Do the spinal cord and optic nerve MRI have a role in diagnosis, monitoring and predicting treatment response in MS?

Jiwon Oh, MD, PhD, FRCPC

St. Michael's Hospital, University of Toronto

ECTRIMS/ACTRIMS Teaching Course

September 11, 2020

Objectives

- To discuss the clinical utility of imaging the spinal cord and optic nerve in the diagnosis, prediction, and monitoring of people with MS

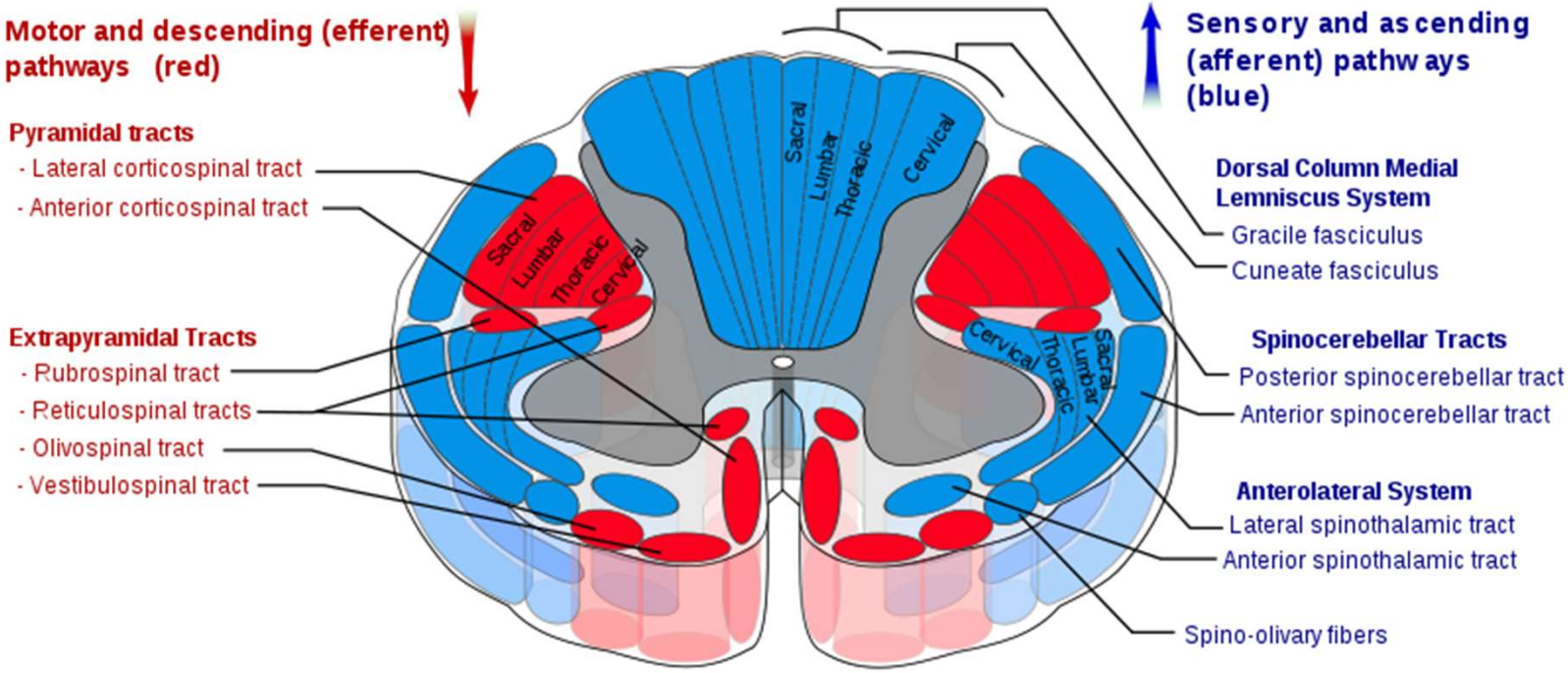
- To discuss recent MAGNIMS/CMSC/NAIMS consensus recommendations regarding imaging the spinal cord and optic nerve in MS clinical practice

Background

- Spinal cord (SC) pathology contributes significantly to disability in MS
    - Charcot: spinal, mixed/cerebrospinal, cephalic
    - Up to 90% of MS patients have cord lesions
    - Lesions found in SC in majority (50-80%) of patients even in “early” MS
- The SC is a useful location to study structure-function relationships

