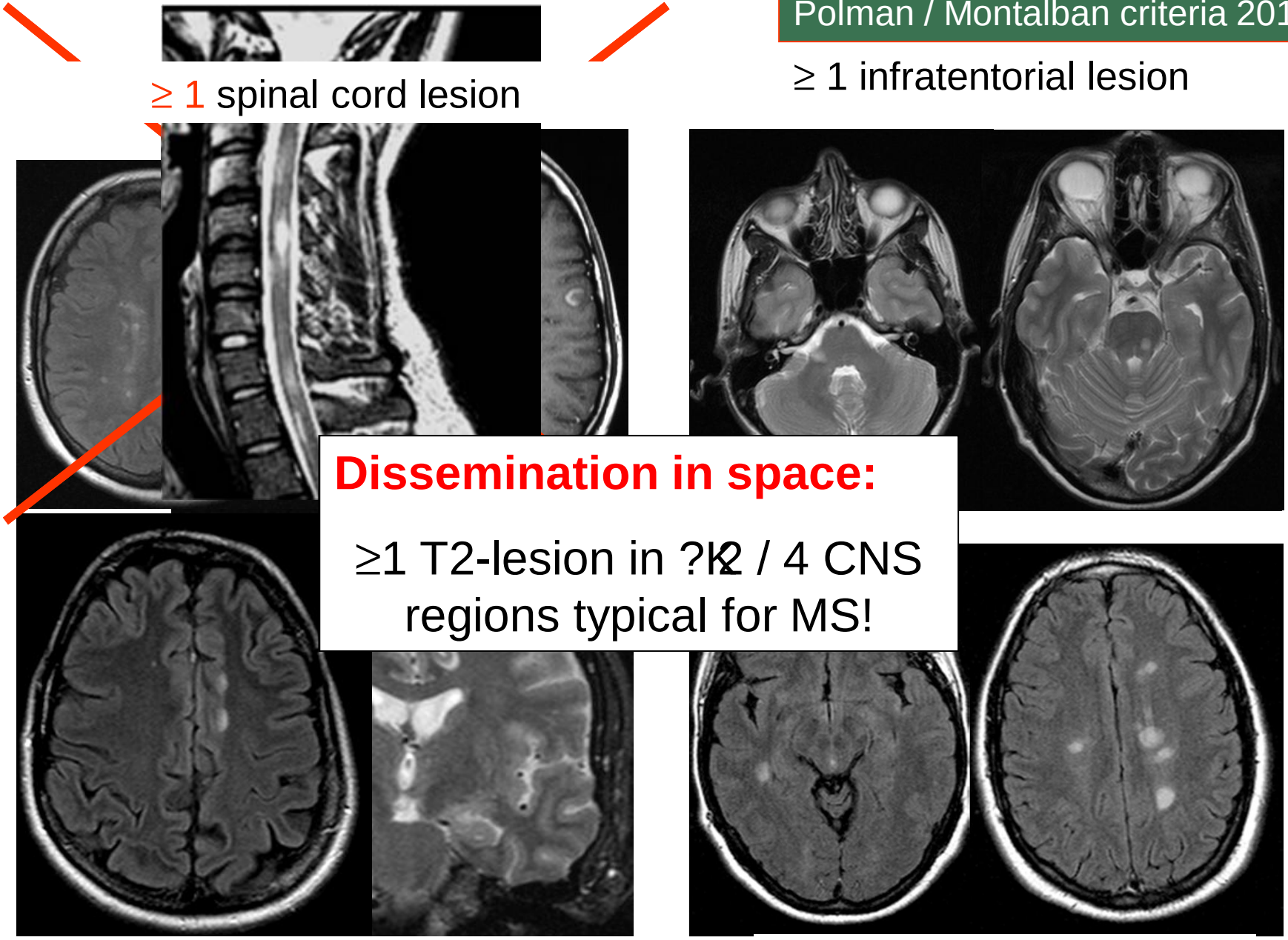
	2001[1]	2005[2]	2010[3]
Dissemination in space	Three of the following: 1. At least one Gd+ lesion or 9 T2 hyperintense lesions if there is a Gd+ lesion 2. At least one infratentorial lesion 3. At least one juxtacortical lesion 4. At least three periventricular lesions *2001:* One spinal cord lesion can substitute for one brain lesion. *2005:* A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: an enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions.		≥1 T2 lesion in at least 2 out of four MS-typical regions of CNS *periventricular, juxtacortical, infratentorial, or spinal cord*
Dissemination in time	A Gd+ lesion > 3 months after onset of initial clinical event at a site not implicated by the event *Or:* Follow-up scan (>3 months): a *new* T2 or Gd+ lesion	*Or:* A *new* T2 lesion at any time compared to a scan >30 days after onset of initial clinical event	Simultaneous presence of asymptomatic Gd+ AND non-enhancing lesions at any time *Or:* A *new* T2 and/or Gd+ lesion(s) on FU MRI irrespective of timing of baseline scan

CNS, central nervous system; FU, follow up; Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging.
[1]McDonald *et al*. Ann Neurol 2001;50:121–7; [2]Polman *et al*. Ann Neurol 2005;58:840–6; [3]Polman *et al*. Ann Neurol 2011;69:292–302.

Polman / Montalban criteria 2010

≥ 1 spinal cord lesion

≥ 1 infratentorial lesion



Dissemination in space:

≥1 T2-lesion in ?2 / 4 CNS regions typical for MS!

≥ 1 juxtacortical lesion

≥ **1** periventricular lesion(s)

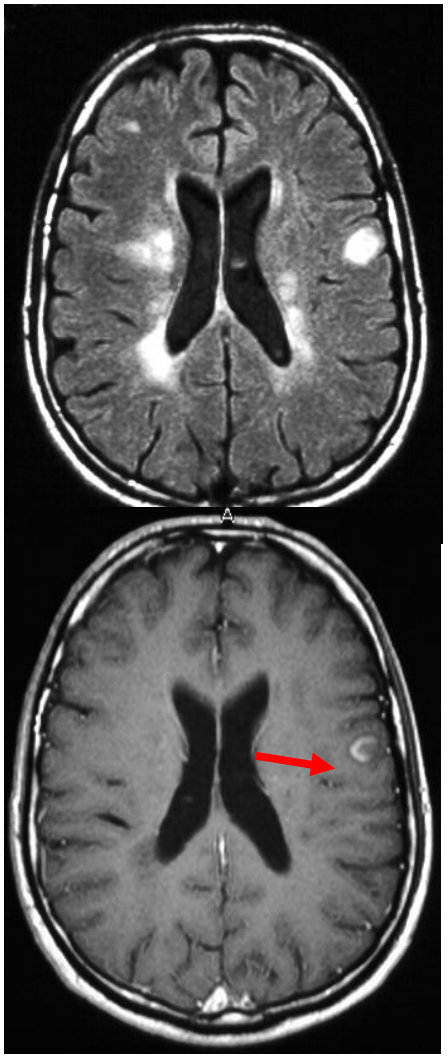
Diagnostic Criteria for Multiple Sclerosis: 2010 Revisions to the McDonald Criteria

Dissemination in time

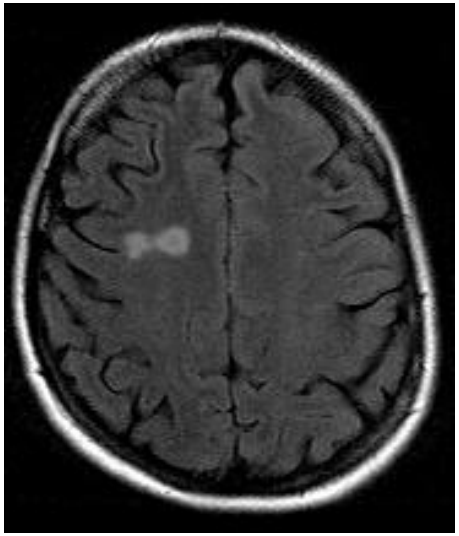
TABLE 2: 2010 McDonald MRI Criteria for Demonstration of DIT

DIT 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

Based on Montalban et al 2010.[24]
MRI = magnetic resonance imaging; DIT = lesion dissemination in time.

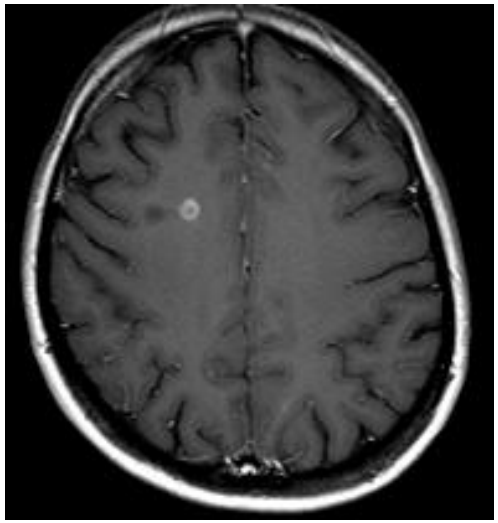


Ann Neurol 2011:69:292-302



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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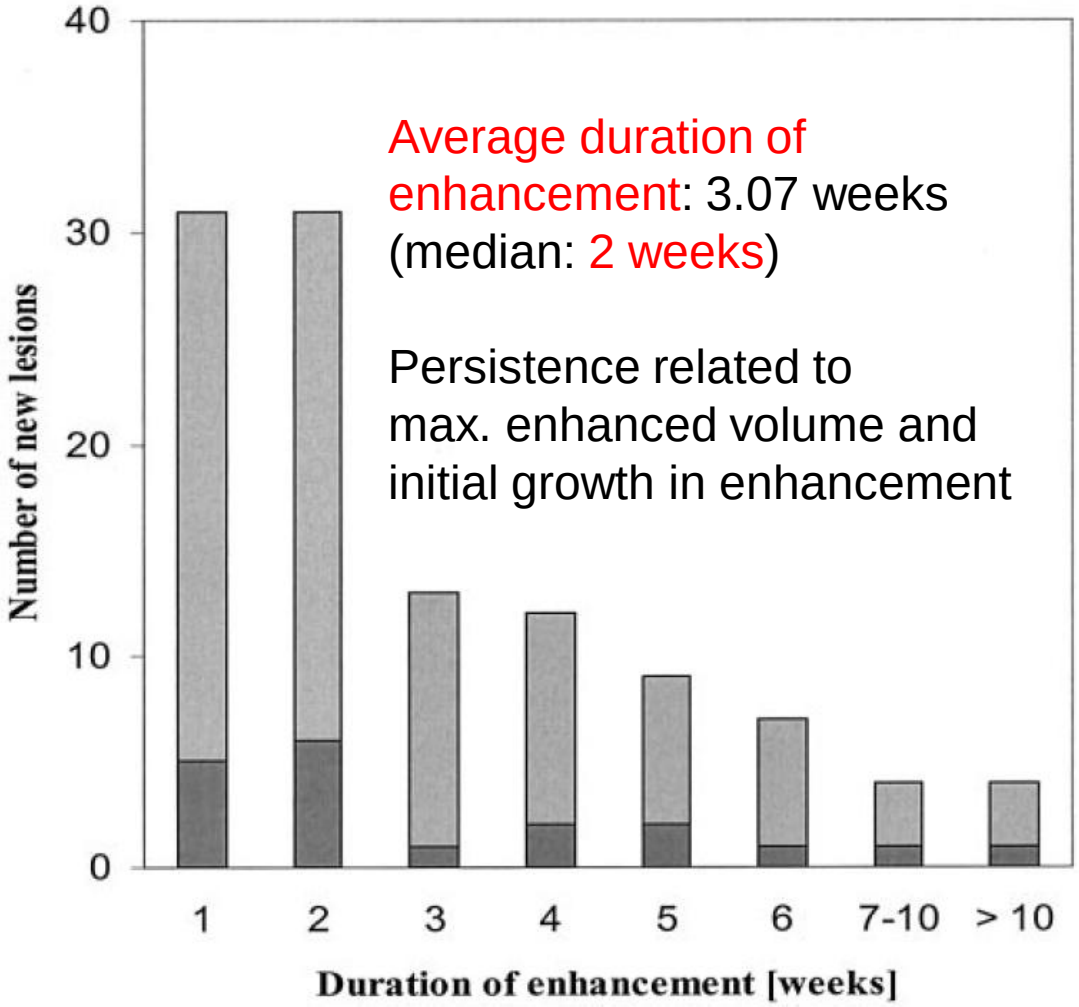

Average duration of enhancement: 3.07 weeks (median: 2 weeks)

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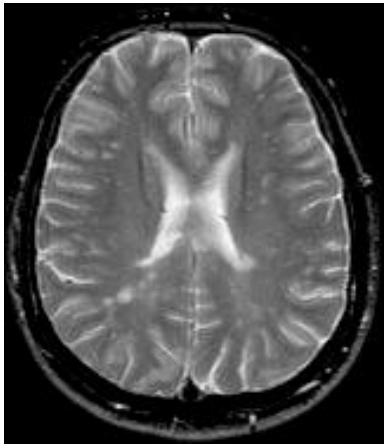
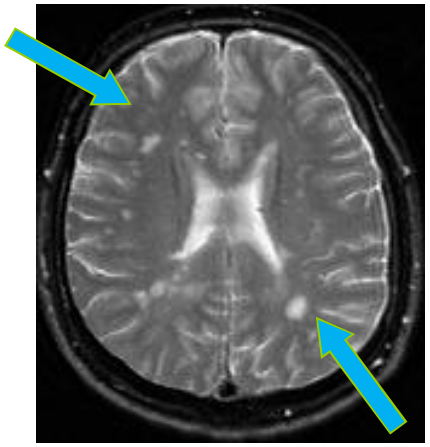
- Serial MRI after MP (31 courses)
- 13 patients with definite MS
- Gd-enhanced MRI before and after MP, then monthly
- 609 active lesions on 195 examinations
- Directly after treatment 78% reduction in number of EL
- No beneficial effect on rate of disappearance of related T2-abnormalities.
- MP effect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

New proposed diagnostic algorithm in patients with typical CIS

Adapted from Montalban X et al., Neurology 2010; 74; 427-434

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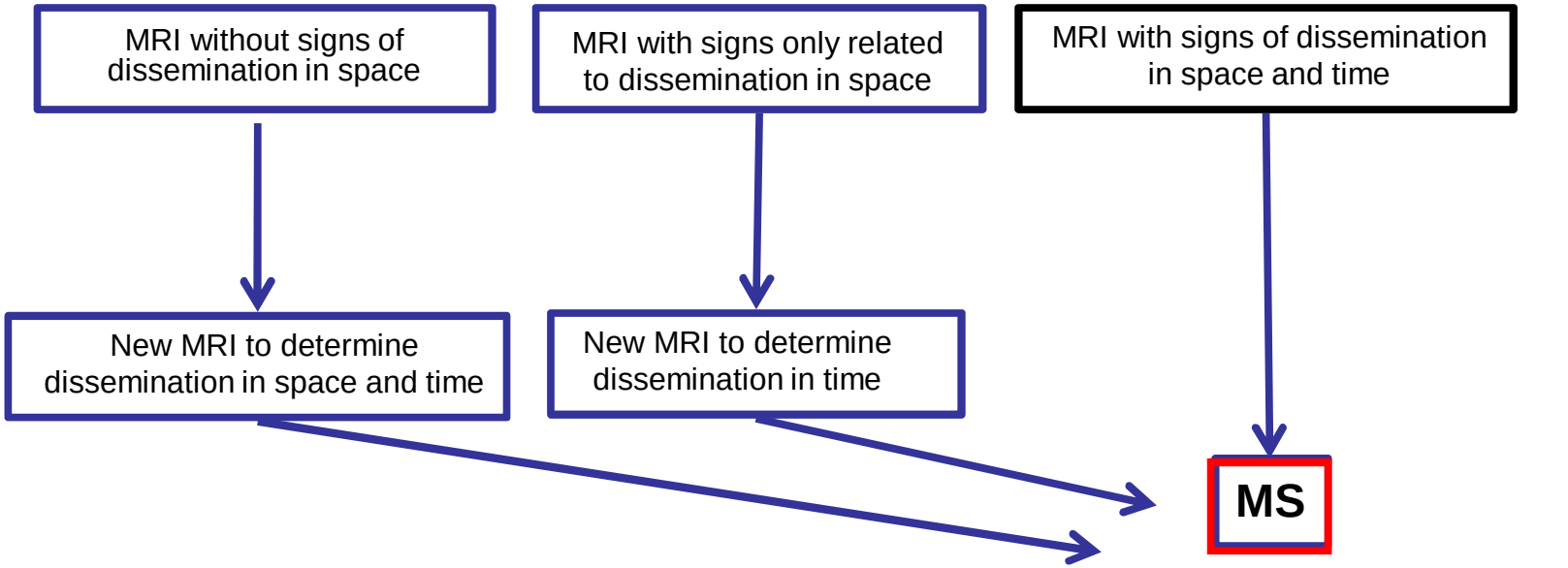

Dissemination in space (DIS)	Dissemination in time (DIT)
?!1 asymptomatic lesion in each of ?!2 characteristic locations • Periventricular • Juxtacortical • Posterior fossa • Spinal Cord	I) Simultaneous presence of asymptomatic Gd enhancing and non-enhancing lesion(s) at any time II) A new T2 lesion and/or Gd/enhancing lesion on follow-up MRI irrespective of timing of baseline scan

evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or 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: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or 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: For DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or Await a second clinical attack[a] implicating a different CNS site; and For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or 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]: 1. Evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions 2. Evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

Polman CH et al., Ann Neurol 2011:69:292-302

Preserved & changed concepts

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- Overall concept of MS diagnosis unchanged
- Dissemination in space (DIS)
  - Further „upgrade“ of spinal cord lesions
  - Lesion count and Gad enhancement dropped
- Dissemination in time (DIT)
  - Possibility to demonstrate DIT using one scan
  - No fixed time interval between clinical attack and „baseline scan“
- No need for application of Gadolinium

Benefits & risks in clinical practice

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- Concentrating on lesion location rather than lesion count facilitates interpretation of MRI
- Elimination of a requested interval between clinical attack and „baseline“ reference scan (which was arbitrary) facilitates patient management
- Accepting concomitant presence of non-enhancing and enhancing lesions as evidence for lesion dissemination in time now takes full advantage of the information provided by MRI