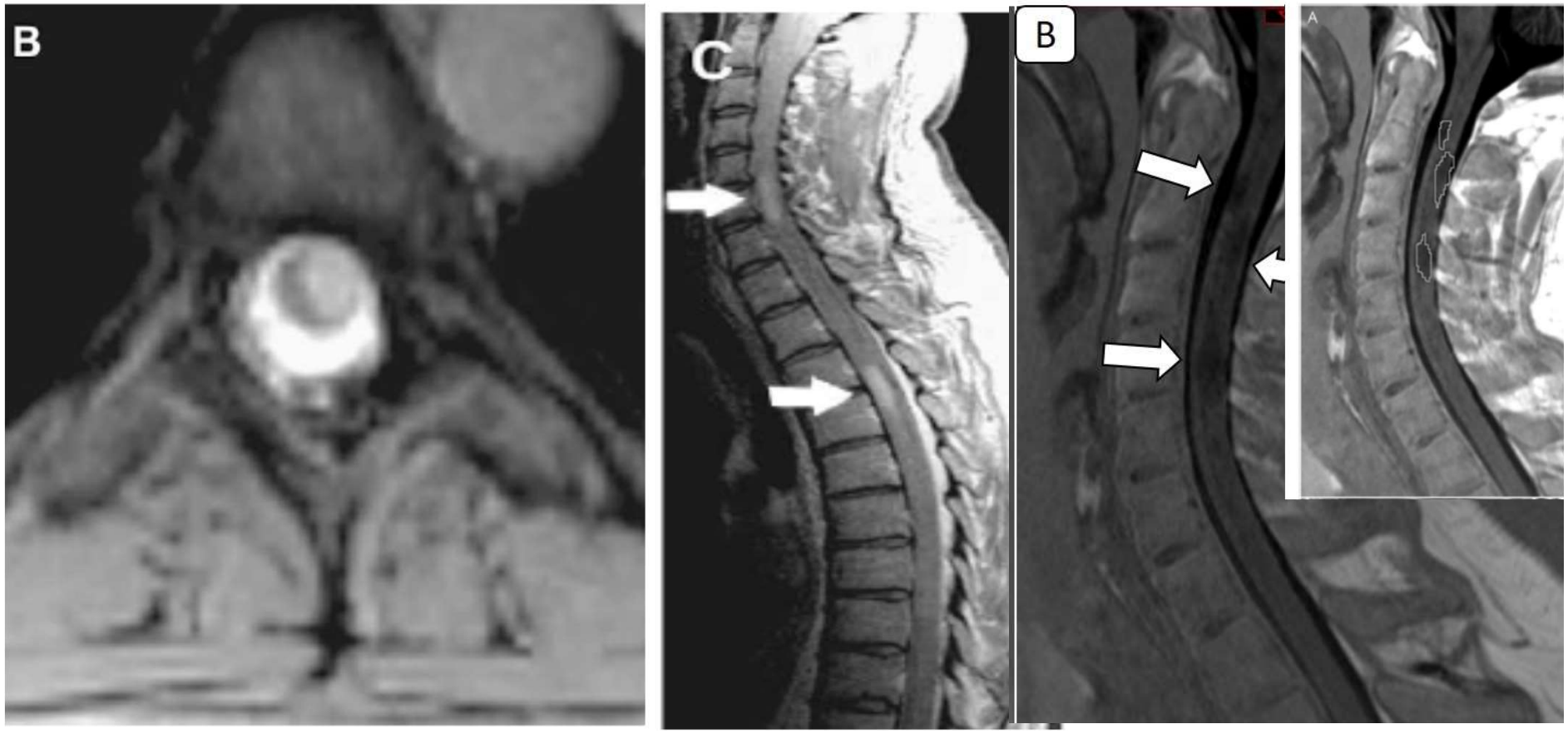
Nijeholt et al, Eur Radiol 2000;10:368–376; Bot et al, Neurology 2004;62:226–233

Spinal Cord Anatomy



Selket and Mikael Haagstrom, Wikimedia Commons 2010

Focal SC Lesions in MS



Bot et al, *Neuroimag Clin N Am* 2009;19: 81–99; Alcaide-Leon et al Neurol: Neuroimmuno and Neuroinflamm 2018

The Evolving Role of SC MRI in MS Diagnostic Criteria

- Initial MRI diagnostic criteria did not include SC MRI findings
  - Fazekas 1988, Paty 1988, Barkhof 1997
- Included in McDonald Criteria (2001), but ambiguous
- Clarification of role of SC lesions in 2005 diagnostic criteria
  - SC lesion can constitute an infratentorial lesion
- 2010 and 2017 criteria:
  - Spinal cord lesion has the same "weight" as a brain lesion to constitute dissemination in space
  - Primary role in diagnosis of PPMS

Fazekas et al, *Neurology* 1988;38:1822–5; Paty et al, *Neurology* 1988;38:180–5, Barkhof et al *Brain* 1997;120:2059–69; McDonald et al *Ann Neurol.* 2001;50(1):121-7; Polman et al *Ann Neurol*. 2005;58(6):840-6; Polman et al *Ann Neurol.* 2011;69(2):292-302; Thompson et al *Lancet Neuro 2018 Feb;17(2):162-173.*

2010 and 2017 Revisions to McDonald MRI Criteria

TABLE 1: 2010 McDonald MRI Criteria for Demonstration of DIS

DIS Can Be Demonstrated by ≥1 T2 Lesion[a] in at Least 2 of 4 Areas of the CNS:
Periventricular
Juxtacortical
Infratentorial
Spinal cord[b]

Based on Swanton et al 2006, 2007.[22,27]
[a]Gadolinium enhancement of lesions is not required for DIS.
[b]If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the Criteria and do not contribute to lesion count.
MRI = magnetic resonance imaging; DIS = lesion dissemination in space; CNS = central nervous system.

TABLE 3: 2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset

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)

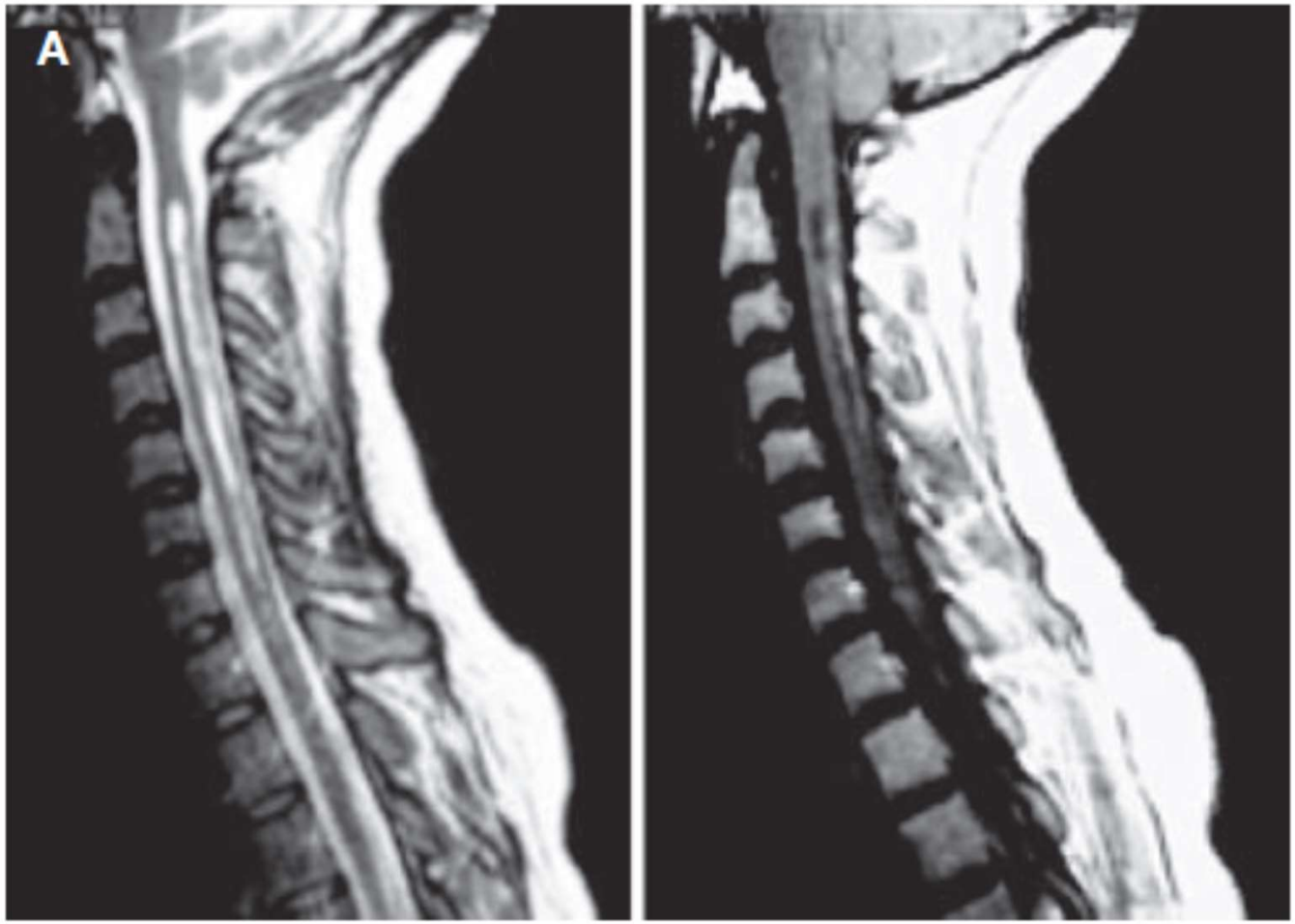
[a]If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the Criteria.
[b]Gadolinium enhancement of lesions is not required.
MS = multiple sclerosis; PPMS = primary progressive MS; DIS = lesion dissemination in space; CSF = cerebrospinal fluid; IgG = immunoglobulin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

Polman et al *Ann Neurol.* 2011;69(2):292-302; Thompson et al *Lancet Neuro 2018 Feb;17(2):162-173.*

Utility of SC MRI in MS Diagnosis

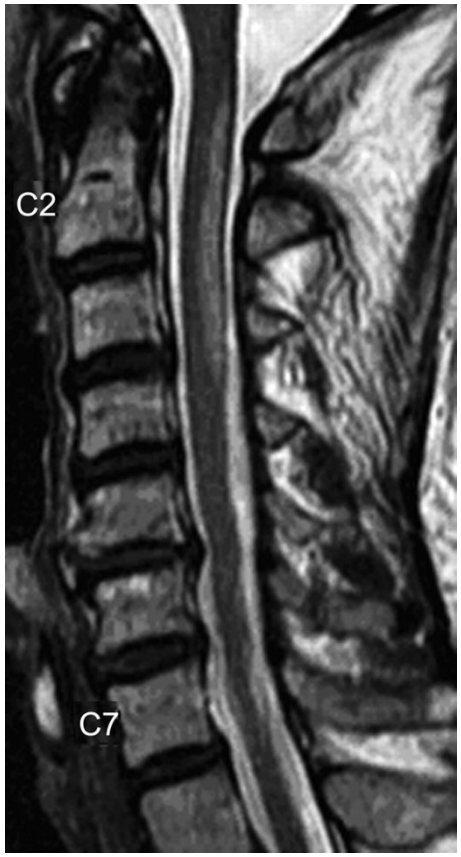
- Can help “rule-in” MS
  - In the setting of a normal or equivocal MRI-brain
- Can help “rule-out” MS
  - In the setting of non-specific changes on MRI-brain
    - “Incidental” findings seldom seen in SC MRI in healthy subjects, even > 50 years
    - White matter abnormalities in brain increases with age (~30% in > 60 years)
- SC MRI is useful in differentiating MS from other disorders that affect the SC

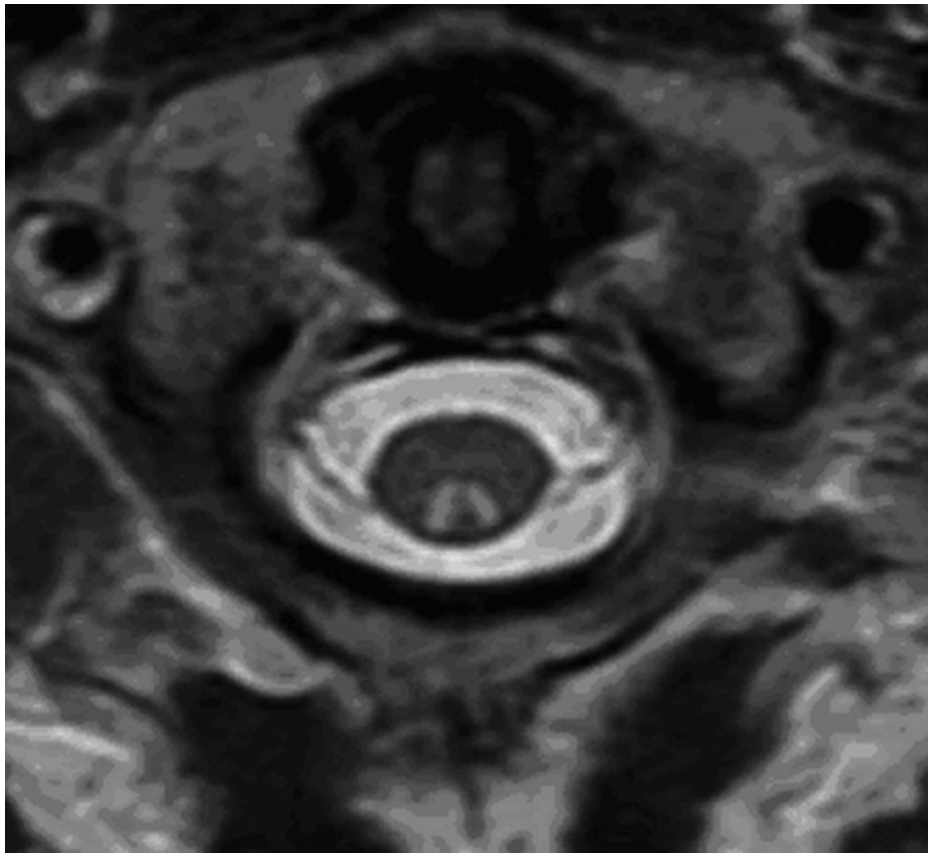
Neuromyelitis Optica (Devic's Disease)