Benefits & risks in clinical practice

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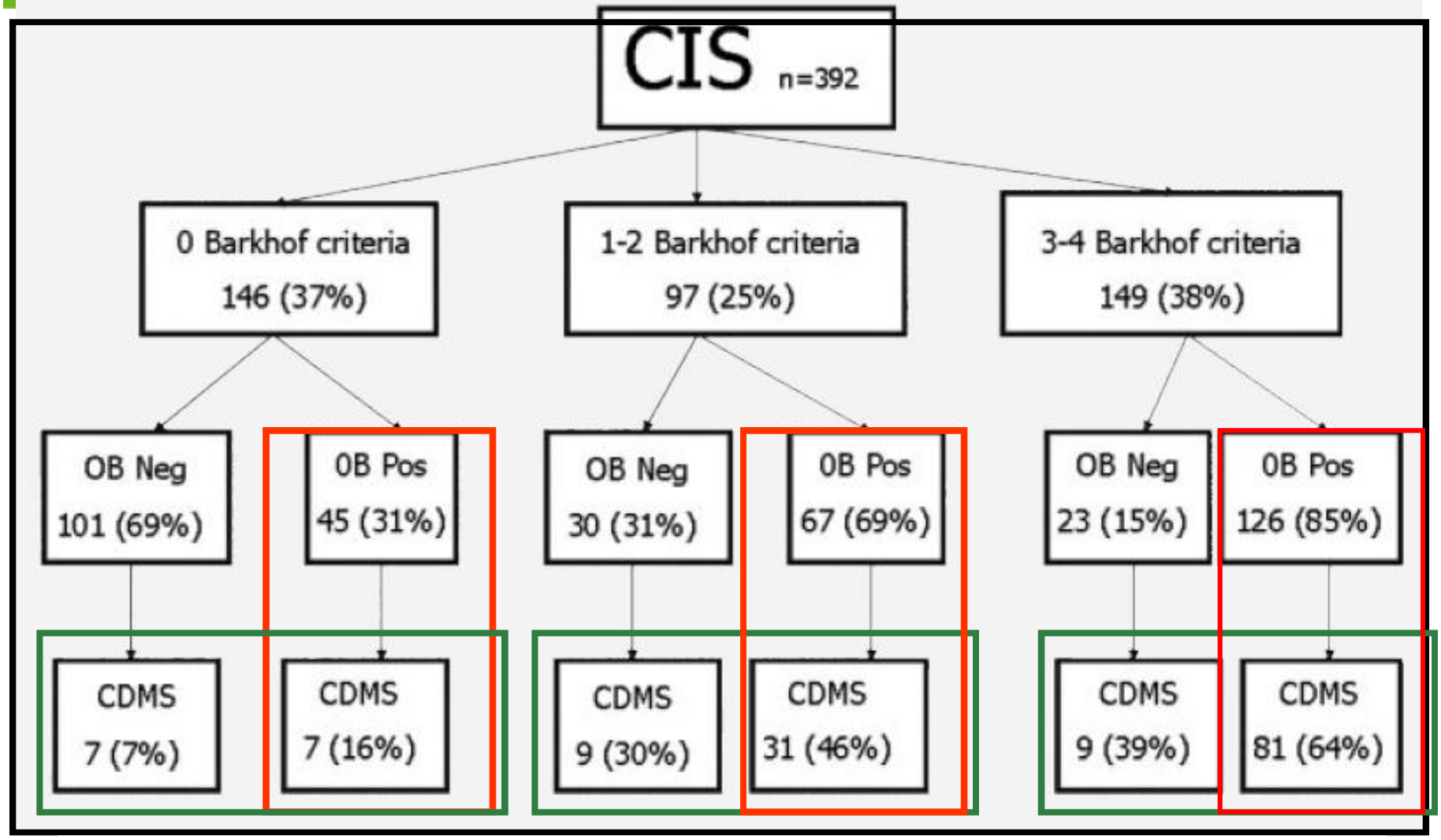
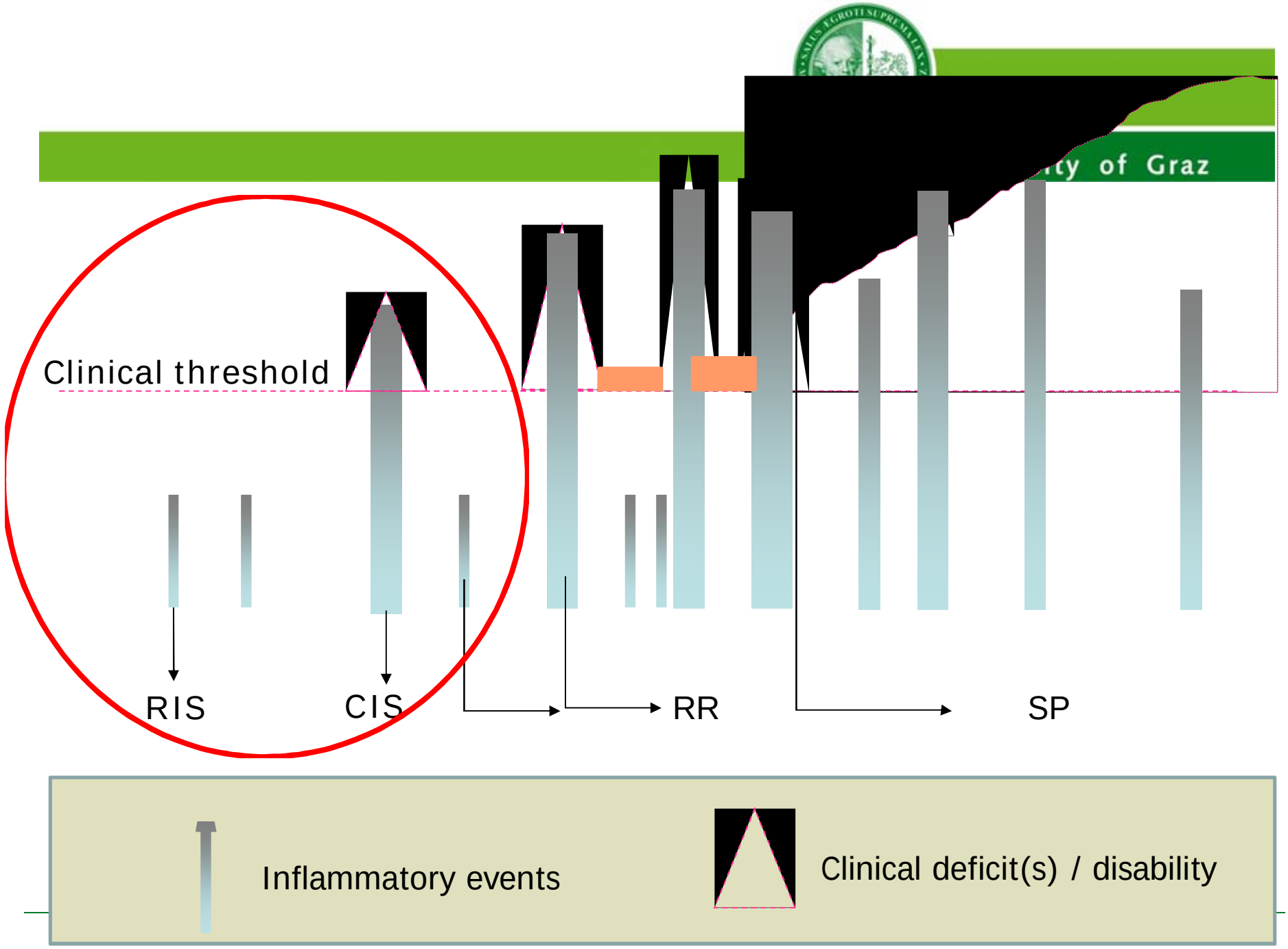
- Very few lesions and a minimal change over time may suffice for a diagnosis of MS
- The incentive to obtain Gadolinium enhanced scans (and for CSF examination) has been downgraded
- This may ultimately compromise diagnostic specificity when applied by non-experts

Risk of conversion to CDMS – the role of oligoclonal bands from CSF



Tintoré M. et al., Neurology 2008 Mar 25;70(13 Pt 2):1079-83.


Clinical threshold
RIS
CIS
RR
SP
Inflammatory events
Clinical deficit(s) / disability

Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile

C Lebrun,[1] C Bensa,[2] M Debouverie,[3] J De Seze,[4] S Wiertlievski,[5] B Brochet,[6] P Clavelou,[7] D Brassat,[8] P Labauge,[9] E Roullet,[2] on behalf of CFSEP

J Neurol Neurosurg Psychiatry 2008;**79**:195–198. doi:10.1136/jnnp.2006.108274

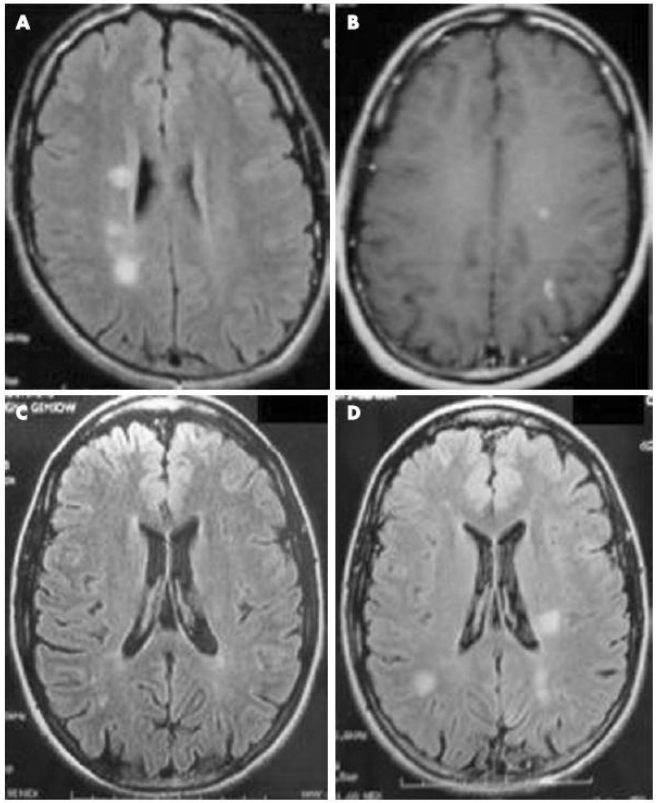


Figure 1 (A) T2 weighted fluid attenuated inversion recovery (FLAIR) brain MRI showing hypersignals suggestive of multiple sclerosis. (B) Gadolinium enhancement of two lesions. (C) T2 weighted FLAIR brain MRI showing hypersignals with (D) dissemination in time on the MRI 6 months later.

ABSTRACT

The concept of preclinical multiple sclerosis is now well recognised, and a diagnosis of silent brain T2 lesions is frequent because of the ease of performing MRI. Nevertheless, patients with incidental brain MRI fulfilling Barkhof– Tintoré criteria are more rare. We report a descriptive retrospective study of clinical and 5 year MRI follow-up in patients with subclinical demyelinating lesions fulfilling MRI Barkhof–Tintoré criteria with a normal neurological examination. 30 patients were identified and the first brain MRI was performed for various medical events: headaches (n = 14), migraine with (n = 2) or without (n = 4) aura, craniocerebral trauma (n = 3), depression (n = 3), dysmenorrhoea (n = 2), epilepsy (n = 1) and cognitive changes (n = 1). Mean time for the second brain MRI was 6 months (range 3–30). 23 patients had temporospatial dissemination (eight with gadolinium enhancement). 11 patients had clinical conversion: optic neuritis (n = 5), brainstem (n = 3), sensitive symptoms (n = 2) and cognitive deterioration (n = 1). Eight (72%) already had criteria of dissemination to space and time before the clinical event. Mean time between the first brain MRI and clinically isolated syndrome (CIS) was 2.3 years. To our knowledge, this is the first cohort of CIS with preclinical follow-up. Early treatment should be discussed in view of the predictive value on conversion of the MRI burden of the disease.

Incidental MRI anomalies suggestive of multiple sclerosis

The radiologically isolated syndrome

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ABSTRACT

Background: The discovery and broad application of MRI in medicine has led to an increased awareness in the number of patients with incidental white matter pathology in the CNS. Routinely encountered in clinical practice, the natural history or evolution of such individuals with respect to their risk of developing multiple sclerosis (MS) is unclear.

Objective: To investigate the natural history of patients who exhibit incidental imaging findings highly suggestive of MS pathology.

Methods: Detailed clinical and radiologic data were obtained from asymptomatic patients with MRI anomalies suggestive of MS.

Results: The cohort consisted of 41 female and 3 male subjects (median age = 38.5, range: 16.2–67.1). Clinical evaluations were performed in 44 patients at the time of initial imaging; longitudinal clinical follow-up occurred for 30 patients, and longitudinal MRI data were acquired for 41 patients. Neurologic examination at the time of the initial MRI scans was normal in nearly all cases. While radiologic progression was identified in 59% of cases, only 10 patients converted to either clinically isolated syndrome or definite MS. The presence of contrast-enhancing lesions on the initial MRI was predictive of dissemination in time on repeat imaging of the brain (hazard ratio [HR] = 3.4, 95% confidence interval [1.3, 8.7], $p = 0.01$).

Conclusion: Individuals with MRI anomalies highly suggestive of demyelinating pathology, not better accounted for by another disease process, are very likely to experience subsequent radiologic or clinical events related to multiple sclerosis. Additional studies will be necessary to fully define this risk. *Neurology*® 2009;72:800–805

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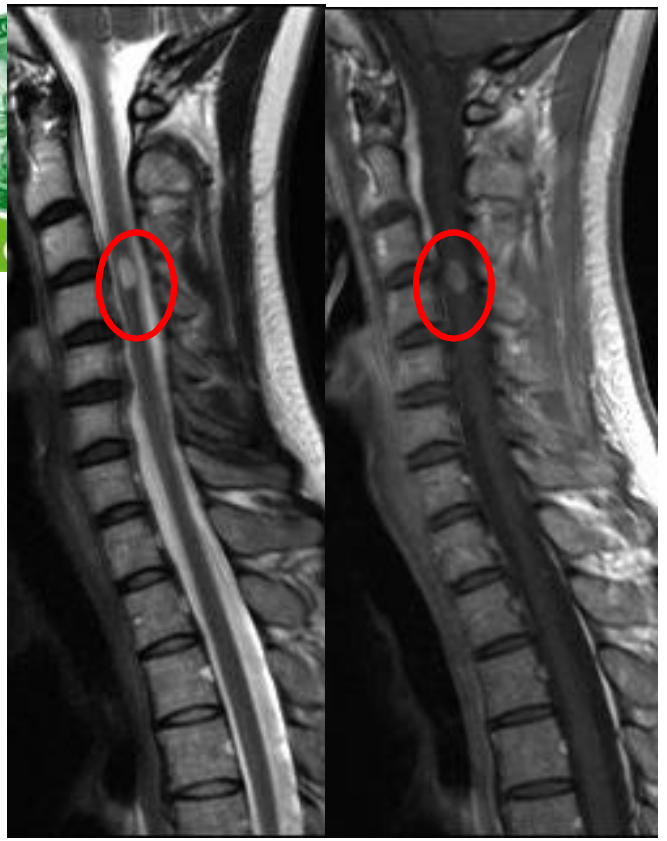
Table 1 Proposed diagnostic criteria for the radiologically isolated syndrome

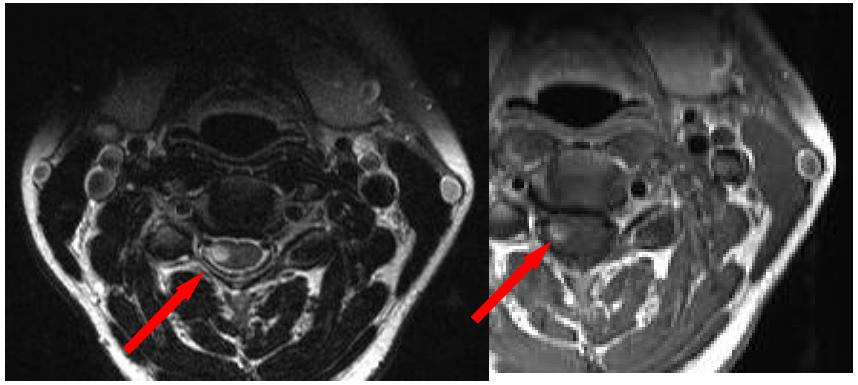
A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:
1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
2. T2 hyperintensities measuring >3 mm and fulfilling Barkhof[7] criteria (at least 3 out of 4) for dissemination in space
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

MS spinal cord lesion characteristics

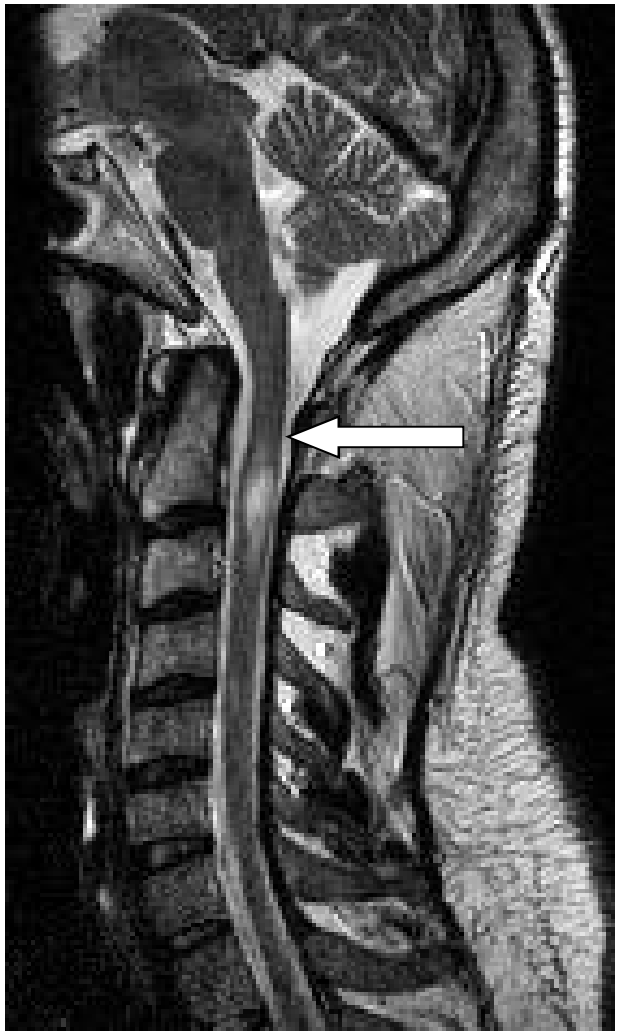
- Cigar shaped (in sagittal plane)
- Extension < 2 vertebral bodies in length and < ½ spinal cord diameter
- Eccentric location
- Mass effect rare
- Cervical cord and posterior columns preferentially affected

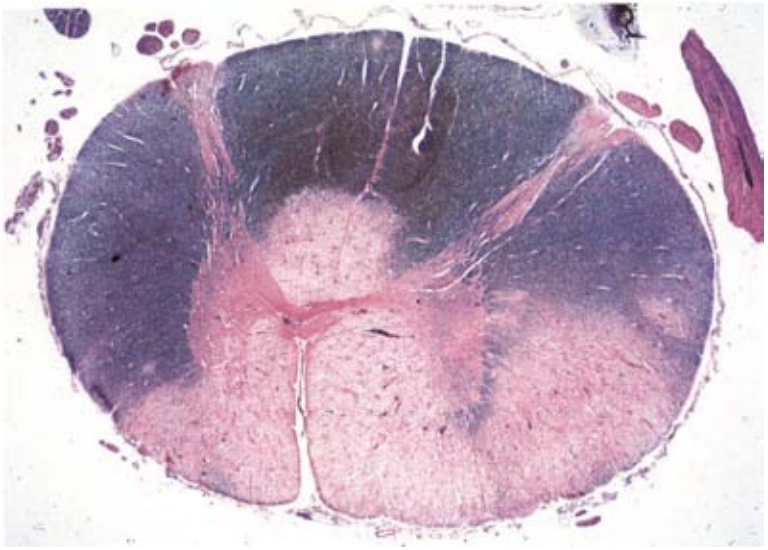


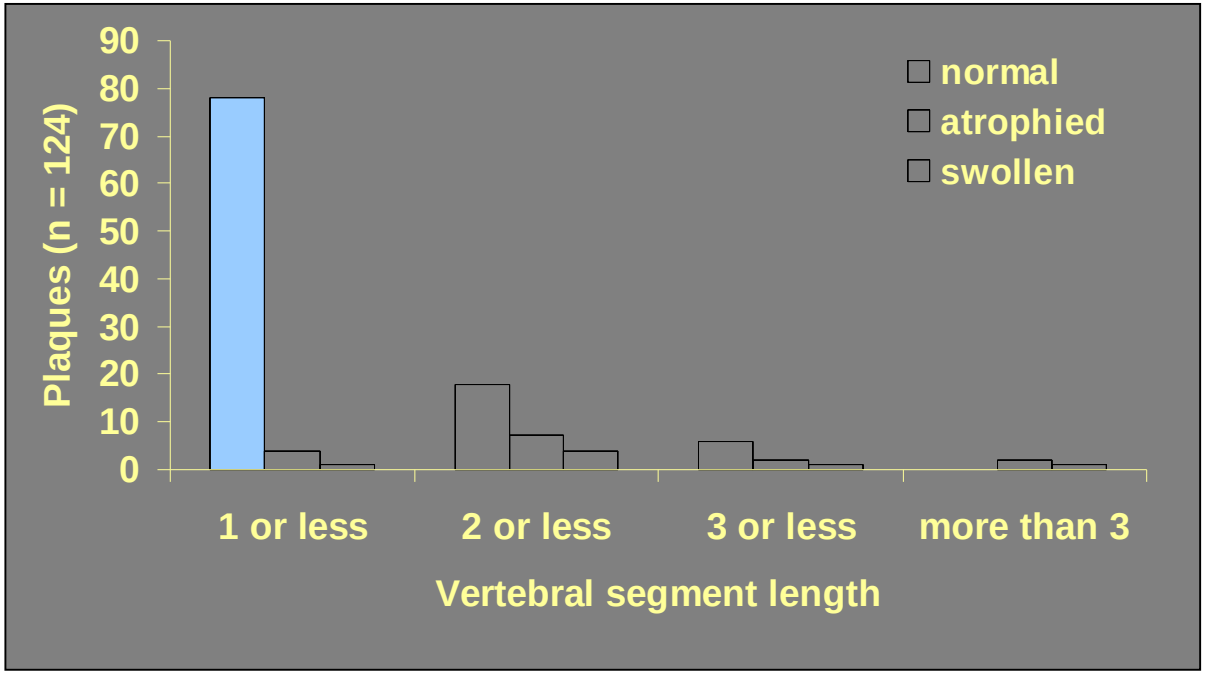
No incidental age-related / vascular spinal cord lesions