Jarius et al Nat Rev Clin Pract Neuro 2007

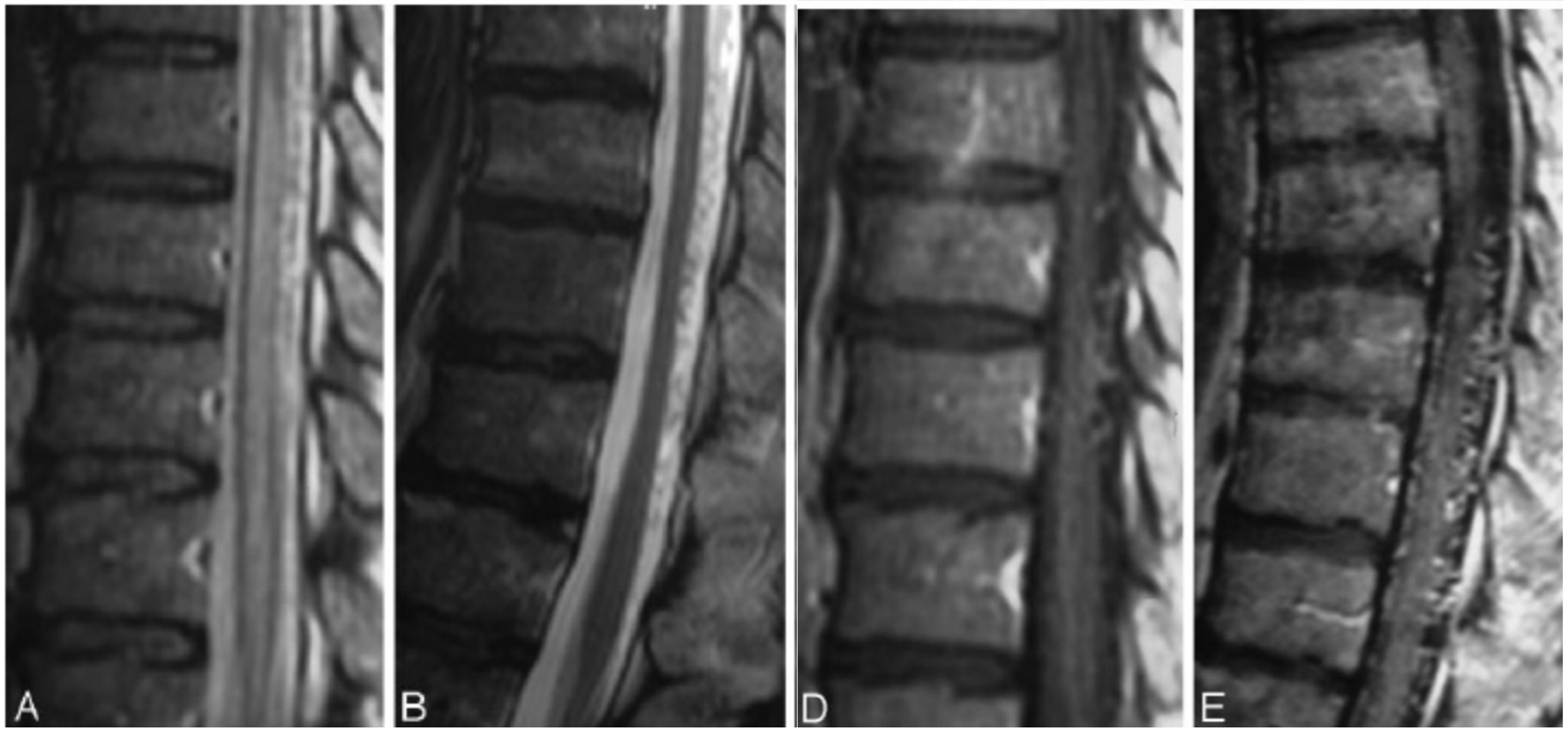
Subacute Combined Degeneration





Kumar A , and Singh A K Neurology 2009;72:e4

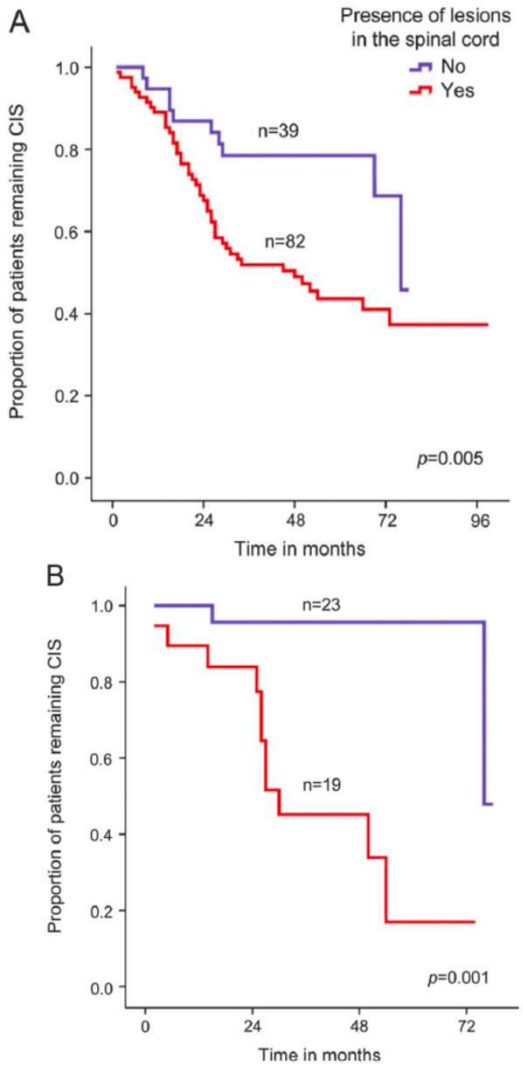
Dural AV-fistula



Krings et al; AJNR 2009

Predictive Value of SC MRI: CIS

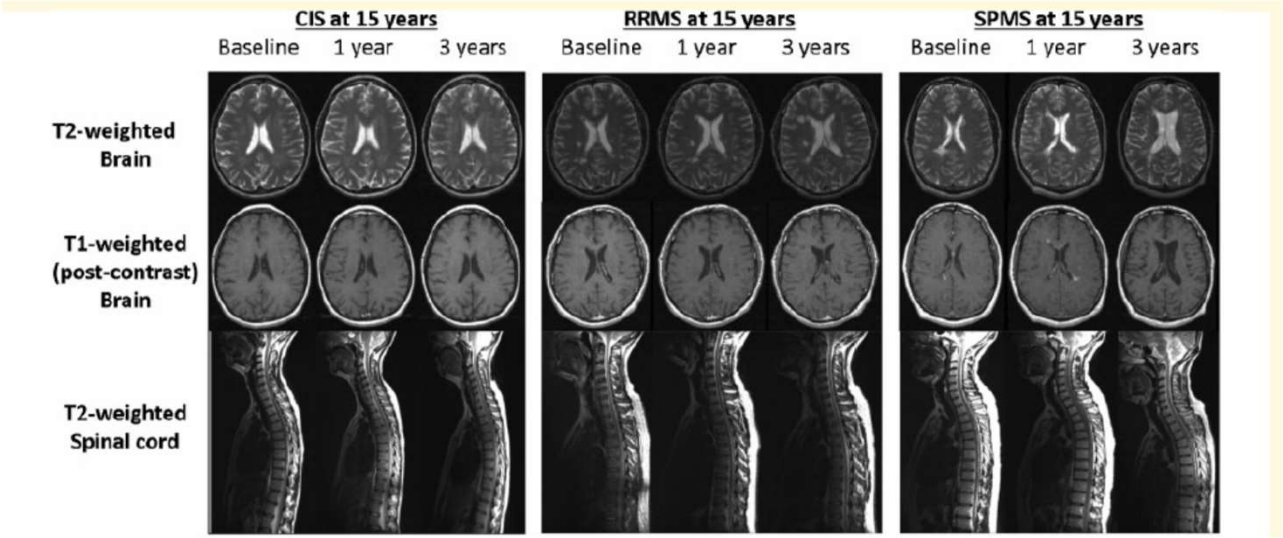
- n=121 CIS
  - 64 month F/U
- In total group (n=121)
  - Presence of SC lesion associated with a higher risk of conversion to CDMS (OR = 3.53 (95% CI: 1.52–8.17))
- In nonspinal CIS patients (n=42):
  - Presence of a SC lesion associated with a higher risk of conversion to CDMS (odds ratio: 14.4; 95% confidence interval: 2.6–80.0)



Sombekke et al, Neurology 2013;80;69-75

Predictive Value of SC Lesions over 15 years: CIS

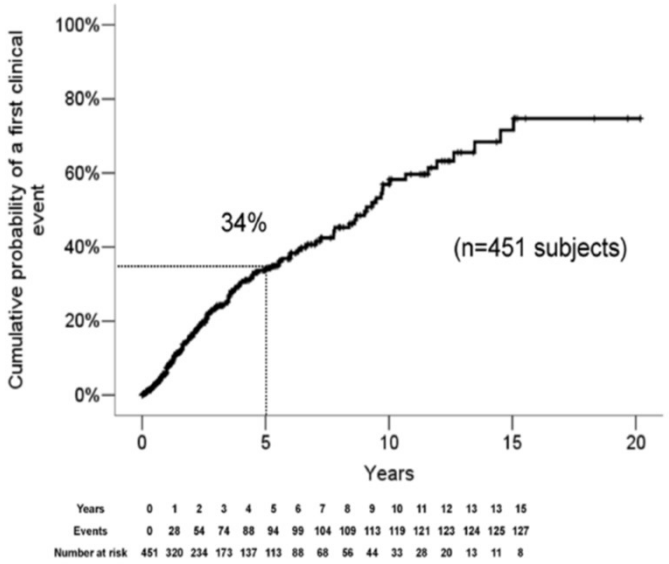
- N=173 CIS patients followed for 15 years
- MRI-brain/SC done at baseline, 1, 3 years
- Baseline SC lesions predictive of SPMS at 15 years
- New SC lesions (together with Gad lesions) predictive of SPMS at 15 years

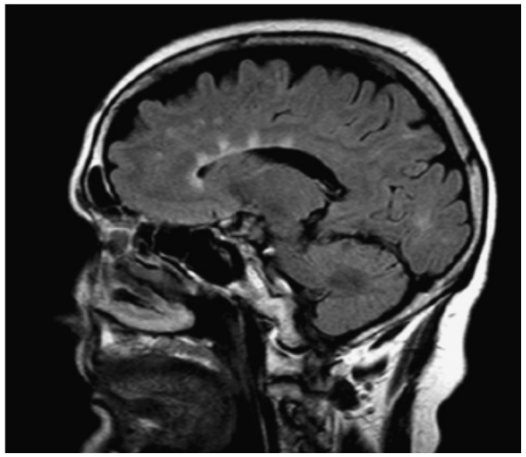


Brownlee et al Brain 2019

Predictive Value of SC MRI: RIS

- N=451
- Retrospective
- Mean age at diagnosis: 37.2 years
- Mean follow-up: 4.4 years
- 34% convert to MS
- 2/3 develop radiological progression
- Similar disease course as “regular” MS post-conversion





Okuda et al. PLoS One 2014; Okuda et al; Neurology 2009;72:800–805

RIS: Known Prognostic Factors

Table 4. Cox regression models containing univariate and multivariate analyses of factors related to time to the first acute or progressive clinical event.