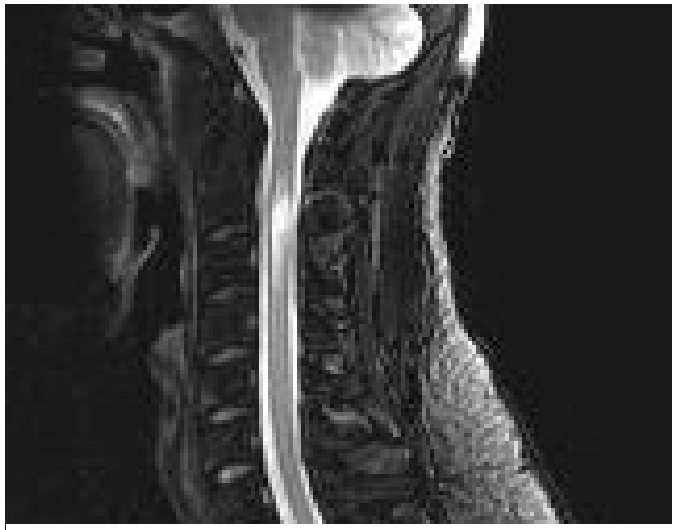
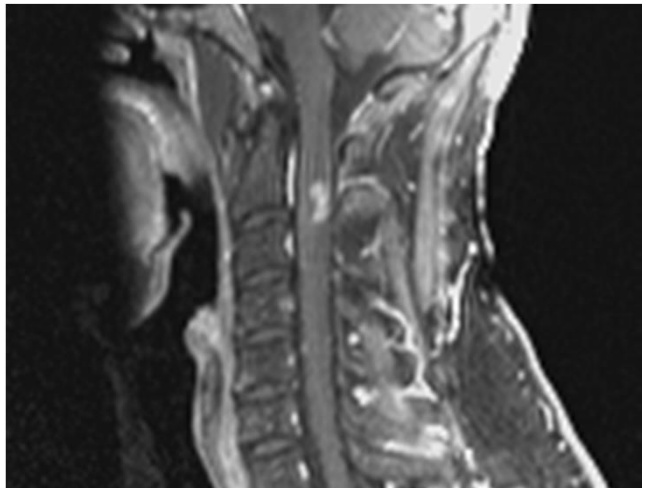
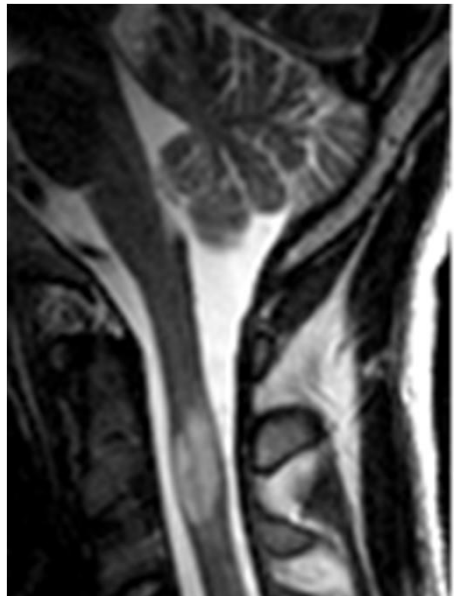
Multiple sclerosis



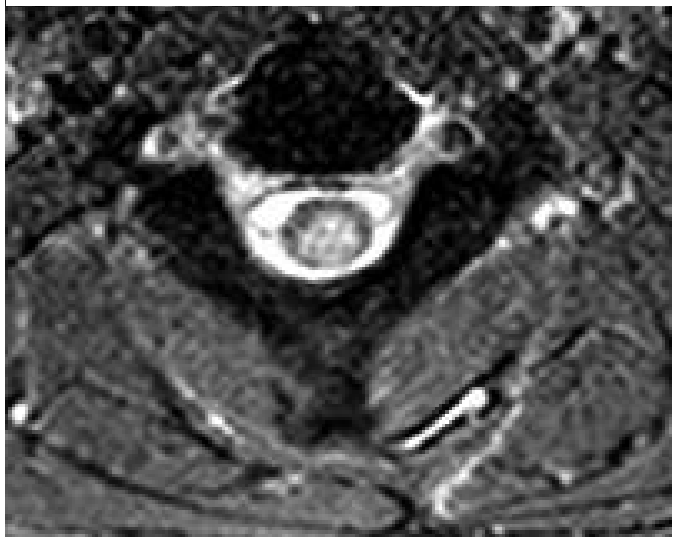
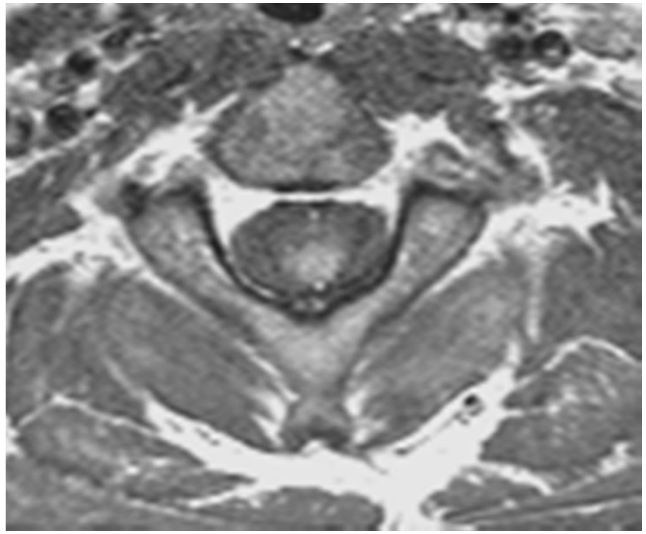
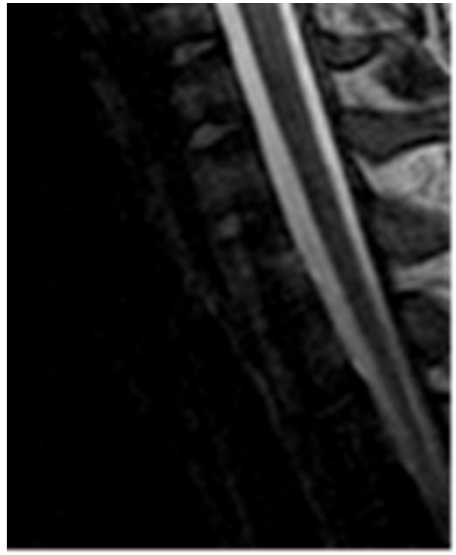




Spinal cord lesions in MS

Absence of spinal cord lesions may argue against MS

Conclusions – MRI in the diagnosis of MS

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- MRI is very sensitive for MS lesions, predominantly in the white matter
- MS lesion characteristics focus on location, gestalt and size
- Specificity of lesion interpretation can be enhanced by application of contrast material and a set of MRI sequences
- Cortical lesions are seen only to a limited extent and with specific sequences (not available in everyday practice)
- MS lesions in the spinal cord have also characteristic features
- Spinal cord MRI requires high technical standards

AGENDA - The role of MRI in the…

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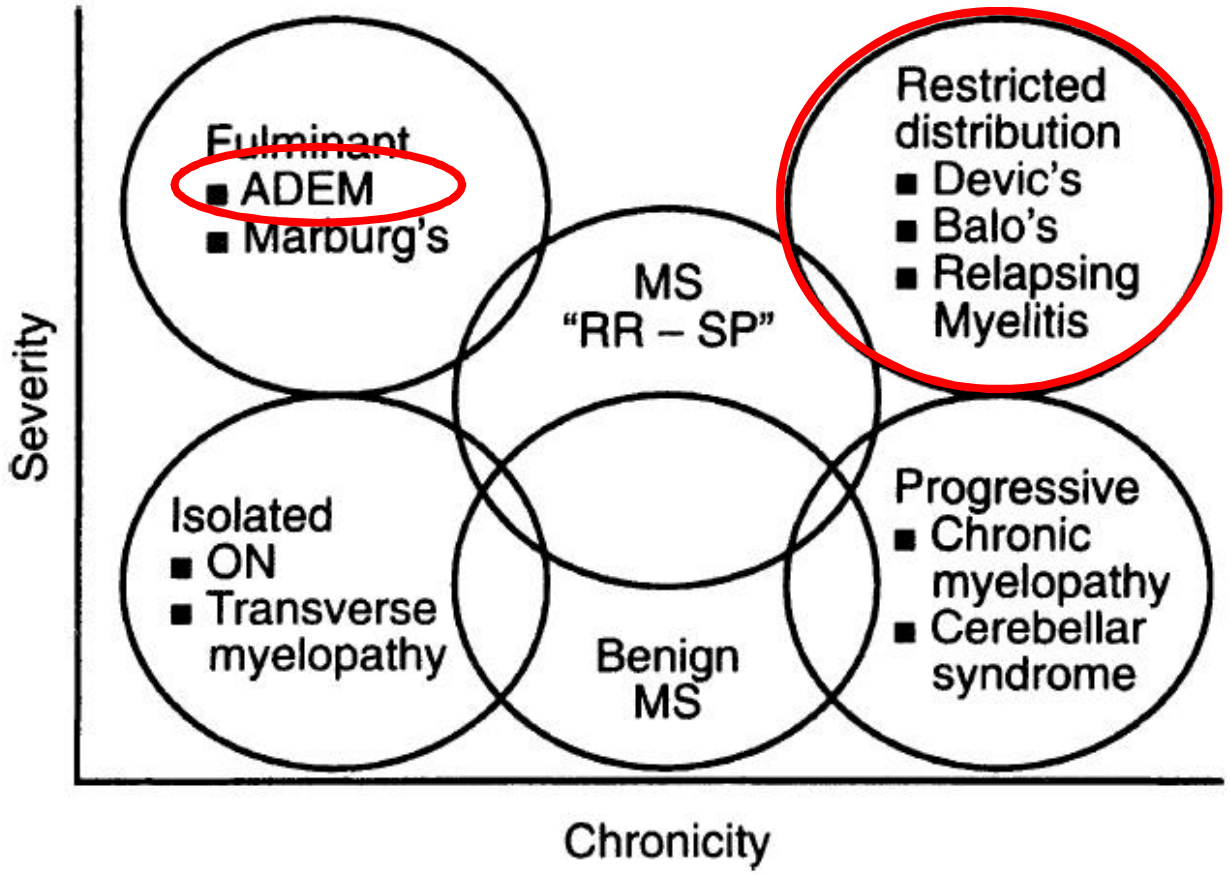
- Dx of MS
- Dx of allied disorders
- Differential Dx

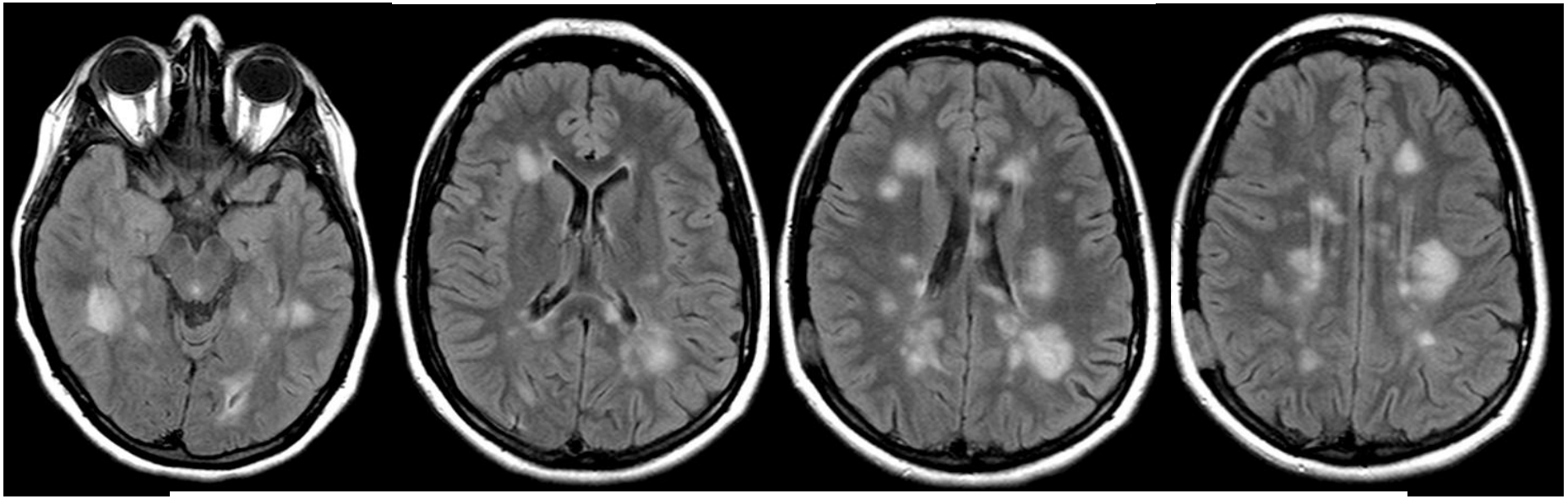
Subtypes of idiopathic inflammatory demyelinating diseases

Medical University of Graz

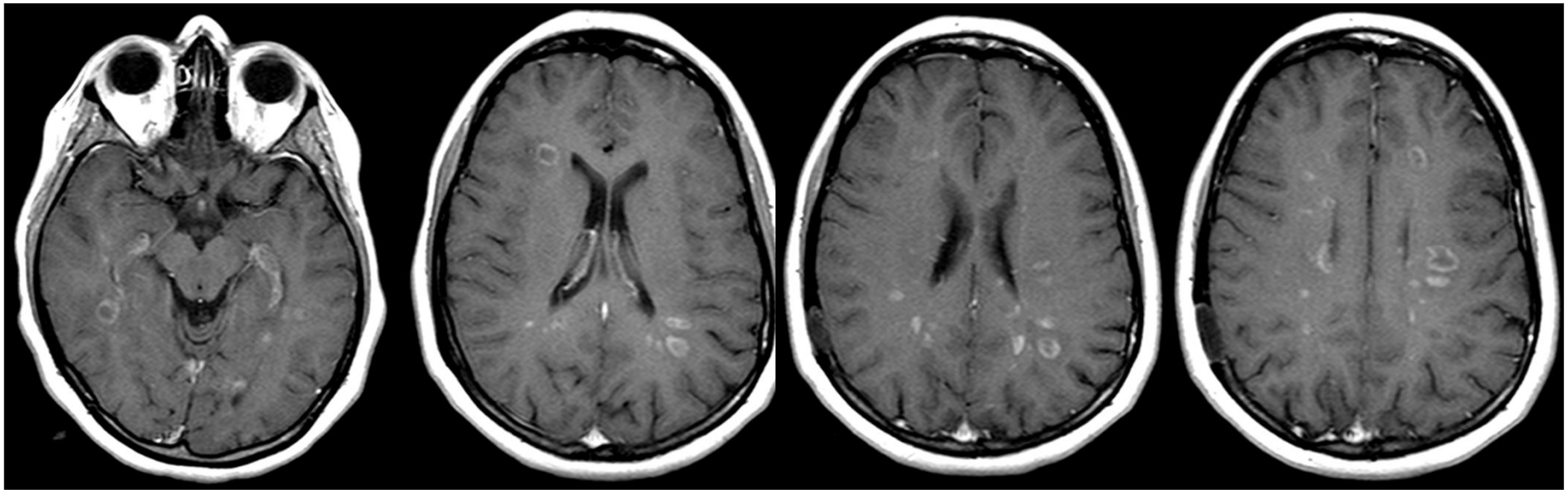


Poser C et al., Clin Neurol Neurosurg 2004; 106:159-171

Mistaking other conditions as „active MS“



Acute disseminated encephalomyelitis (ADEM)



Consensus definitions proposed for pediatric multiple sclerosis and related disorders

Lauren B. Krupp, MD; Brenda Banwell, MD; and Silvia Tenembaum, MD;
for the International Pediatric MS Study Group*

University of Graz

Table *Comparison of typical features of ADEM and MS*

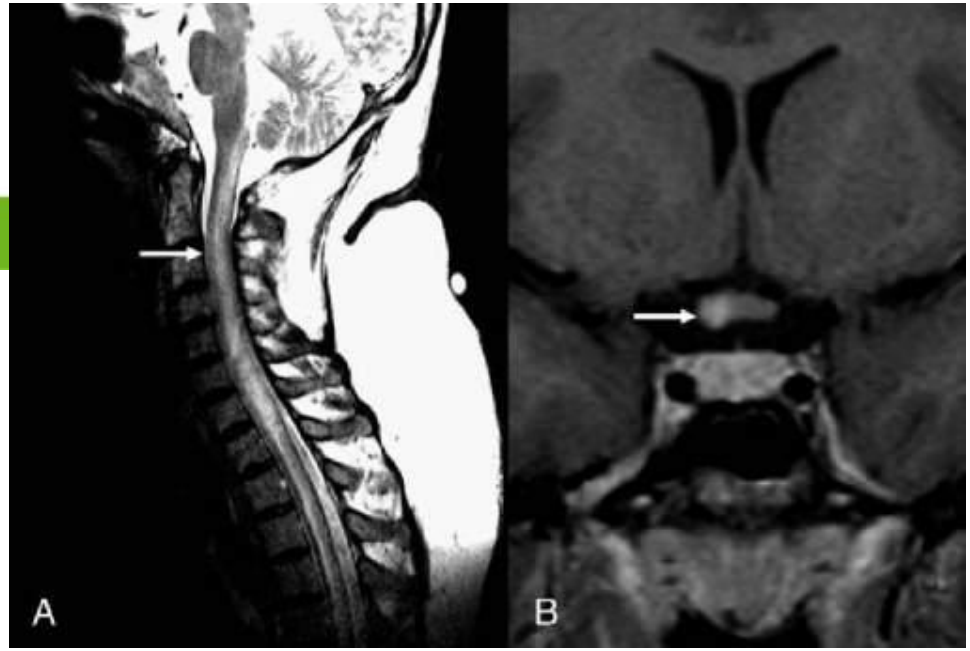
Typical features	ADEM	MS
Demographic	More frequently younger age groups (<10 years); no gender predilection	More frequently adolescents; girls predisposed more than boys
Prior flu-like illness	Very frequent	Variable
Encephalopathy	Required in definition	Rare early in the disease
Seizures	Variable	Rare
Discrete event	A single event can fluctuate over the course of 12 weeks	Discrete events separated by at least 4 weeks
MRI shows large lesions involving gray and white matter	Frequent	Rare
MRI shows enhancement	Frequent	Frequent
Longitudinal MRI findings	Lesions typically either resolve or show only residual findings*	Typically associated with development of new lesions
CSF pleocytosis	Variable	Extremely rare, white blood cell count almost always <50
Oligoclonal bands	Variable	Frequent
Response to steroids	Appears favorable	Favorable

* A subset of patients with acute disseminated encephalomyelitis (ADEM) fail to have a self-limited disease course and instead experience additional relapses and accumulate lesions on neuroimaging. Subsequently, these patients are reclassified as multiple sclerosis (MS).