Variable	n	Univariate Analysis* HR (95% C.I.)	p	Multivariate Analysis* HR (95% C.I.)	p
Age	451	0.97 (0.96–0.99)	<0.001	0.98 (0.96–0.99)	0.009
Sex (Male)	451	1.64 (1.10–2.44)	0.015	1.93 (1.24–2.99)	0.004
Positive Family MS History	451	2.20 (1.31–3.70)	0.003		
Ethnicity	451		0.99		
Abnormal CSF[§]	300	1.78 (1.11–2.87)	0.017		
Periventricular lesions presence	446	0.84 (0.21–3.90)	0.8		
Infratentorial lesions presence	446	1.26 (0.88–1.83)	0.2		
Juxtacortical lesions presence	444	0.94 (0.50–1.77)	0.84		
Cervical or thoracic spinal cord lesion	383	3.26 (2.18–4.86)	<0.001	3.09 (2.06–4.62)	<0.001
Contrast enhancement on RIS MRI	381	1.09 (0.70–1.69)	0.70		

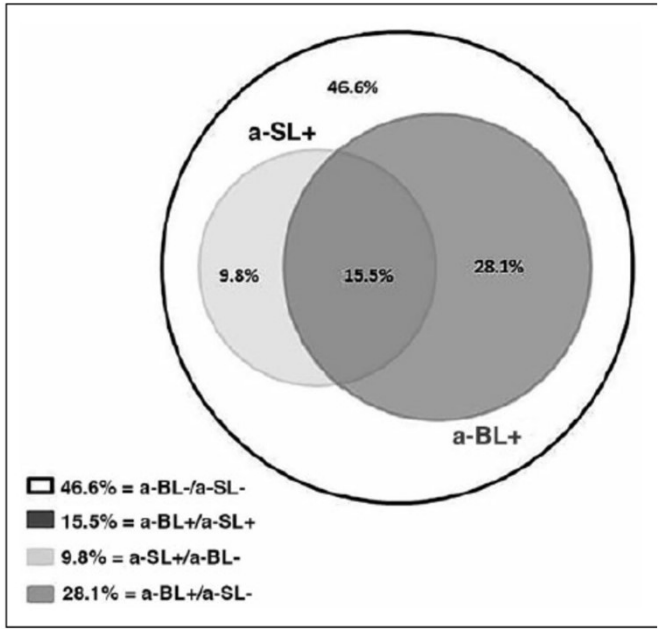
*Adjusted for Center and date of RIS diagnosis.
HR = hazard ratio; CSF = cerebrospinal fluid.
[§] = IgG index >0.7 or the presence of >2 unique oligoclonal bands within the CNS.
doi:10.1371/journal.pone.0090509.t004

Okuda et al. PLOS One 2014

Spinal Cord MRI in Disease Monitoring

- May be of utility in some situations

- MRI-brain/SC done on MS patients at baseline, and at a follow-up time point 12-36 months later
  - Single center, n=103, median follow-up 17 months
- 25% of patients had an asymptomatic SC lesion
- 44% of patients had an asymptomatic brain lesion
- 9.8% had an ISOLATED asymptomatic SC lesion detected (with no asymptomatic brain lesion)



Zecca et al, MS J 2014

Recommended MAGNIMS/CMSC/NAIMS Standardized SC MRI Protocol for MS Diagnosis

- TWO of the following sagittal sequences:
  - T2w (turbo/fast) SE with moderately long echo times
  - Proton-density (PD) (turbo/fast) SE
  - Short-tau inversion recovery (STIR)

- Single acquisition of a T2w sequence not sufficient
  - Limited sensitivity
  - Second sequence needed to confirm the presence of lesions and exclude artefacts.

- Axial T2w (turbo/fast) SE sequences can improve the diagnostic certainty
- If contrast required: Gd-enhanced T1w (turbo/fast) SE sequence

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

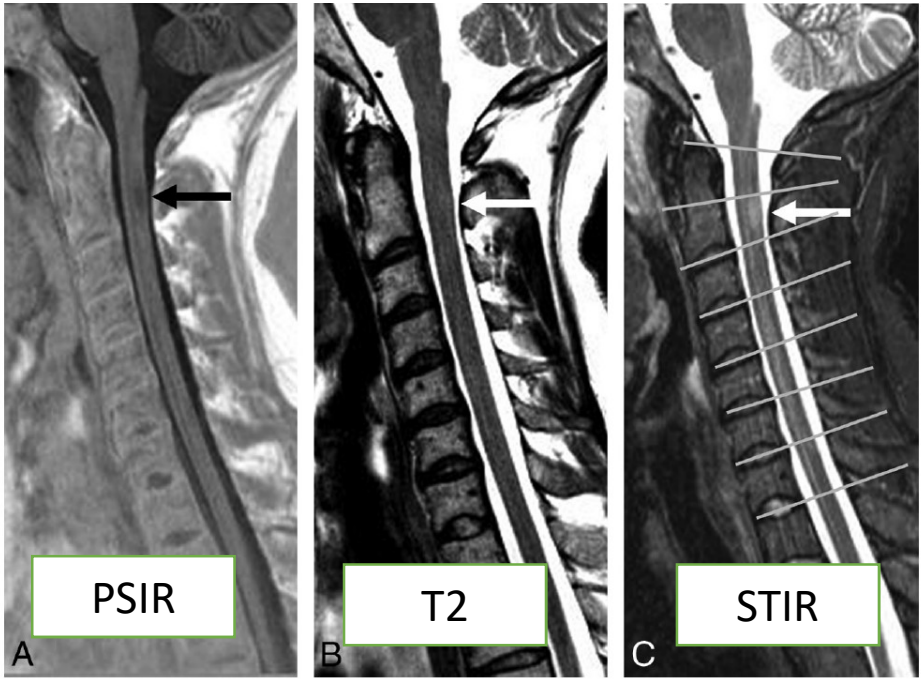
Recommended Standardized SC MRI Protocol for MS Diagnosis