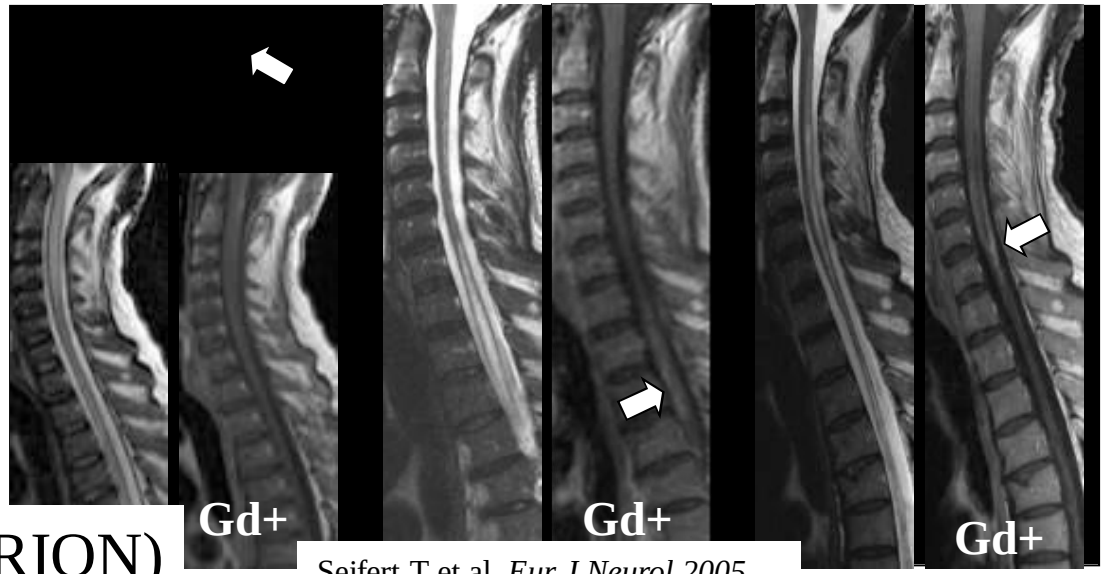
Neurology 2007;68;S7-S12

Neuromyelitis optica (NMO)

- Spinal cord imaging
  - continuous lesion ?3 vertebral segments
  - longitudinal extension („linear“ converging lesion)
  - T2 signal alteration often comprising entire diameter
  - T1-hypointensity
  - variable enhancement
- MRI of the brain
  - Parenchyma entirely or almost unremarkable (<3 lesions)
  - enhancement optic nerve(s) & chiasma opticum (85%)



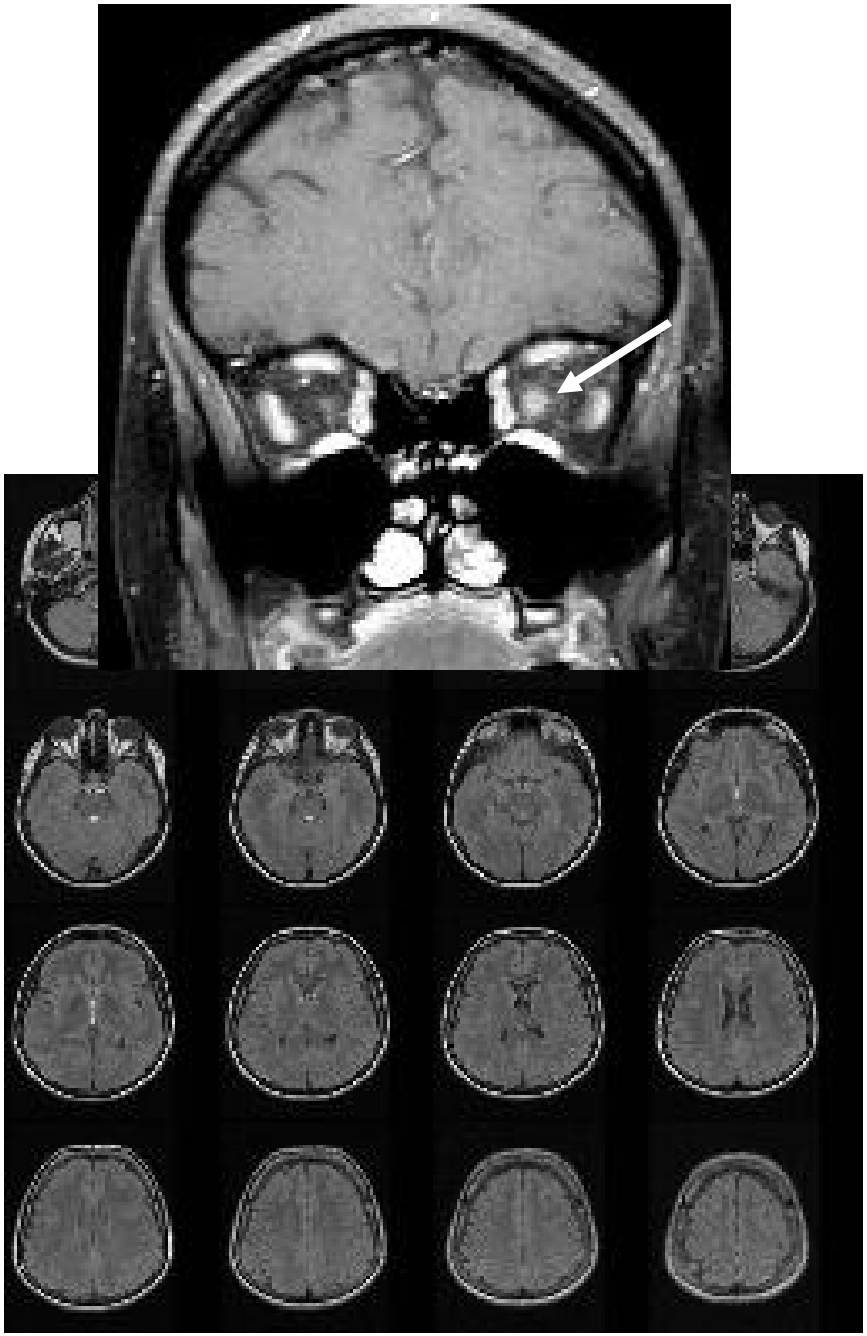
Jacob et al *J Neuroimmunol* 2007

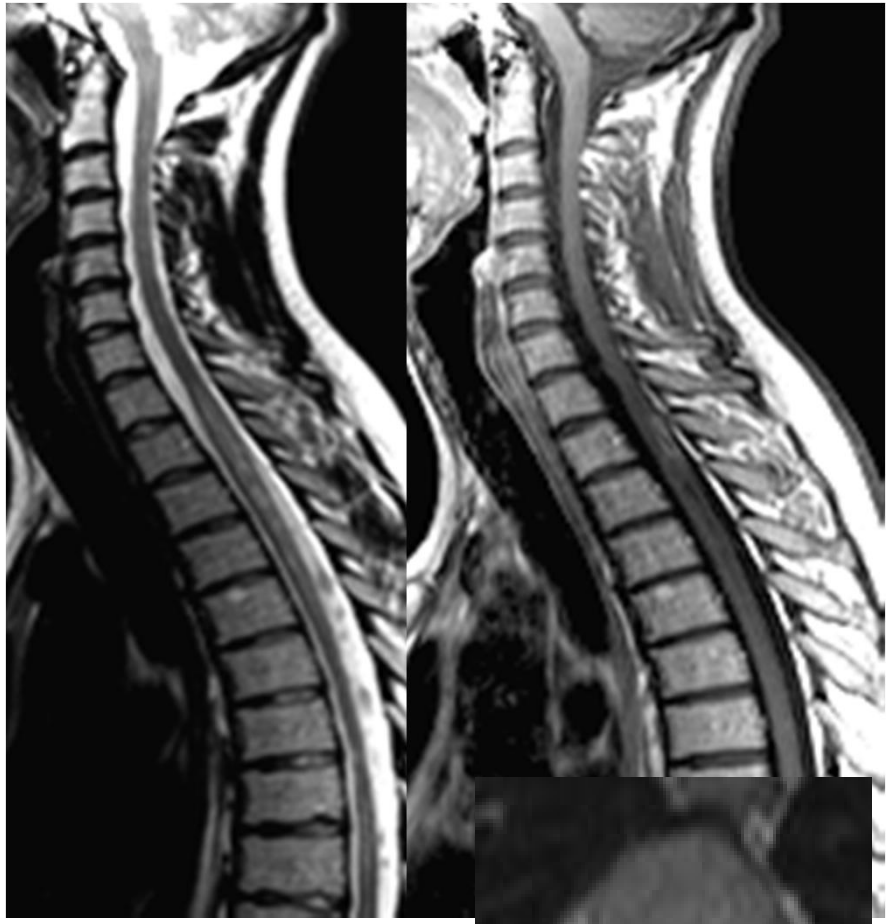


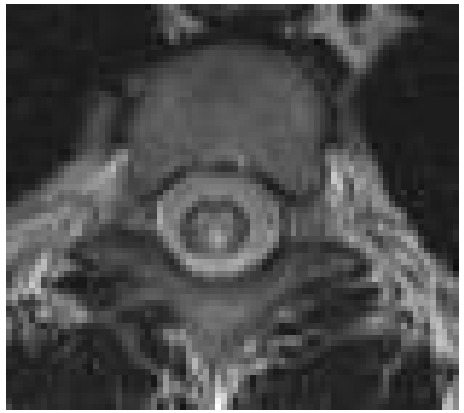
Seifert T et al. *Eur J Neurol 2005*

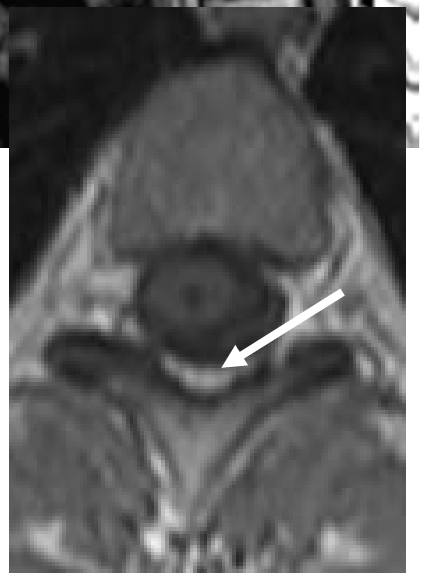
Relapsing myelitis ?

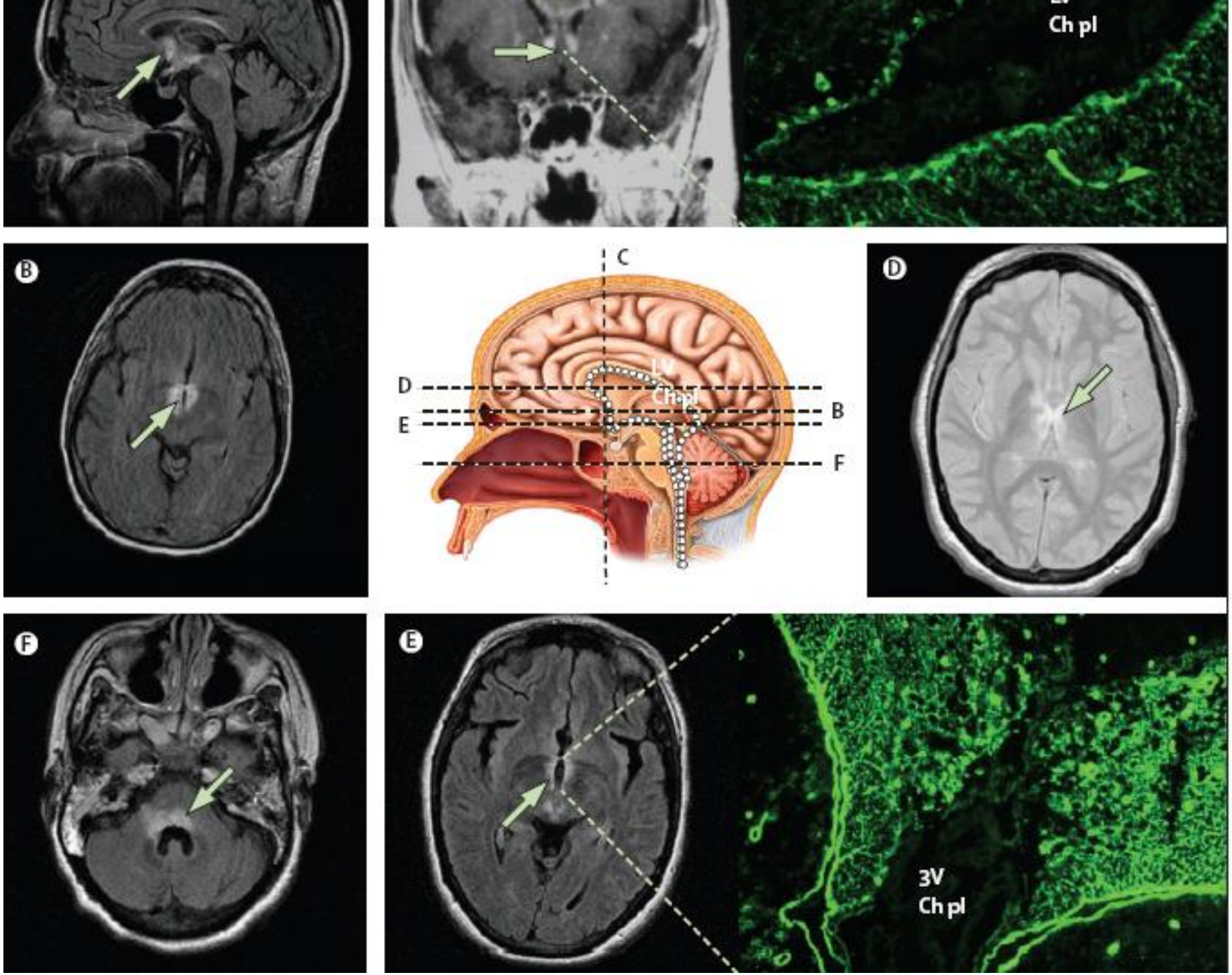
Recurrent optic neuritis (CRION)











Wingerchuk DM et al., Lancet Neurol 2007

Revised diagnostic criteria for neuromyelitis optica

D.M. Wingerchuk, MD, FRCP(C); V.A. Lennon, MD, PhD; S.J. Pittock, MD; C.F. Lucchinetti, MD; and B.G. Weinshenker, MD, FRCP(C)

Proposed diagnostic criteria for neuromyelitis optica (Wingerchuk et al., 2006)

Optic neuritis

Acute myelitis

And at least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

10-25% of clinical cases of NMO are antibody negative

Neurology 2006;66:1485-1489

J Neurol (2008) 255:1–10
DOI 10.1007/s00415-007-0754-x

REVIEW

A. Seewann
C. Enzinger
M. Filippi
F. Barkhof
A. Rovira
A. Gass
D. Miller
X. Montalban
A. Thompson
T. Yousry
M. Tintore
N. de Stefano
J. Palace
M. Rovaris
C. Polman
F. Fazekas
for the MAGNIMS network

MRI characteristics of atypical idiopathic inflammatory demyelinating lesions of the brain

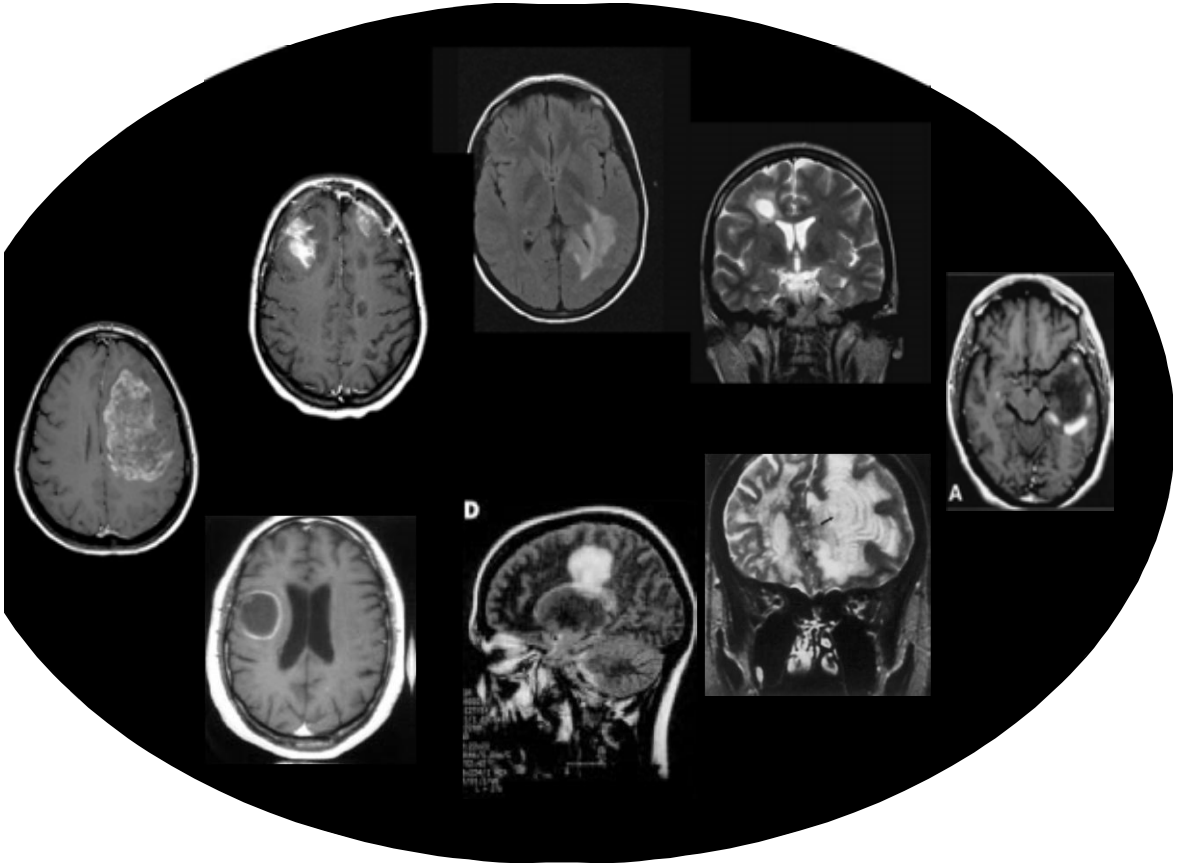
A review of reported findings

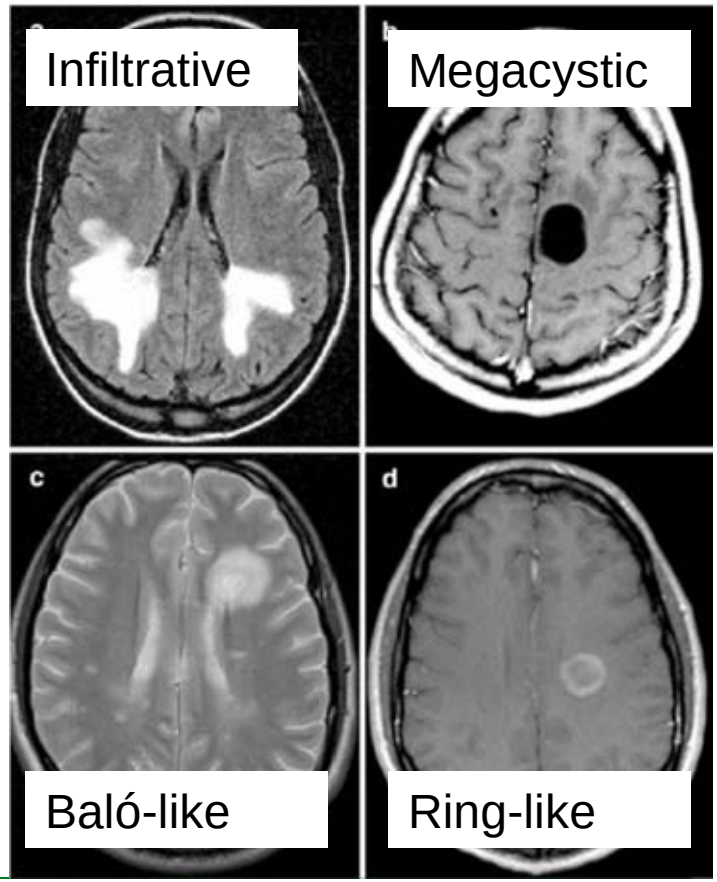
J Neurol (2013) 260:2016–2022
DOI 10.1007/s00415-013-6918-y

ORIGINAL COMMUNICATION

Atypical idiopathic inflammatory demyelinating lesions: prognostic implications and relation to multiple sclerosis

Mirja Wallner-Blazek · Alex Rovira · Massimo Fillipp · Mara A. Rocca · David H. Miller · Klaus Schmierer · Jette Frederiksen · Achim Gass · Hugo Gama · Charles P. Tilbery · Antonio J. Rocha · José Flores · Frederik Barkhof · Alexandra Seewann · Jacqueline Palace · Tarek Yousry · Xavier Montalban · Christian Enzinger · Franz Fazekas





Atypical IIDLs – concomitant MS-typical lesions

Wallner-Blazek et al, J Neurol 2013

Medical University of Graz

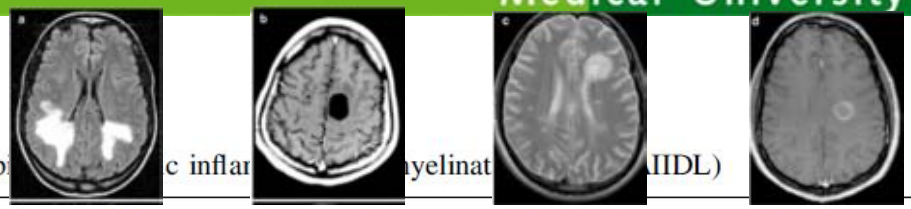


Table 3 Findings at presentation with an atyp c inflar yelinat IIDL)

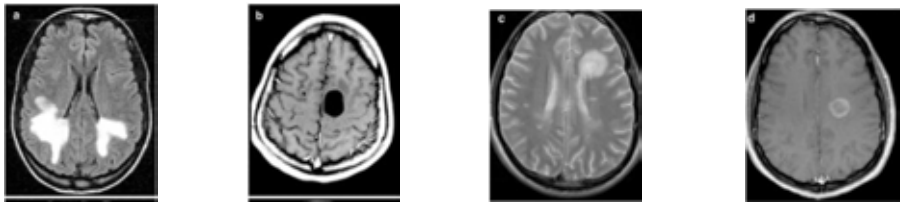
	Infiltrative ($n = 35$)	Megacystic ($n = 16$)	Baló-like ($n = 10$)	Ring-like ($n = 16$)	Other ($n = 13$)
Demographics					
Age in years, mean (range)	33.9 (18–55)	42.8 (19–64)	32.5 (19–62)	32.8 (18–51)	32.8 (26–39)
Gender (female/male)	24/11	10/6	8/2	10/6	9/4
Clinical findings					
First attack, *n* (%)	29 (82.8)	11 (68.7)	9 (90)	11 (68.7)	10 (77)
Presenting symptoms					
Optic neuritis (%)	1 (2.8)	0	0	0	0
Motor (%)	8 (22.9)	5 (31.3)	4 (40)	6 (37.5)	4 (30.8)
Sensory (%)	5 (14.3)	6 (37.5)	3 (30)	3 (18.8)	2 (15.4)
Brainstem (%)	3 (8.6)	0	0	2 (12.5)	0
Multifocal (%)	11 (31.4)	1 (6.2)	3 (30)	5 (31.2)	7 (53.8)
Other (%)	7 (20.0)	4 (25.0)	0	0	0
MRI findings					
1 AIIDL (with first attack)	31 (27)	12 (8)	7 (6)	12 (8)	10 (9)
≥2 AIIDLs (with first attack)	4 (2)	4 (3)	3 (3)	4 (3)	3 (1)
Presence of MS-typical lesions, all (%)	15 (42.9)	8 (50)	6 (60)	11 (68.7)	8 (61.5)
Patients with first attack (%)	10/29 (34.5)	3/11 (27.3)	5/9 (55.6)	7/11 (63.6)	6/10 (60.0)
Patients with previous attacks (%)	5/6 (83.3)	5/5 (100)	1/1 (100)	4/5 (80.0)	2/3 (66.7)

Atypical IIDLs – Follow-up

Medical University of Graz

Table 4 Follow-up of patients with atypical idiopathic inflammatory demyelinating lesions (AIIDLs)

	AIIDL subtypes				
	Infiltrative ($n = 34$)	Megacystic ($n = 13$)	Baló-like ($n = 6$)	Ring-like ($n = 13$)	Other ($n = 11$)
Duration of follow-up in years, mean ± SD	4.2 ± 2.7	4.8 ± 3.0	1.8 ± 1.6	3.0 ± 1.8	4.8 ± 3.0
Clinical					
No further attack, patient number (%)	22 (64.7)	10 (76.9)	4 (66.7)	5 (38.5)	8 (72.7)
1 attack, patient number (%)	5 (14.7)	2 (15.4)	2 (33.3)	5 (38.5)	0 (0)
≥2 attacks, patient number (%)	7 (20.6)	1 (7.69)	0	3 (23.0)	3 (27.3)
EDSS at last follow-up, mean (range)	2.5 (0–7)	2 (1–4)	1.5 (0–2)	3.5 (0–6.5)	2.0 (0–6)
MRI					
New AIIDLs (same/other type)	1/0	0/1	0	1/2	0/1
New MS-typical lesions (yes/no)	10/18	2/9	1/5	9/4	7/4

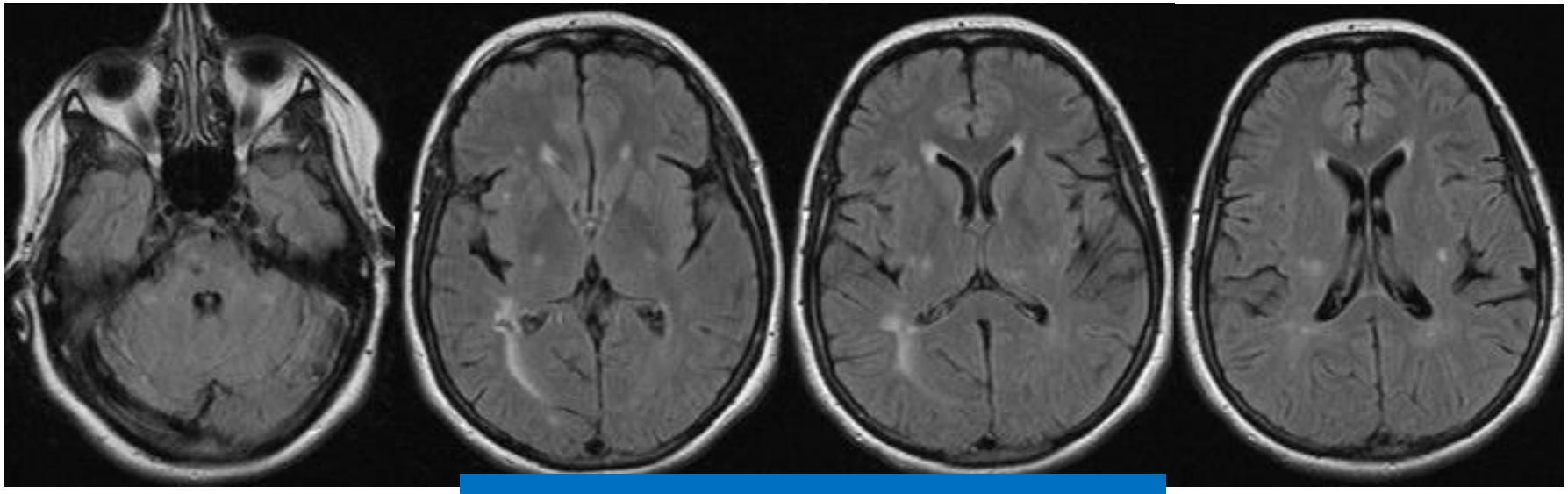


Wallner-Blazek et al, J Neurol 2013 Aug;260(8):2016-22

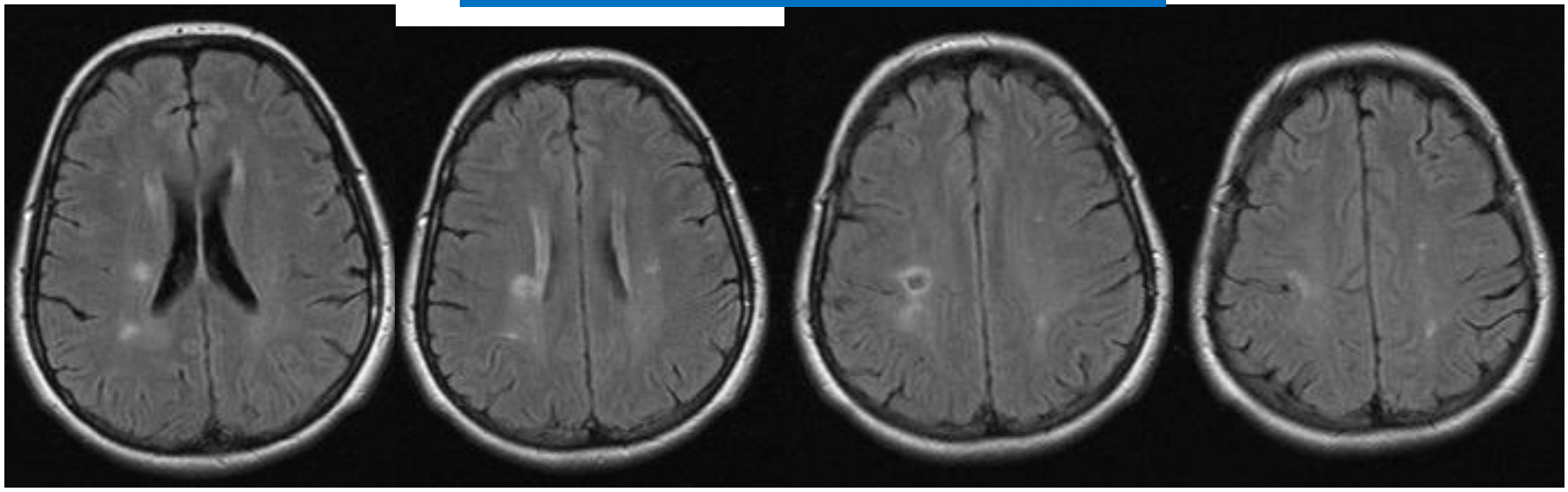
AGENDA - The role of MRI in the…

Medical University of Graz

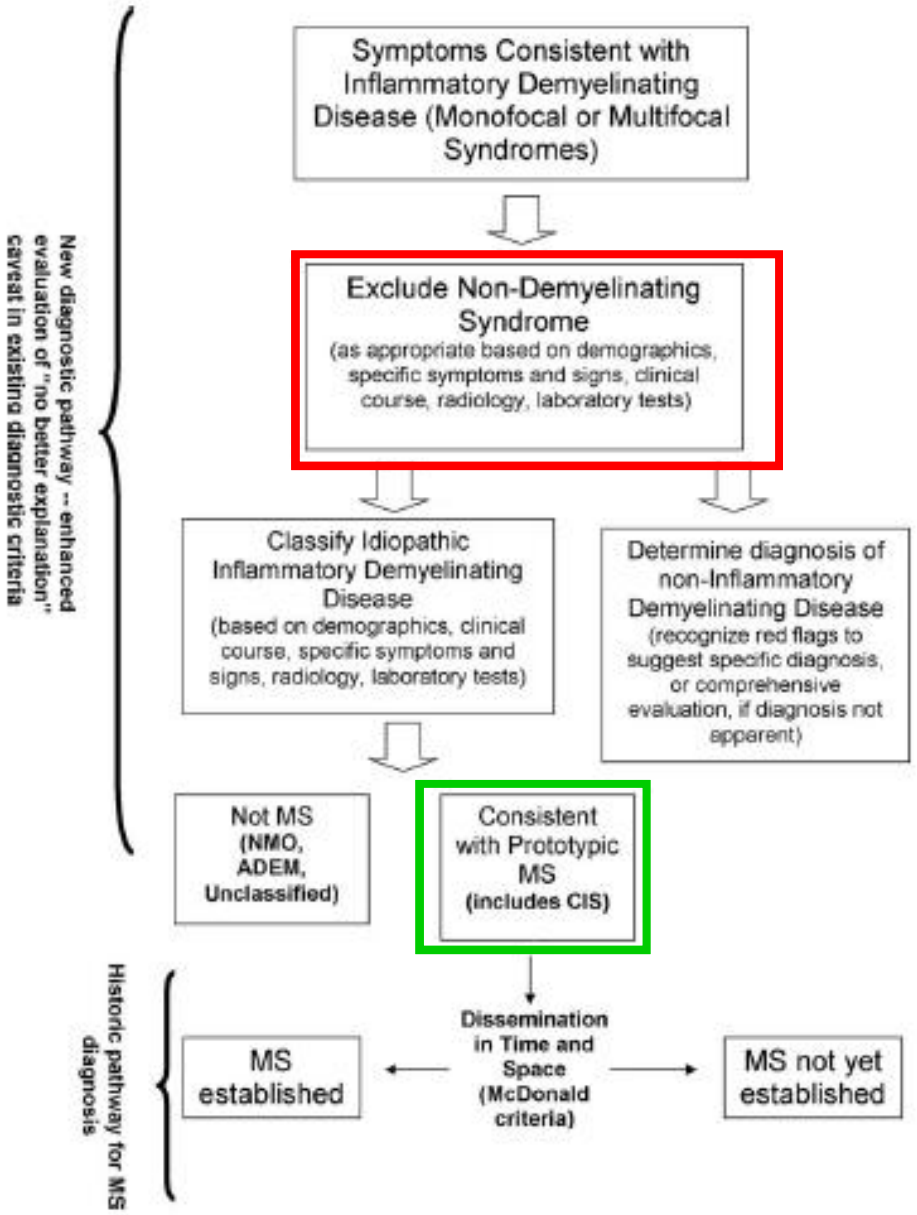
- Dx of MS
- Dx of allied disorders
- Differential Dx



Multiple Sclerosis ?



Steps in MS differential diagnosis



Miller DH et al., Multiple Sclerosis 2008;14:1157-1174

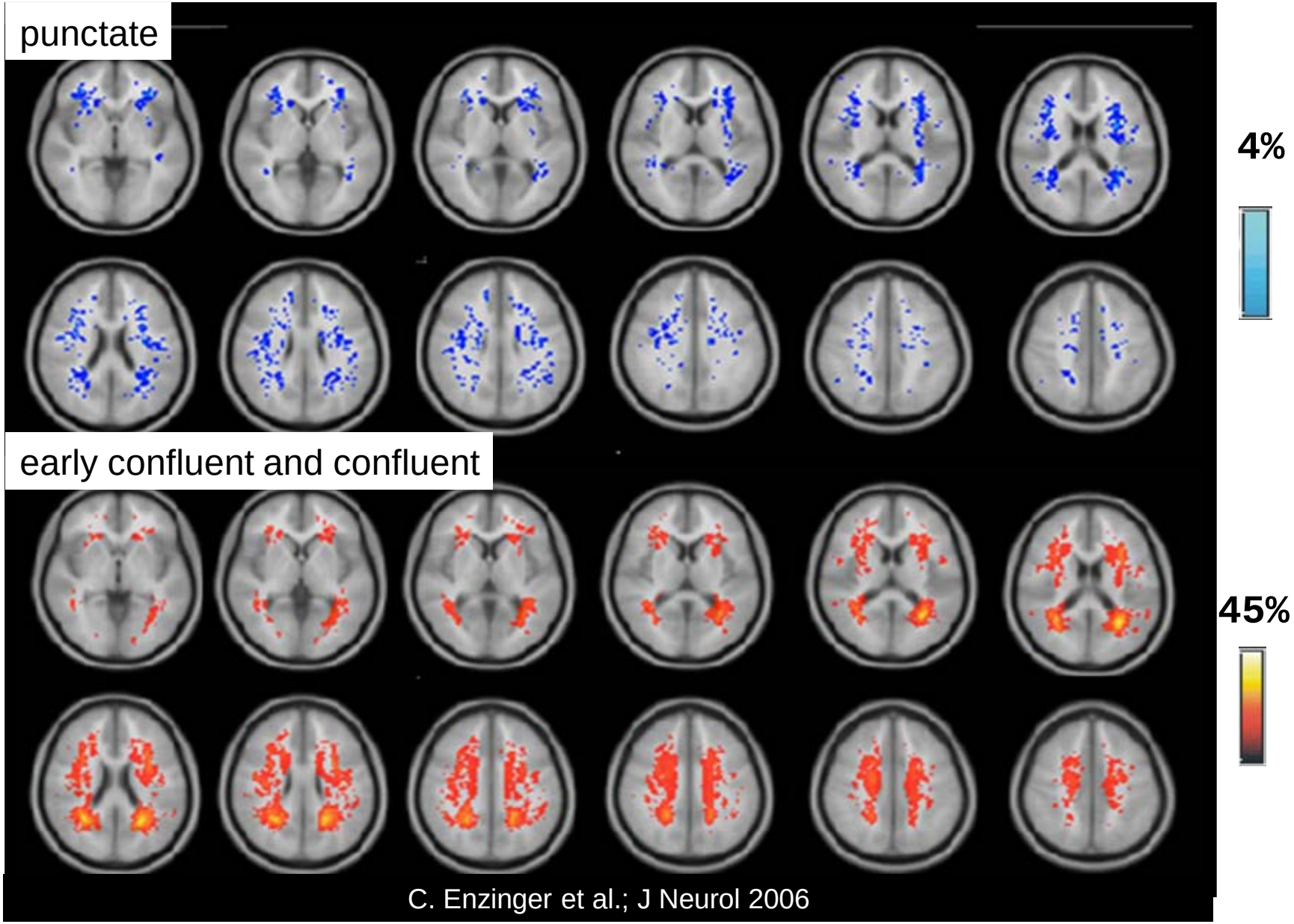
- Exclude non-demyelinating diseases
  - Clinical symptoms, signs and course
  - Radiology – MRI
  - Laboratory tests

MS like MRI findings / disorder of non idiopathic inflammatory demyelinating etiology

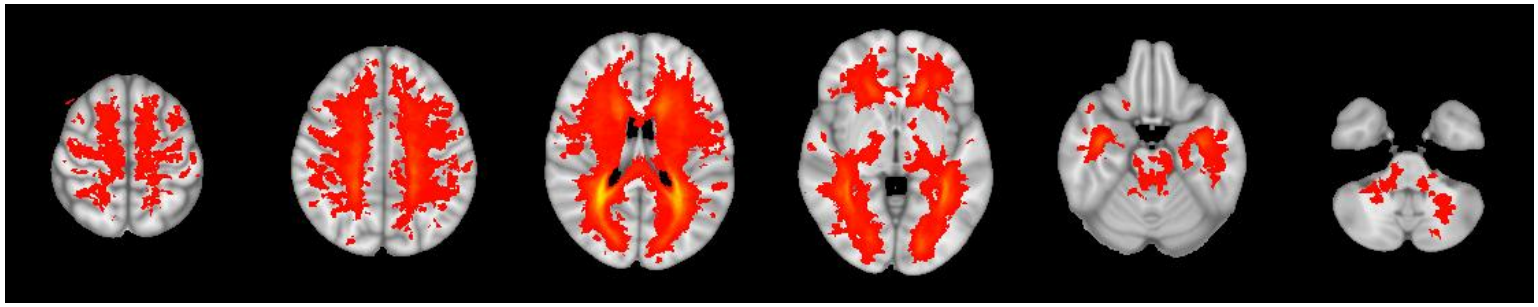
- Age-related white matter changes
- Behcet disease
- Bacterial infections (syphilis, Lyme disease)
- Cerebral autosomal dominant arteriopathy, subcortical infarcts and leukoencephalopathy
- Cervical spondylosis or stenosis
- HIV infection
- Human T-lymphotrophic virus I/II
- Ischemic optic neuropathy (arteriitic and nonarteriitic)
- Leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
- Neoplasms (e.g., lymphoma, glioma, meningioma)
- Migraine
- Sarcoidosis
- Sjögren syndrome
- Stroke and ischemic cerebrovascular disease
- Systemic lupus erythematosus, antiphospholipid antibody syndromes and related collagen / vascular disorders
- Unidentified bright objects
- Vascular malformations
- Vasculitis (primary CNS or other)
- Vitamin B 12 deficiency

Frohman EM et al., Neurology 2004

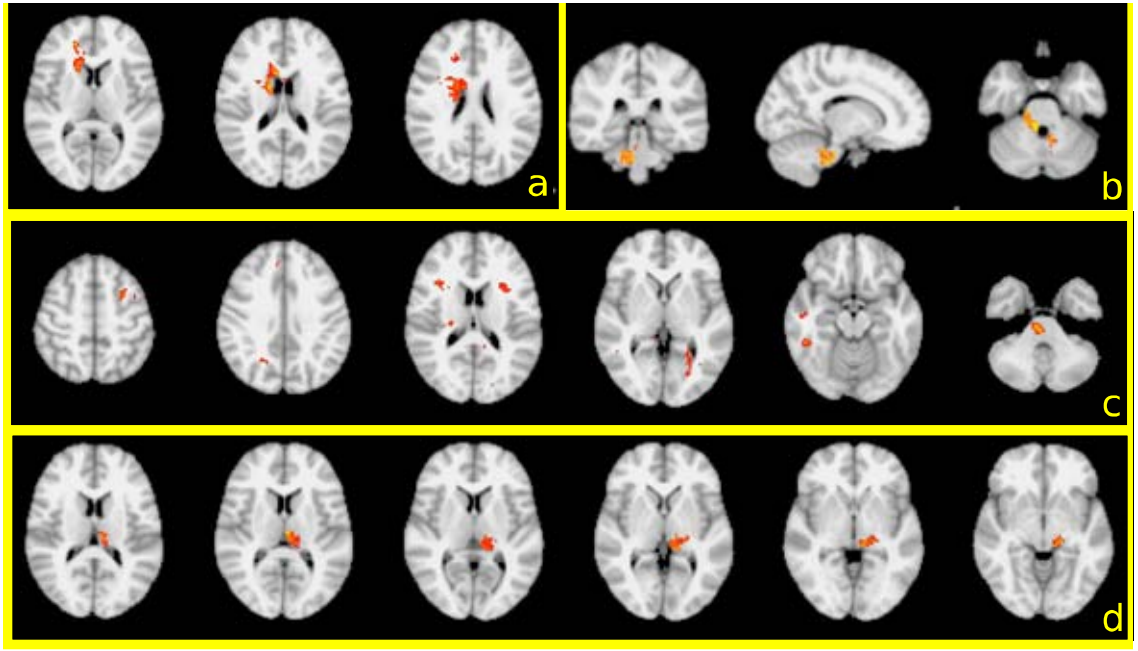
Age related white matter hyperintensities (WMH)



Spatial distribution of cerebral MS lesions



Lesion probability map in 121 MS patients. At each voxel the number of subject who had a lesion at that particular location is represented.