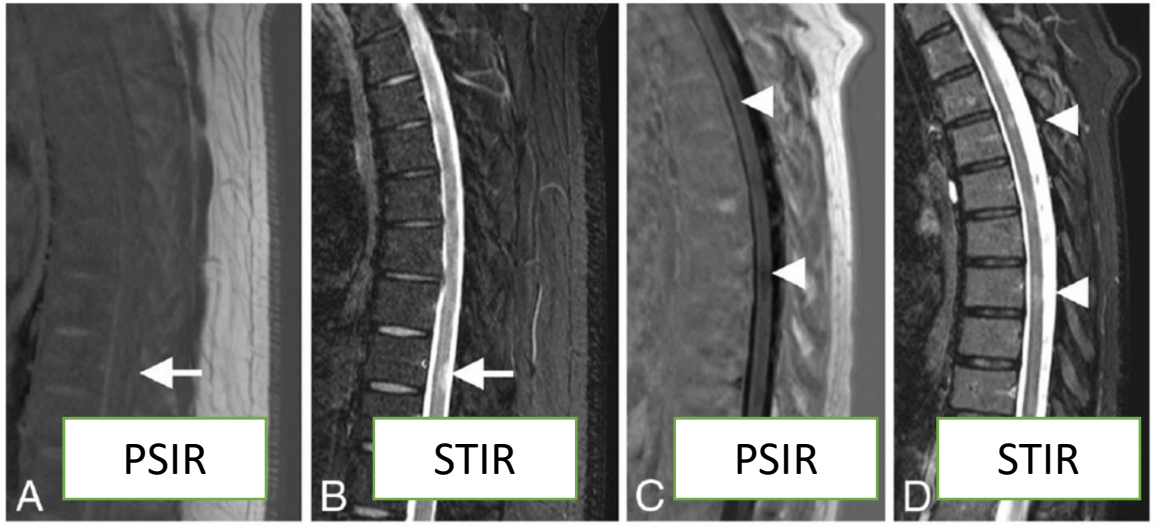
- Sagittal scans should cover the whole SC when possible
  - If not possible, covering only the upper half of the SC (C1 to T5) is a reasonable compromise for disease monitoring (unless clinical suspicion of lower SC lesion)
  - Minority of MS patients have lesions exclusively located below T5

- C-spine: Can consider using 3D-heavily T1w sequences (PSIR and MPRAGE)
  - Higher sensitivity vs. STIR and long-echo T2w images
  - But clinical experience is still limited, therefore use as a fourth alternative to T2/PD/STIR in experienced centers

- T-spine: limited experience with T1w sequences – not recommended
  - Lower sensitivity of PSIR vs. STIR sequences

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis





Alcaide-Leon et al AJNR 2016

Recommended Standardized SC MRI Protocol for MS Diagnosis

- No evidence that scanning at higher magnetic field strengths (3T) leads to a higher SC lesion detection rate

- Use of sagittal Gd-enhanced T1w sequences for diagnostic purposes recommended
    - Should be performed immediately after the Gd-enhanced brain MRI if both brain/spine performed in same session

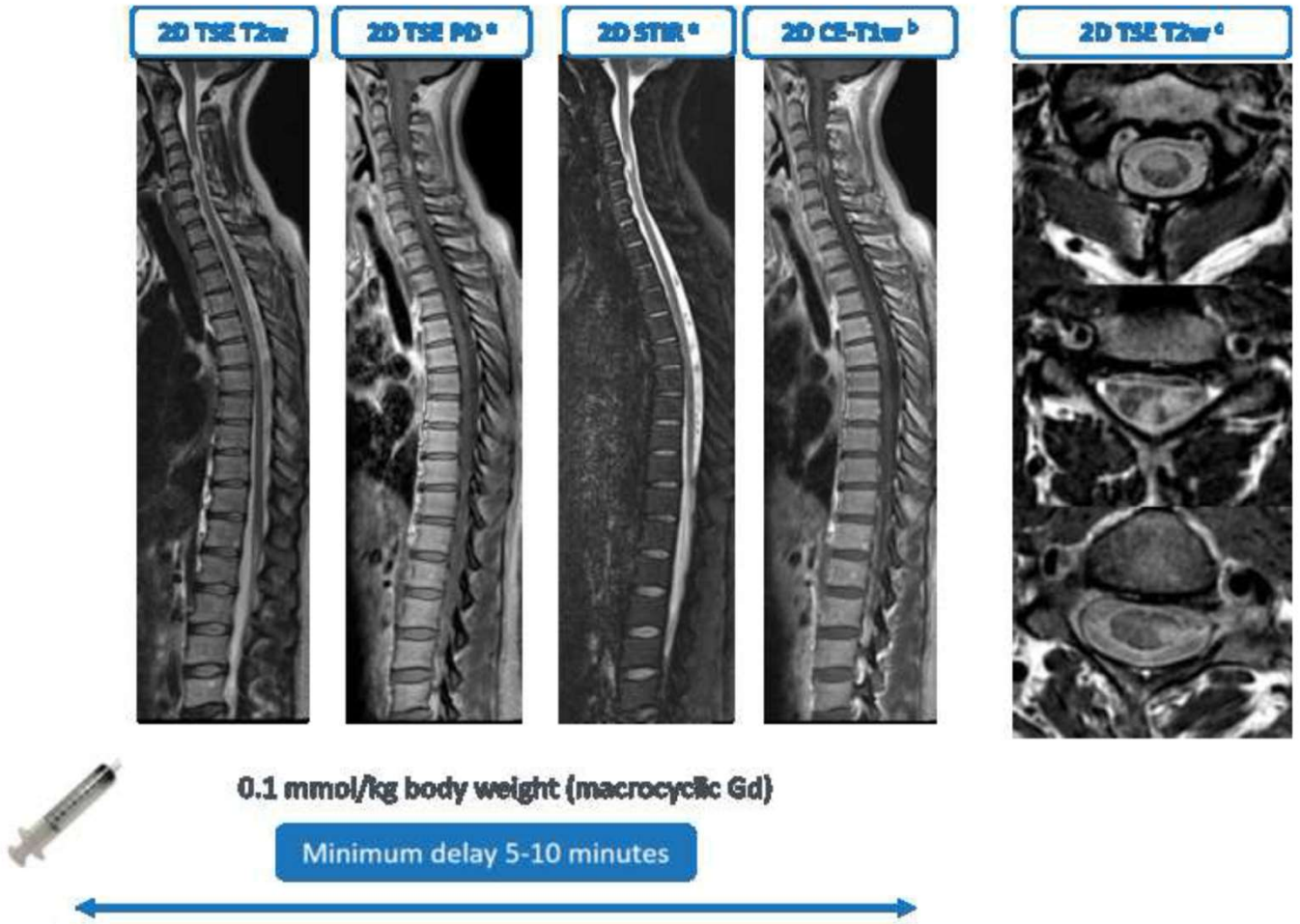
Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