Lesion probability correlating with EDSS subscores.

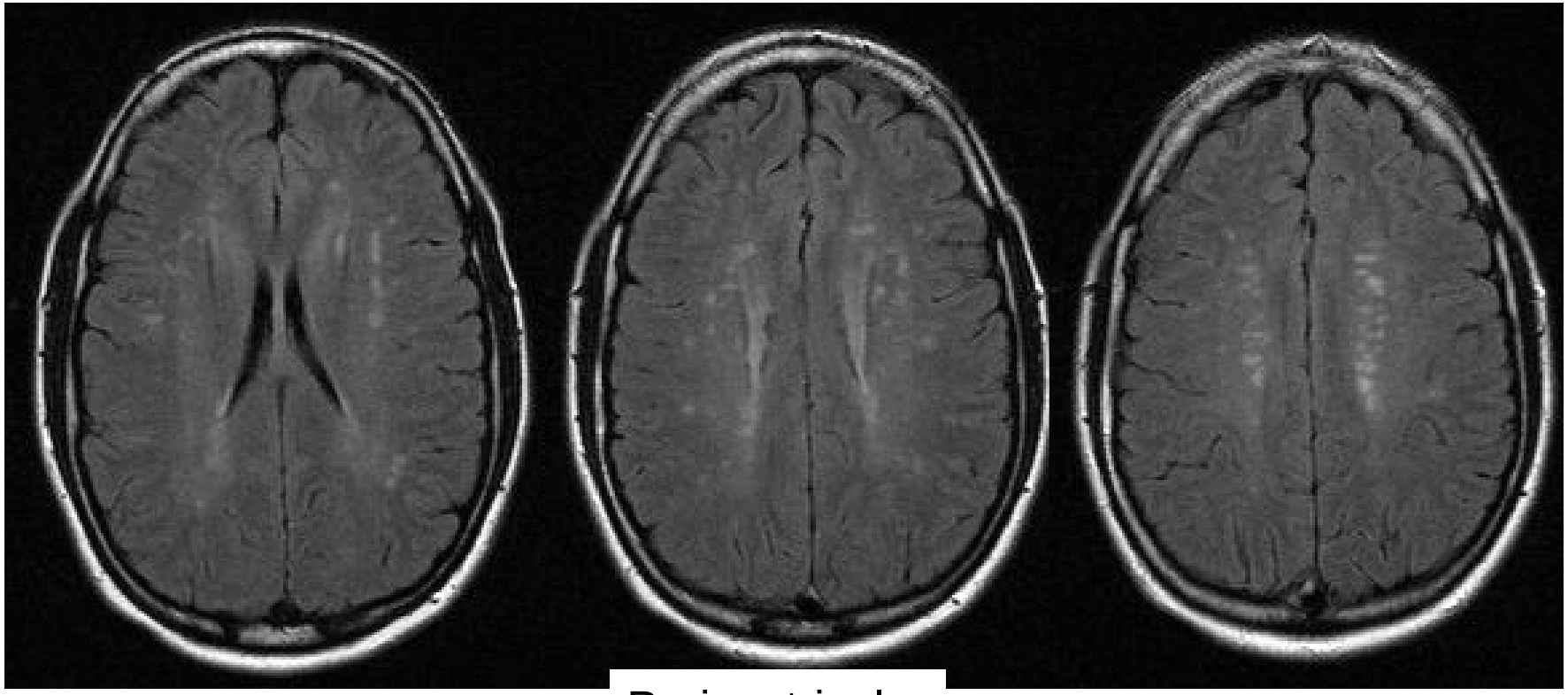
a - brainstem symptoms,

b – coordination,

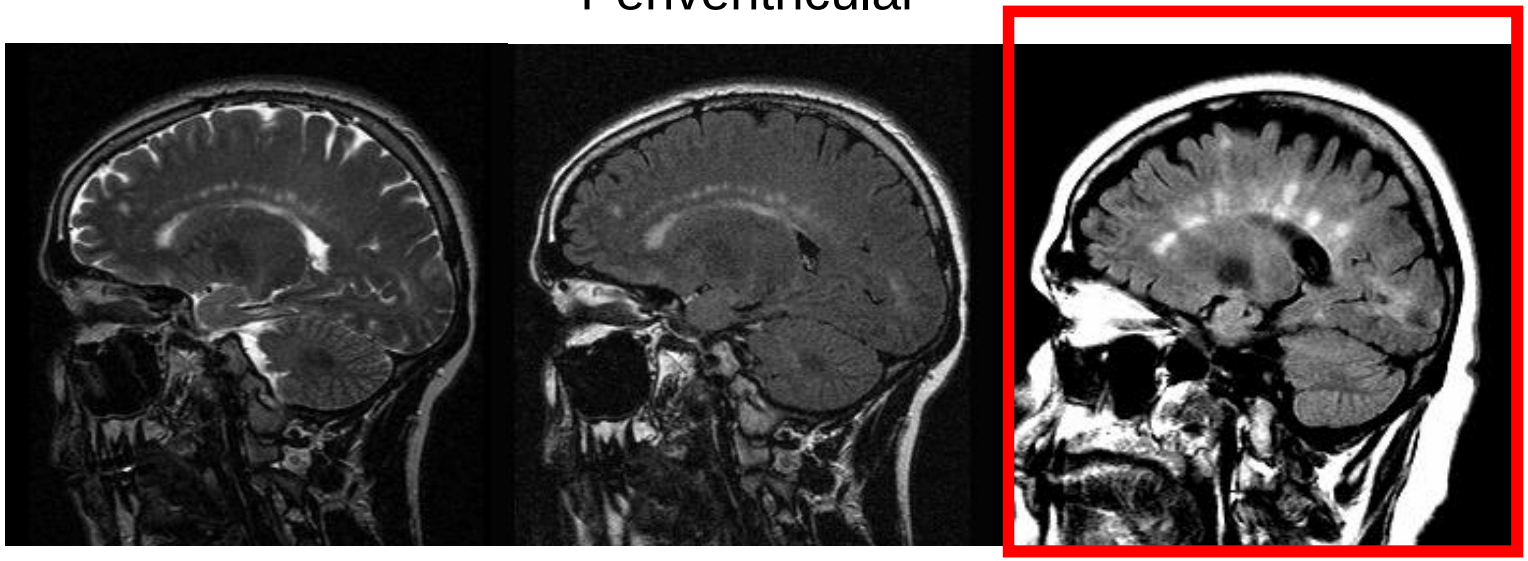
c – mental function,

d – sensory functions.

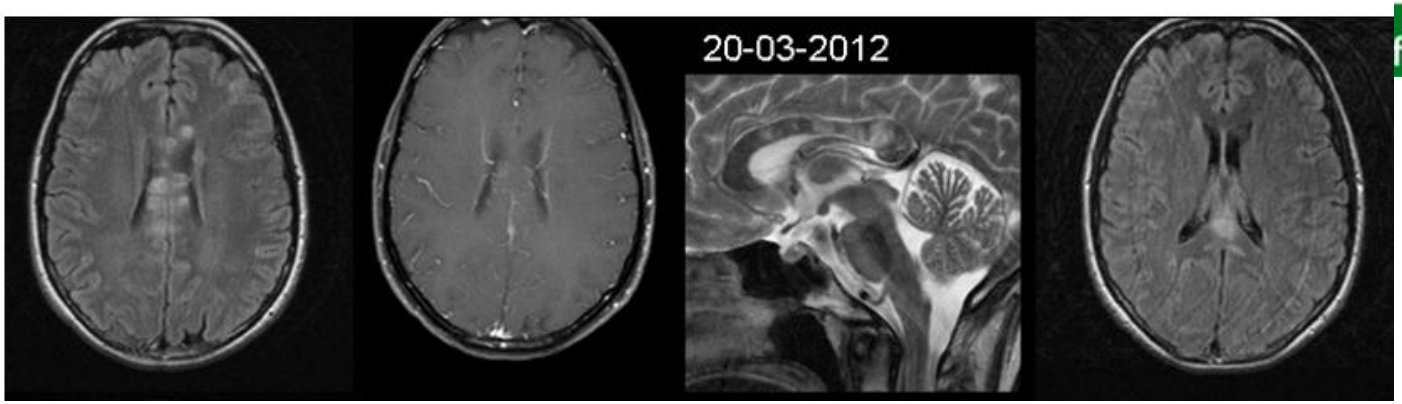
T. Kincses et al.; MSJ 2011



Periventricular

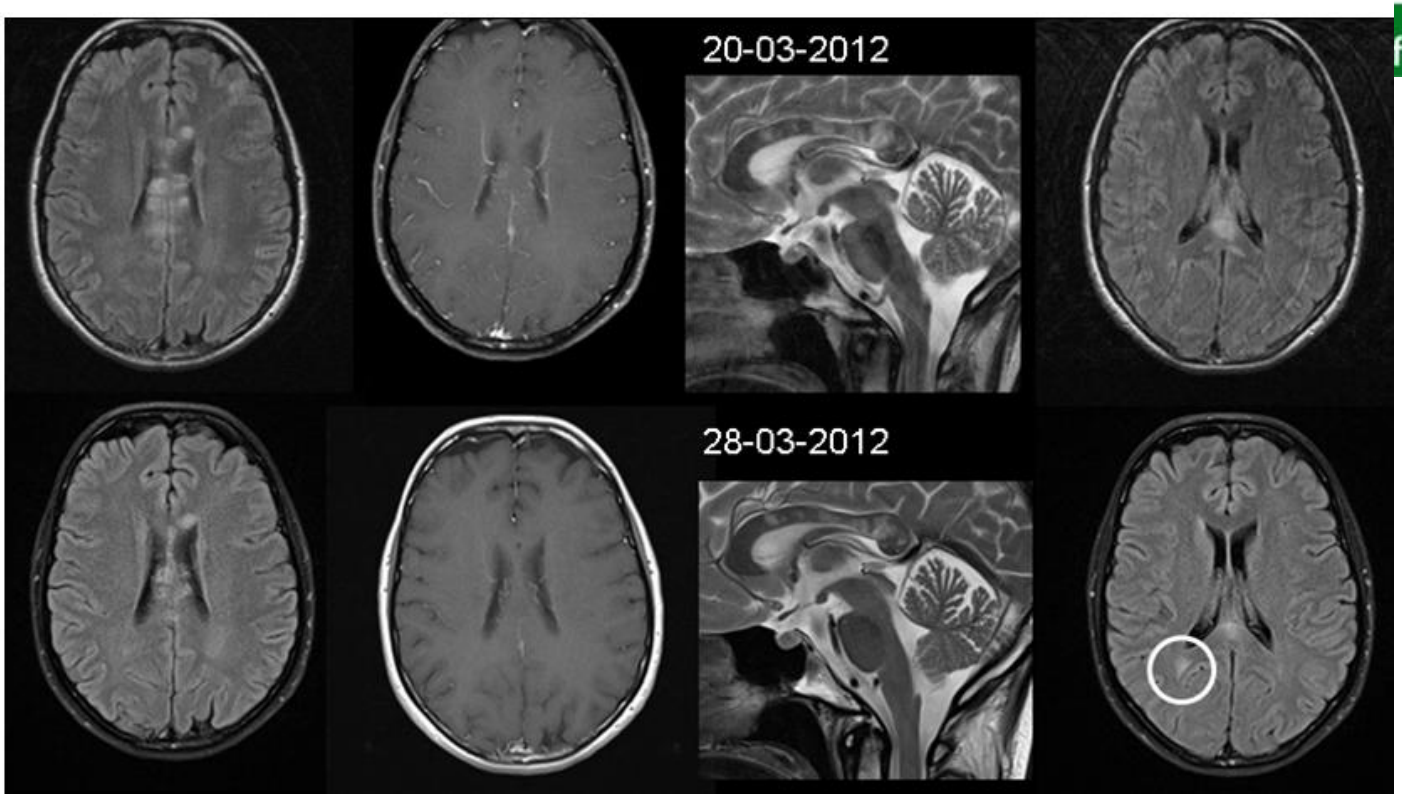


Mistaking other conditions as „active MS“ – atypical location of lesions

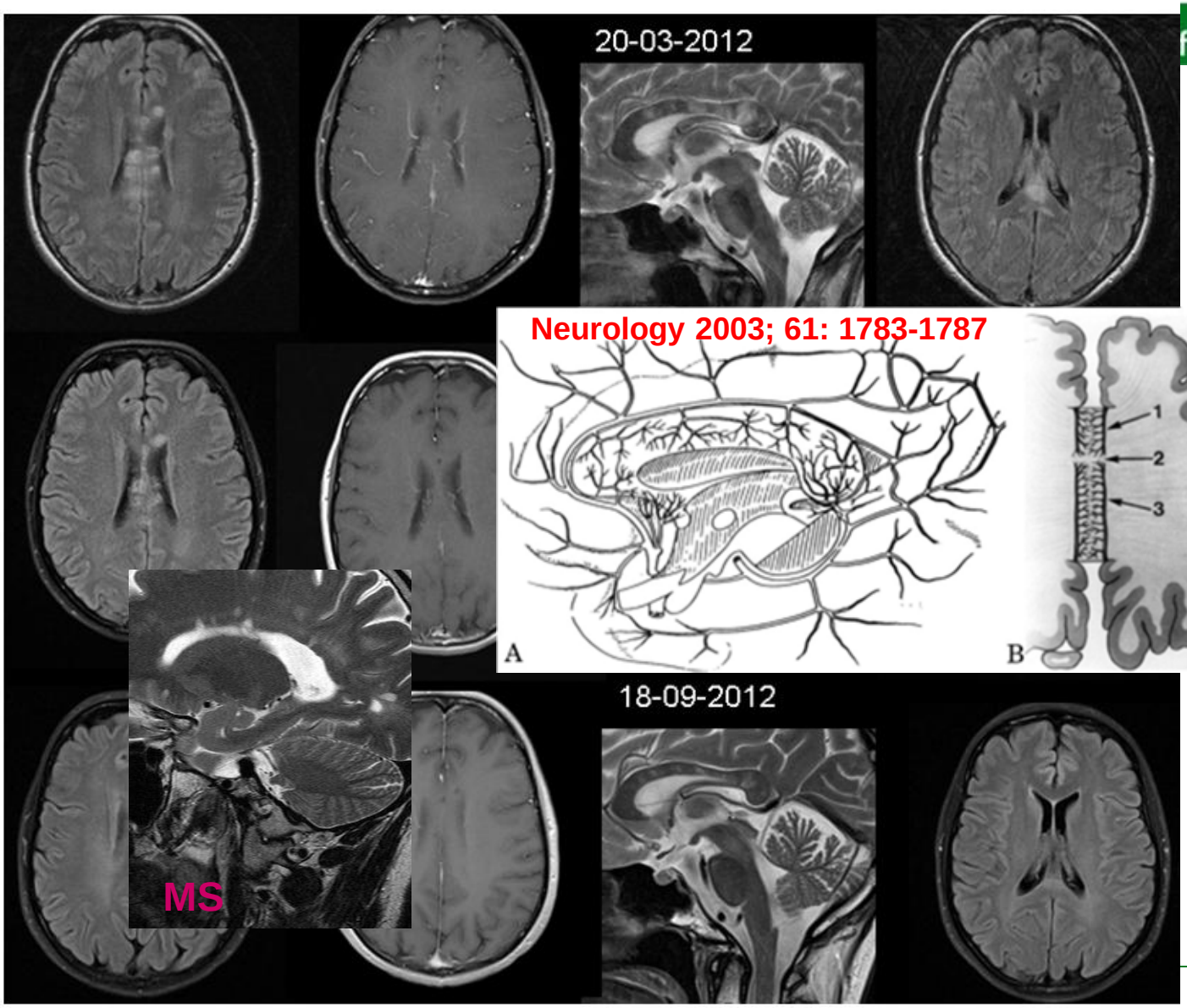


45, f, disturbed vision left eye, vertigo, paraesthesia lt arm

Mistaking other conditions as „active MS“ – atypical location of lesions



Mistaking other conditions as „active MS“ – SUSAC Syndrome



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journal homepage: www.elsevier.con

A brief review of Susac syndrome

I. Kleffner [a,*], T. Duning [a], H. Lohmann [a], M. Deppe [a], T. Basel [b], J. I
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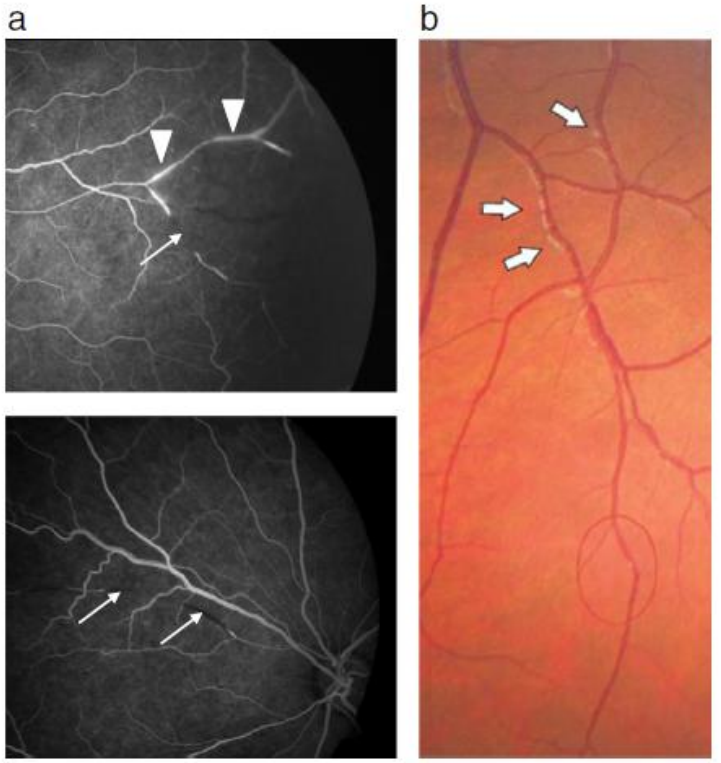

Fig. 4. a) Fluorescein angiographies with an occlusion of retinal vessels (arrows), hyperfluorescence of the vessel wall, and leakage of the vessel wall (arrowheads). b) Gass plaques (arrows).

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ABSTRACT

Susac syndrome was named after J.O. Susac who first described the syndrome in 1979. It is characterized by the clinical triad of encephalopathy, branch retinal artery occlusion, and sensorineural hearing loss. It mainly occurs in young women. This underdiagnosed disease needs to be considered in the differential diagnosis of a broad variety of disorders. In Susac syndrome, autoimmune processes leading to damage and inflammation-related occlusion of the microvessels in brain, retina, and inner ear are thought to play a causal role. The diagnosis is based primarily on the clinical presentation, the documentation of branch retinal artery occlusion by fluorescence angiography, and characteristic findings on cerebral MRI, that help in distinguishing Susac syndrome from other inflammatory entities, like multiple sclerosis. Antiendothelial cell antibodies could be detected in some patients. Patients are successfully treated with immunosuppression, however, the best regimen still needs to be defined. As a result of the rarity of the disease, controlled therapeutic trials are missing so far. In this review, we want to demonstrate the clinical features, natural history, treatment, and clinical course of Susac syndrome, illustrated by a typical case history.

Review

MRI and the diagnosis of multiple sclerosis: expanding the concept of "no better explanation"

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Although the diagnosis of multiple sclerosis relies on the demonstration of disease dissemination in space and time, the exclusion of other neurological disorders is also essential. The limited specificity of abnormalities disclosed by MRI may increase the likelihood of diagnosis of multiple sclerosis in patients affected by other disorders. The available criteria for diagnosis of multiple sclerosis have not taken advantage of the potential of MRI to detect features "not suggestive" of multiple sclerosis. Recognition of such features in the work-up of patients suspected of having multiple sclerosis may reduce the likelihood of a false positive diagnosis of the disorder in some, while suggesting the correct alternative diagnosis in other patients. On the basis of this, a workshop of the European MAGNIMS (Magnetic Resonance Network in Multiple Sclerosis) was held to define a series of MRI red flags in the setting of clinically suspected multiple sclerosis that is derived from evidence-based findings and educated guesses. The presence of such red flags should alert clinicians to reconsider the differential diagnosis more extensively. In this review we will report on the conclusions of this international consensus, which should represent a first step beyond the concept of "no better explanation", and inform future diagnostic criteria for multiple sclerosis.

Lancet Neurol 2006; 5: 841–52

See Reflection and Reaction page 808

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Red Flags (Brain)

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- No MS typical location of at least a few lesions
- No T1 hypointensity of larger lesions
- Complete tissue destruction (lacunar state)
- Cortical enhancement
- Microbleeds
- Specific lesion patterns, e.g. lesions predominantly in watershed area
- …..

Red Flags (Spinal cord)

- Longitudinally extensive signal changes
- Complete parenchymal destruction
- Significant mass effect
- Evidence for bleeding / hemosiderin deposits
- Concomitant subarachnoid / epidural changes
- …..

Which patient suffers from MS ?

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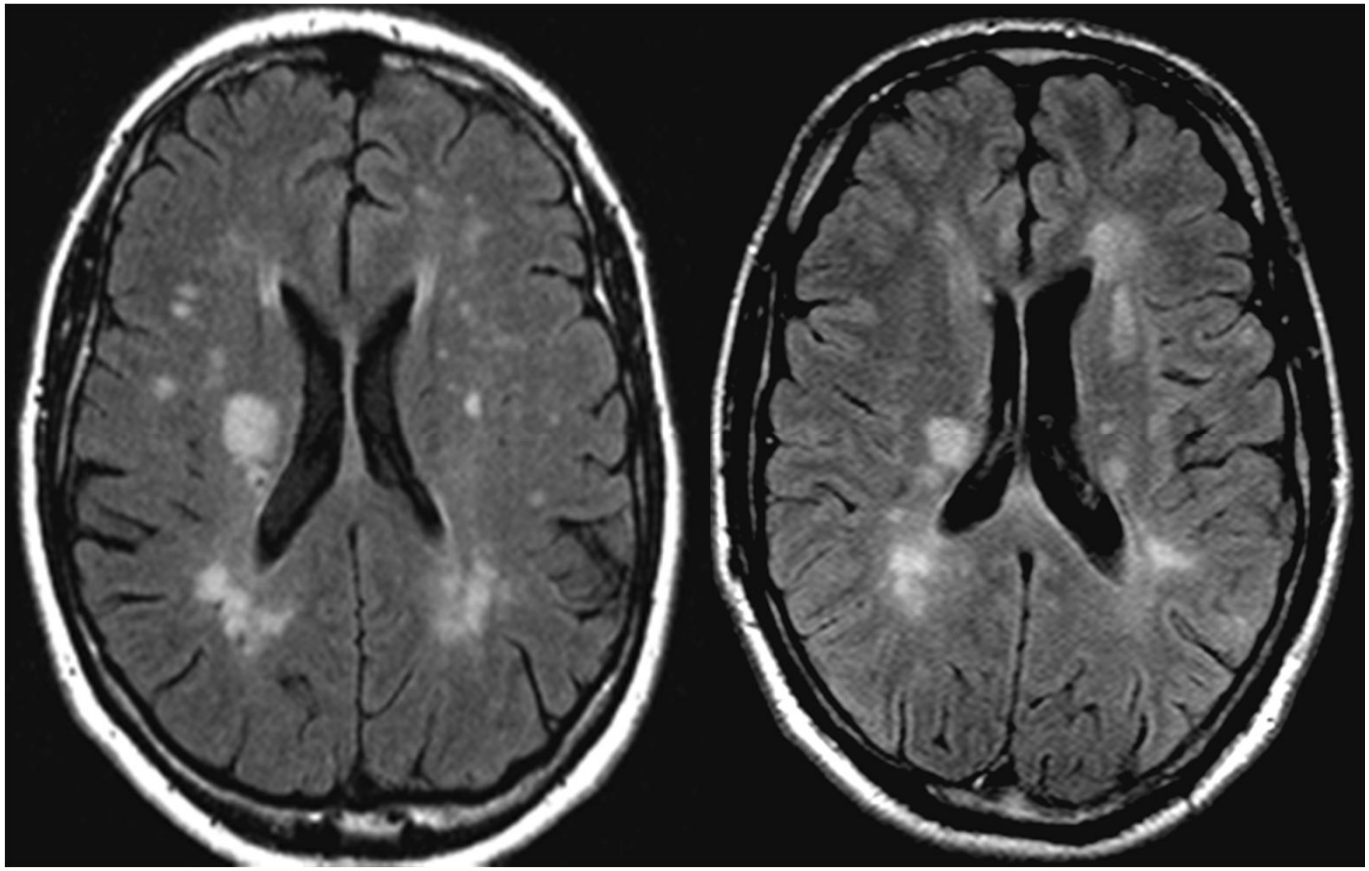
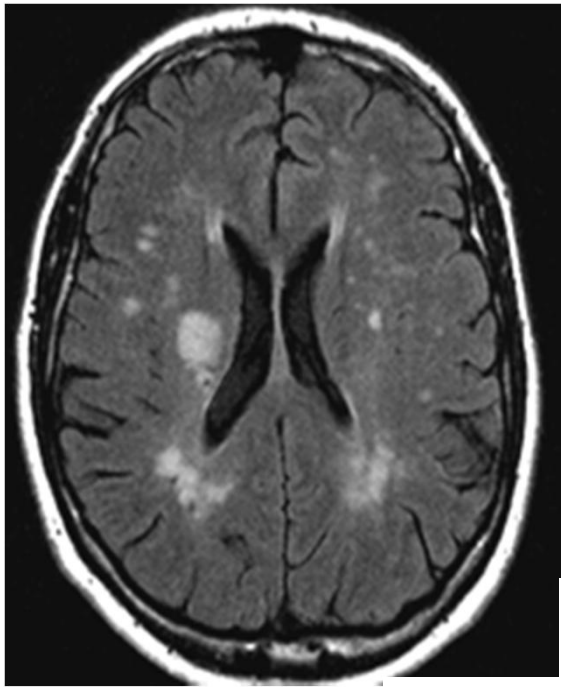
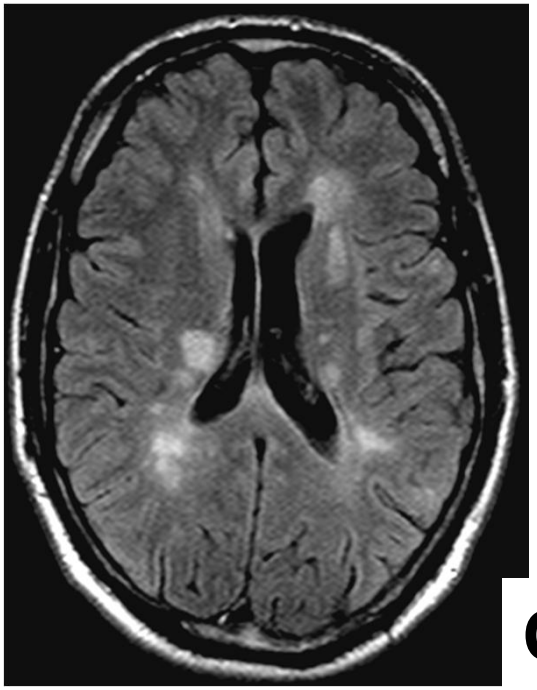
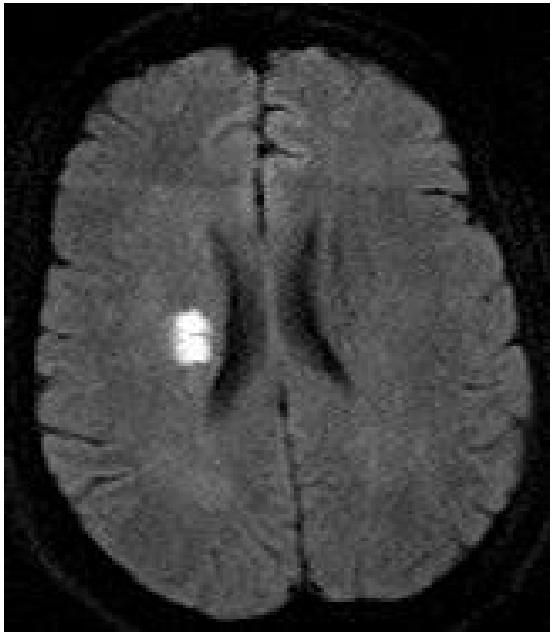


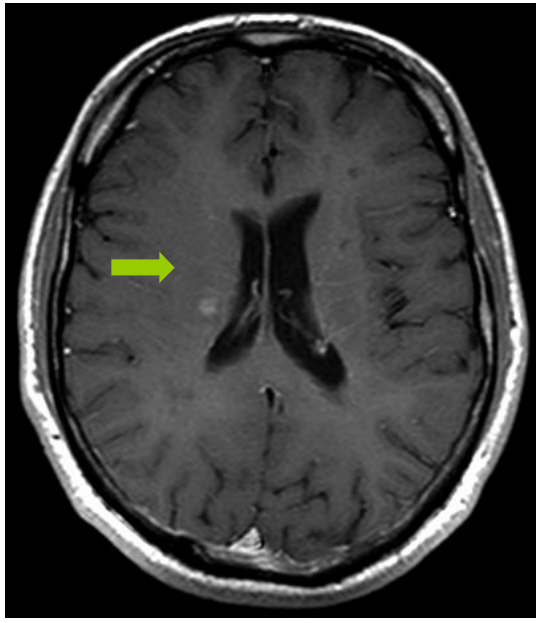


DWI

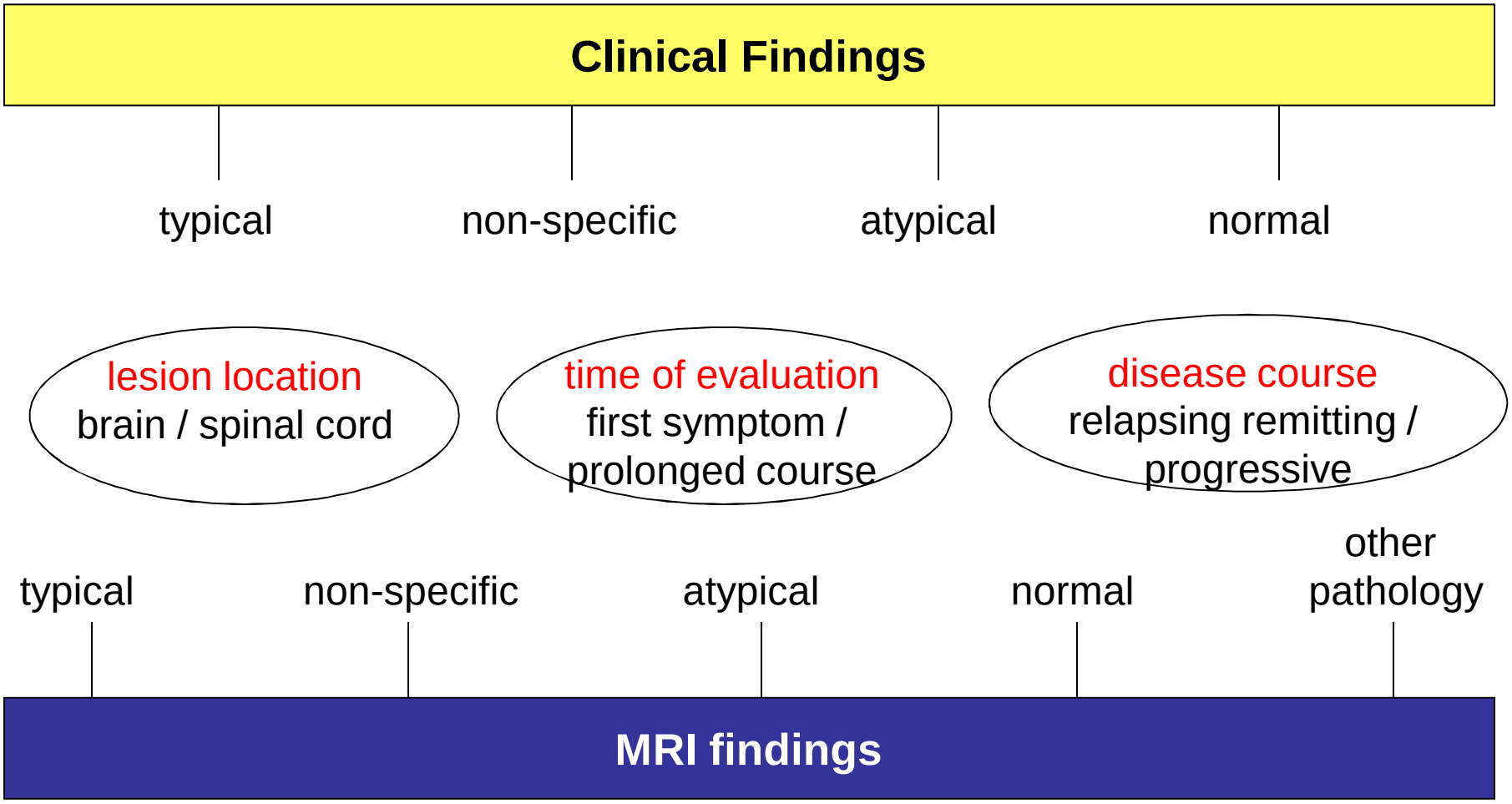


Gd-T1





Diagnosing MS



Other diagnostic aids – CSF, VEP, laboratory

Follow-up

Relevance for **monitoring (and selection of) treatment**

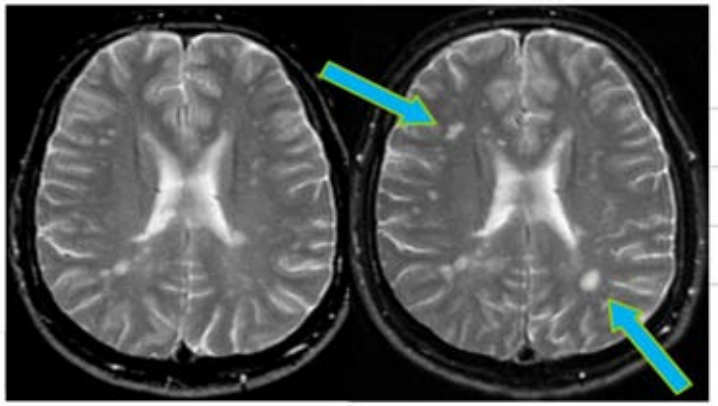


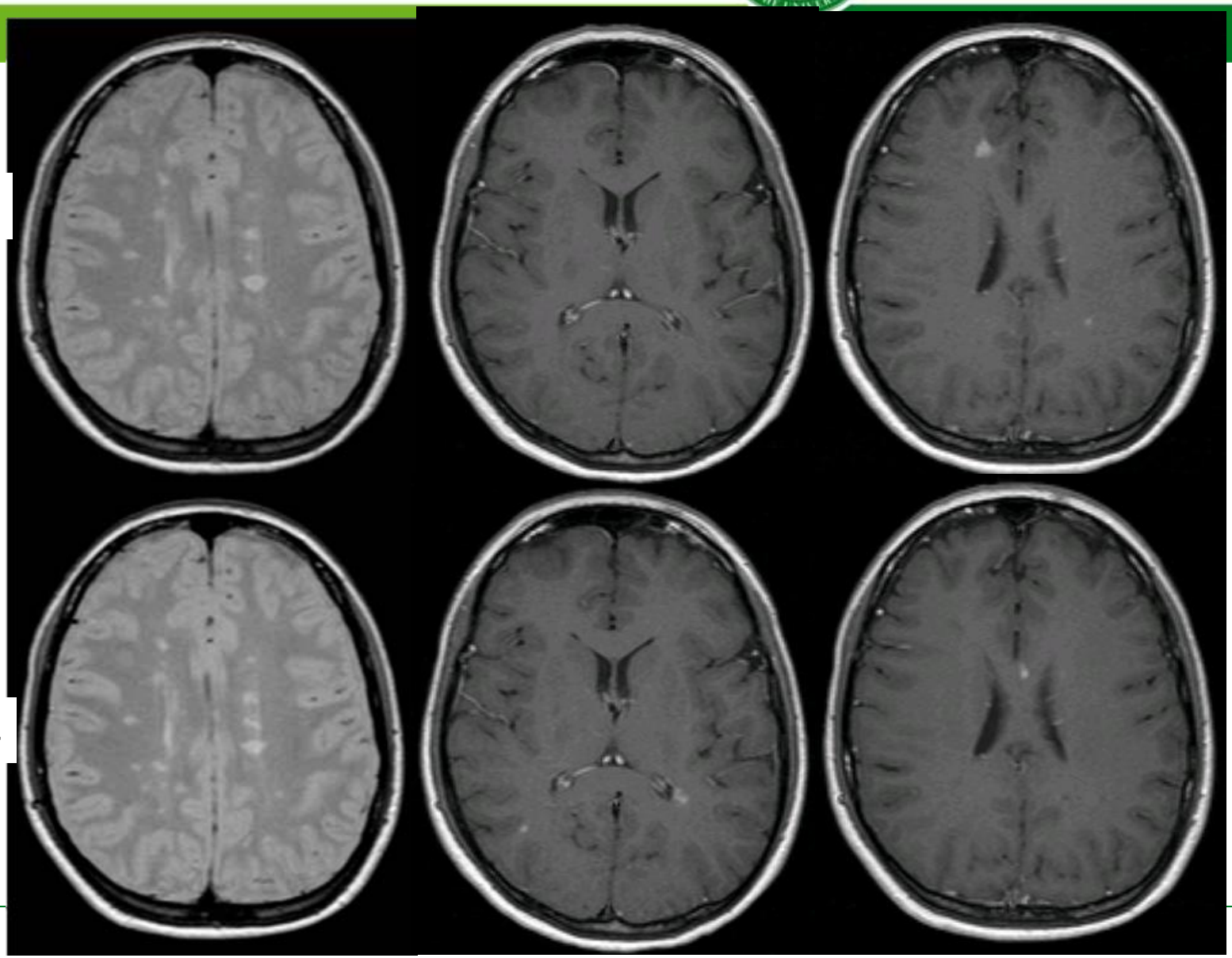
Table 1. MRI Variables with Proven Utility for Monitoring Treatment Effects in MS

MRI Variable	Pathophysiologic Information Provided	MS Phase/Type to be Used in	Utility for Clinical Practice
Gadolinium-enhancing lesions	Acute area of focal inflammation	CIS, RRMS, SPMS, PPMS?	Yes
New T2 lesions	New area of tissue damage	CIS, RRMS, SPMS, PPMS?	Yes
Enlarging T2 lesions	Enlarging area of tissue damage	RRMS, SPMS	No
T1 lesions (*black holes*)	Lesion with marked tissue damage	RRMS, SPMS	?
T2 lesion load	Total area of clearly abnormal brain tissue	CIS, RRMS, SPMS?	No
T1 lesion load	Total area of marked tissue destruction	RRMS, SPMS?	No
Brain atrophy/volume measures	Changes in brain volume due to several factors	CIS, RRMS, SPMS, PPMS	No

Abbreviations: CIS = clinically isolated syndromes, RRMS = relapsing–remitting MS, SPMS = secondary progressive MS, PPMS = primary progressive MS.

Fazekas F et al., J Neuroimaging 2007

Clinical practice



Serial MRI: identical protocol and repositioning are essential

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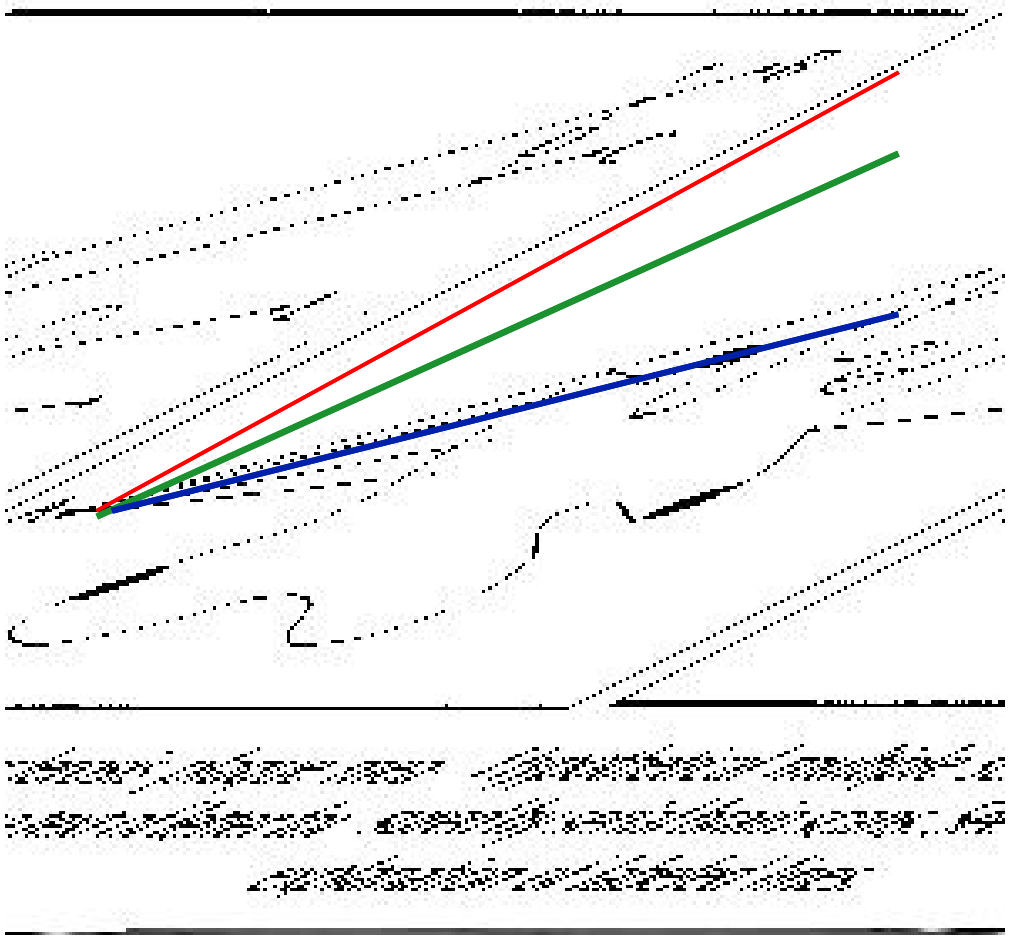

- The shaded portions represent discrete areas of enhancement at the lesion border, and the lines represent possible MRI scan sections originating from different angulations.
- D indicates the displacement resulting from the repositioning error in a follow-up scan.
- Thus, the following results would 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)

Conclusions & recommendations: MRI in the diagnosis of MS

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- The McDonald 2011 criteria allow for a faster and „easier“ diagnosis of MS than preceeding criteria
- It is recommended to obtain Gadolinium enhanced scans at least at the first evaluation of a patient with suspected MS in order to use
  - the full potential of MRI for an early definite diagnosis
  - to exclude other disorders
- Exactly comparable image acquisition (same field strength, scanning parameters, angulation) at follow-up is of paramount importance to rely on a new T2 lesion as evidence for DIT
- Additional CSF examination is recommended at first evaluation for diagnostic and prognostic purposes

Reference slide

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Mistaking other conditions as „active MS“ – atypical lesions

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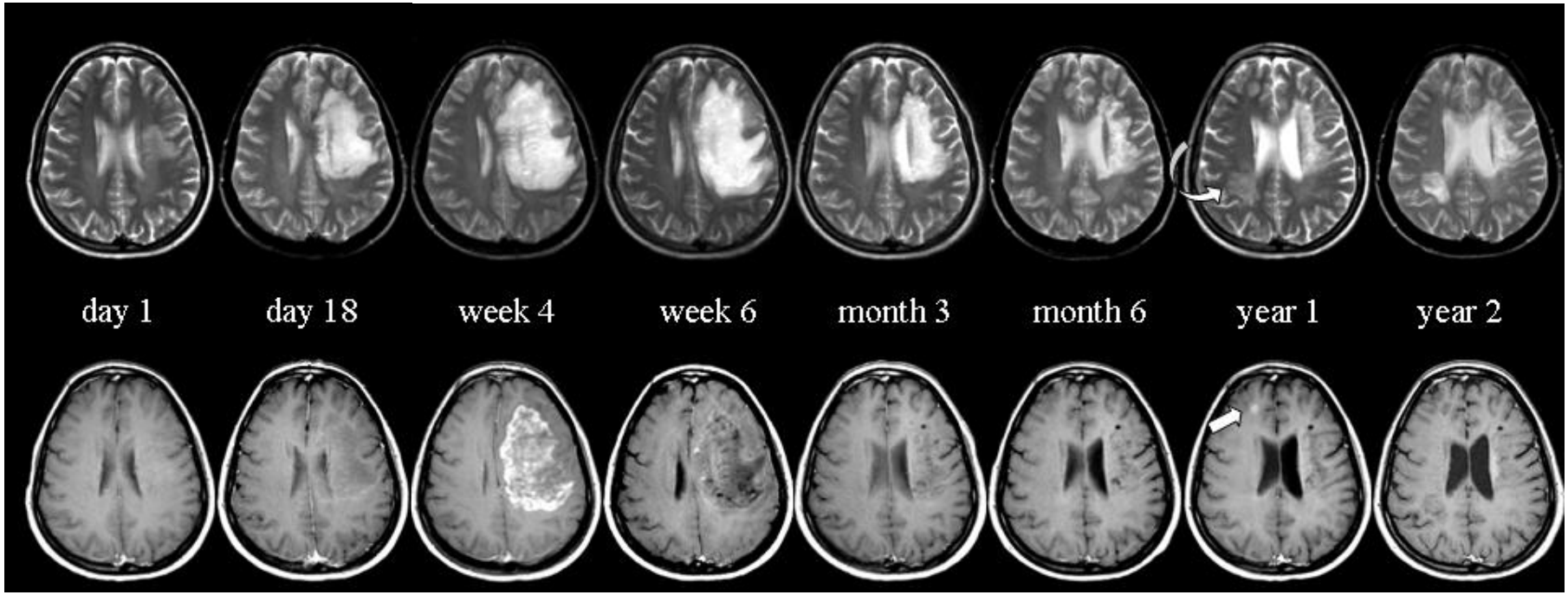
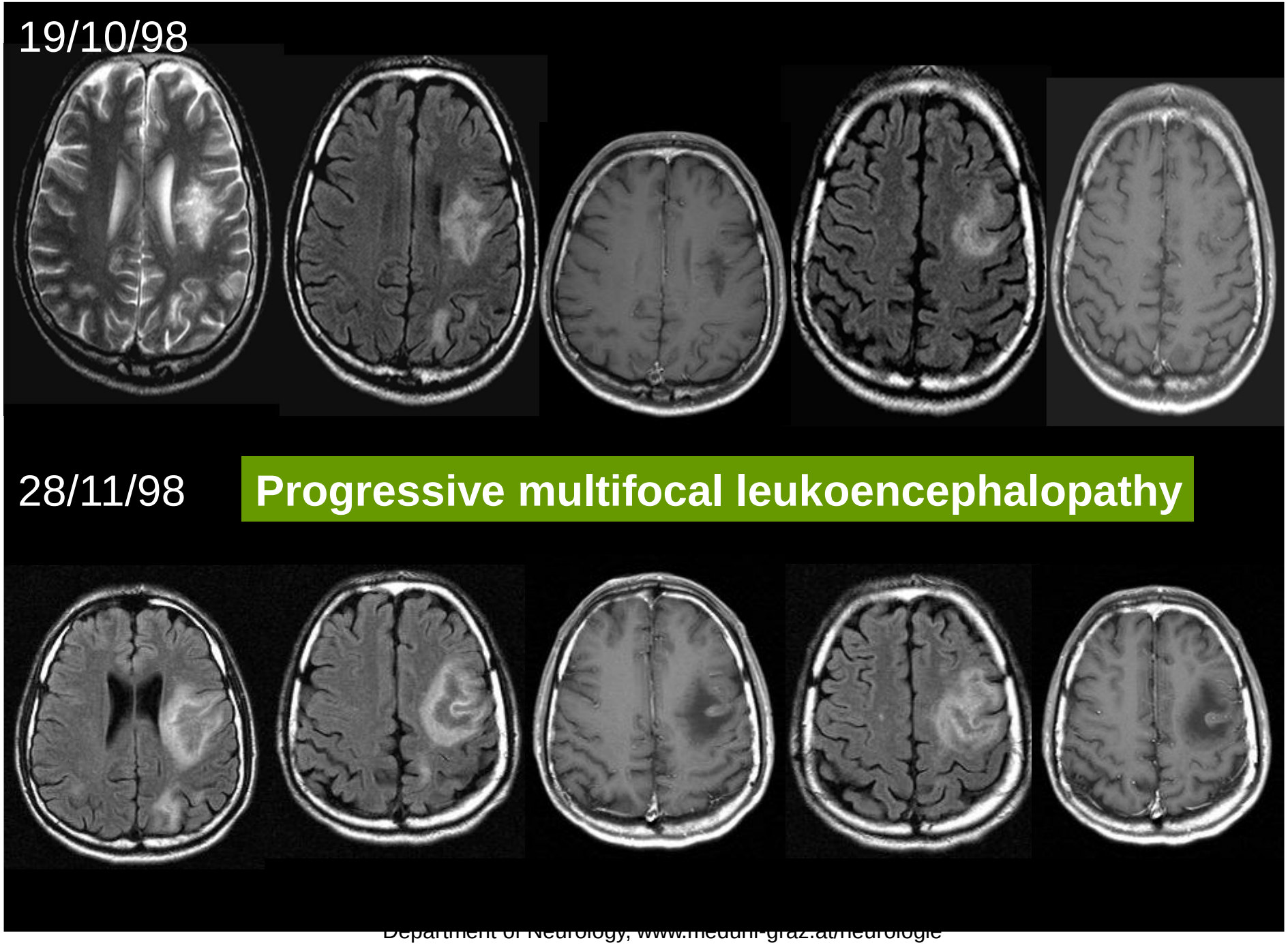


Atypical idiopathic inflammatory demyelinating lesions of the brain:

from 69 reported cases 1984-2004: 27 large ring-like lesions, 11 Balolike and 11 diffusely infiltrating, 8 megacystic

Enzinger C, et al. Mult Scler. 2005; Seewann et al. J Neurol. 2008


19/10/98
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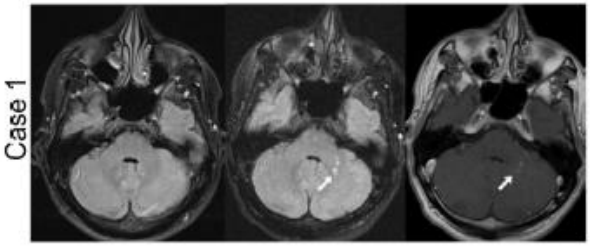
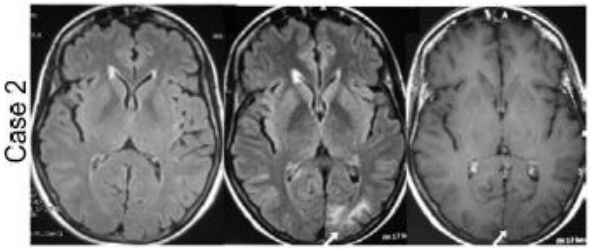
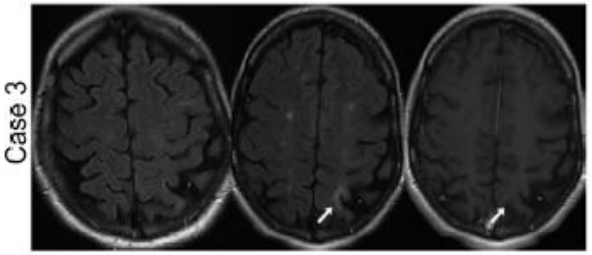
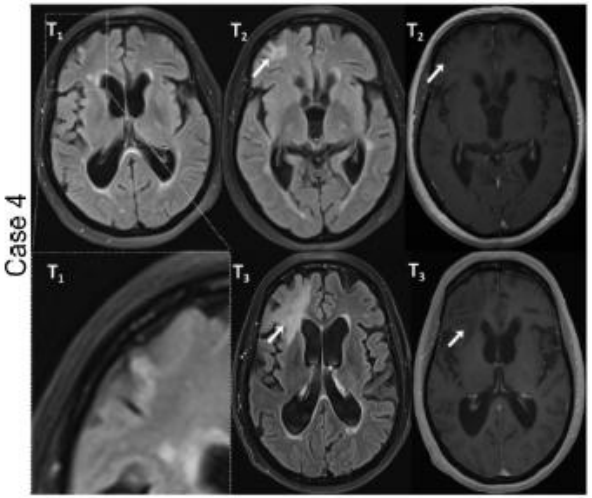
Progressive multifocal leukoencephalopathy

Table 1. Features Visualized on Magnetic Resonance Imaging to Be Considered in the Differential Diagnosis of Multiple Sclerosis and Progressive Multifocal Leukoencephalopathy.*

Feature	Multiple Sclerosis	Progressive Multifocal Leukoencephalopathy
Location of new lesions	Mostly focal; may affect entire brain and spinal cord, in white and possibly gray matter; posterior cranial fossa lesions are rarely seen	Diffuse lesions, mainly subcortical and rarely periventricular, located almost exc[illegible]h occasional extension t[illegible] posterior fossa frequently involved (cerebellum)
Borders	Sharp edges; mostly round or finger-like in shape (especially periventricular lesions), confluent with other lesions; U-fibers may be involved	Ill-defined edges; infiltrating; irregular in shape; confined to white matter, sparing gray matter; pushing against the cerebral cortex; U-fibers destroyed
Mode of extension	Initially focal, lesions enlarge within days or weeks and later decrease in size within months	Lesions are diffuse and asymmetric, extending homogeneously; no confluence with other lesions; confined to white-matter tracks, sparing the cortex; continuous progression
Mass effect	Acute lesions show some mass effect	No mass effect even in large lesions (but lesion slightly abuts cerebral cortex)
On T_2-weighted sequence	Acute lesions: hyperintense center, isointense ring, discrete hyperintensity outside the ring structure Subacute and chronic lesions: hyperintense, with no ring structure	Diffuse hyperintensity, slightly increased intensity of newly involved areas compared with old areas, little irregular signal intensity of lesions
On T_1-weighted sequence	Acute lesions: densely hypointense (large lesions) or isointense (small lesions); increasing signal intensity over time in 80 percent; decreasing signal intensity (axonal loss) in about 20 percent	Slightly hypointense at onset, with signal intensity decreasing over time and along the affected area; no reversion of signal intensity
On FLAIR sequence	Hyperintense, sharply delineated	Hyperintensity more obvious, true extension of abnormality more clearly visible than in T_2-weighted images
With enhancement	Acute lesions: dense homogeneous enhancement, sharp edges Subacute lesions: ring enhancement Chronic lesions: no enhancement	Usually no enhancement even in large lesions; in patients with HIV, some peripheral enhancement is possible, especially under therapy
Atrophy	Focal atrophy possible, due to focal white-matter degeneration; no progression	No focal atrophy

NEJM 2006;354

	before PML	First radiological signs of PML		PML diagnosis and management	Outcome
	FLAIR	FLAIR	T1+Gd		
Case 1				• 29 yo male, 38 infusions, EDSS 4.0 • No new symptoms • Gd-enhancement of initial MRI lesion, 28d after last natalizumab (NTZ) infusion • Prior IS (mitoxantrone) • Unknown JCV Ab status prior to PML • JCV PCR on CSF: 712 copies/mL • PLEX and IVMP (5x1gr) at time of Dx 7w after last NTZ infusion, followed by 24w oral MP tapering course	• No new symptoms (stable EDSS and MSFC course), no late-IRIS development • Negative JCV DNA PCR on CSF 12w after PLEX initiation • No hypointense T1 lesion, long-lasting Gadolinium enhancement vanishing 33w after PLEX and coalescence of T2 lesions.
Case 2				• 45 yo female, 33 infusions, EDSS 4.0 • No new symptoms of which patient is aware but inferolateral right quadranopsy on formal visual testing • No Gd-enhancement of initial MRI lesion, 15-20d after last NTZ infusion • Prior IS (mitoxantrone) • Unknown JCV Ab status prior to PML • JCV PCR on CSF: 284 copies/mL • PLEX at time of Dx 3w after last NTZ infusion + Cidofovir + Probenecid	• Negative JCV DNA PCR on CSF 12w after PLEX initiation • Development of an hypointense T1 lesion and disappearance of late-IRIS associated gadolinium enhancement after 24w
Case 3				• 40 yo female, 44 infusions, EDSS 3.5 • No new symptoms • No Gd-enhancement of initial MRI lesion, 18d after last NTZ infusion • No prior IS • Positive JCV Ab prior to PML • JCV PCR on CSF: 15016 copies/mL • PLEX at time of Dx 3w after last NTZ infusion + Norset + Mefloquine	• Right hemihypoesthesia and dyspraxia concurrent of late-IRIS development with edema 3-4w after PLEX, treated with IVMP (10x1g) followed by a short oral MP tapering course. Persistent right sensory deficit and dyspraxia. • No further control CSF analysis for DNA PCR detection • Development of an hypointense T1 lesion and slow disappearance of late-IRIS associated gadolinium enhancement.
Case 4				• 60 yo female, 49 infusions, EDSS 6.5. • No new symptoms at the time of first MRI signs of PML. T1 timepoint was considered stable but a linear hyperintense cortical/juxta-cortical lesion was retrospectively suspected. T2 was misinterpreted as a new plaque. Despite monthly clinical evaluation, a progressive cognitive and behavioral disturbance with increase in lower left limb paresis was only captured at T3 timepoint, i.e., 35w after T1 and 20w after T2. At the time of diagnosis (T3), PML FLAIR lesion volume had massively increased. • No Gd-enhancement of initial unequivocal MRI lesion (T2), nor at the time symptoms were detected (T3, 27d after last NTZ infusion) when PML lesion was then hypointense in T1-weighted sequence • No prior IS • Unknown JCV Ab status prior to PML	• No obvious worsening of cognitive and motor symptoms concurrent of late-IRIS development 5w after PLEX, then treated with IVMP (2x5x1g) followed by an oral MP tapering course. Persistent major cognitive impairment and moderate lower left limb paresis • Development of a persistent hypointense T1 lesion and slow disappearance of late-IRIS associated gadolinium enhancement • JCV PCR on CSF still weakly positive (25 copies/mL) 12w after T3

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THE EARLIER, THE SMALLER, THE BETTER FOR NATALIZUMAB-ASSOCIATED PML: IN MRI VIGILANCE VERITAS?

Phan-Ba R, et al., Neurology 2012;79;1067; Published online before print August 22, 2012

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