Table 3: Standardized spinal cord MRI protocol

	MS diagnosis	Efficacy monitoring and assessment of disease activity in patients not treated [5]
Sagittal T2 (TSE/FSE) / PD(TSE/FSE) / STIR[1]	recommended	optional
Sagittal 3D heavily T1w (PSIR or MPRAGE)[2]	optional	optional
Axial T2w (TSE/FSE) or GRE[3]	optional	optional
Sagittal T1w (TSE/FSE) pre contrast	optional	optional
Sagittal T1w (TSE/FSE) post contrast[4]	recommended	optional
Axial T1w (TSE/FSE) post contrast[4]	optional	optional

[1] At least two out of these three sequences
[2] Only for the cervical segment. One of these sequences could replace T2, PD, or STIR
[3] To corroborate and characterize lesions detected on sagittal images, or to detect lesions in spinal cord segments with high clinical suspicious of involvement
[4] Standard doses of 0.1 mmol/kg bodyweight, macrocyclic gadolinium chelates only. No additional gadolinium necessary if cord examination immediately follows gadolinium enhanced brain MRI
[5] Spinal cord MRI for assessing treatment efficacy and monitoring disease activity is not recommended on regular basis but is advised for special clinical conditions only (see Table 4).

MS=multiple sclerosis, (TSE/FSE)=turbo spin echo/fast spin echo, PD=proton density, STIR=short tau inversion recovery, PSIR=phase sensitive inversion recovery, MPRAGE=magnetization prepared rapid acquisition of gradient echoes, GRE=gradient recalled echo.



Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

Recommended Use of SC MRI for Prognosis

- Useful in early MS
- CIS: development of MS, SPMS, disability accrual
  - Detection of SC lesions at diagnosis and with disease monitoring
- RIS: development of MS
  - Detection of asymptomatic SC lesions at diagnosis

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

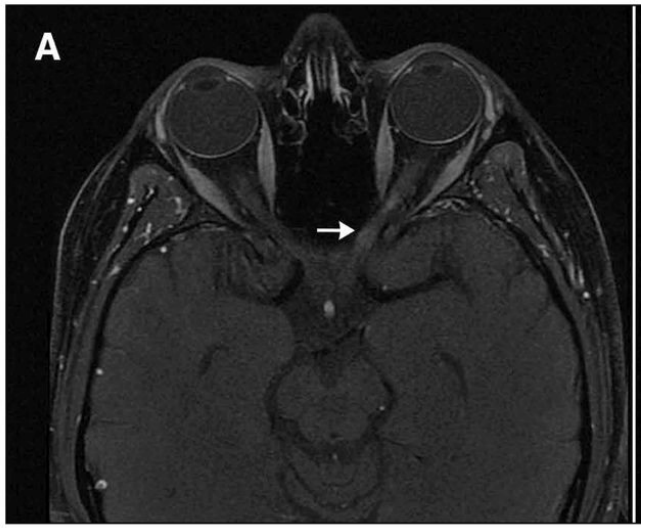
Recommended Use of SC MRI for Disease Monitoring

- In specific situations to detect active SC lesions and exclude other diagnoses:
  - MS patients with spinal cord phenotype at diagnosis
  - MS patients with frequent SC relapses
  - Disease progression that cannot be explained by brain MRI
  - Atypical SC relapse/symptoms

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

The Optic Nerve in MS

- Commonly affected in MS
- Useful location to study structure-function relationships
- Can be difficult to image using MRI
- Generally not routinely recommended but can be useful in specific situations
  - Diagnosis: with atypical features, to r/o other causes; pediatric patients
  - Monitoring: with atypical features, to ensure no concurrent pathology, patients with recurrent optic nerve disease
- Other non-MRI based techniques (optical coherence tomography)that can indirectly image the optic nerve may be more useful



Garrett et al CMAJ 2016; Saidha et al JAMA Neuro 2013

Recommended Optic Nerve Protocol in MS Diagnosis and Monitoring

- If indicated, standardized acquisition protocol should be used
  - Axial and coronal fat-suppressed T2w or STIR
  - Fat-suppressed Gd-enhanced T1w sequences (Table 1) should be applied
- Should be interpreted in conjunction with a clinical, neurophysiological and OCT

	Optic Nerve MRI
Field strength	≥1.5T
Slice thickness	≤ 2-3 mm, no gap
In-plane resolution	≤ 1mm x 1mm
Coverage	Optic nerve and chiasm
Axial scan orientation	Aligned to orientation of optic nerve and chiasm

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

Indications for optic nerve MRI in diagnosis and disease monitoring

Clinical situation	Indication and objective
Diagnosis	• CIS: differential diagnosis in case of suspected: - Atypical isolated optic neuritis; relapsing isolated optic neuritis; chronic relapsing inflammatory optic neuropathy - Other diseases affecting the optic nerve: NMOSD, infectious diseases, post vaccination, sarcoidosis, tumours, etc. - Optic neuritis in paediatric patients
Monitoring	• MS patients with new visual symptoms suggestive of comorbidity affecting the optic nerve • MS patients with chronic progressive optic nerve symptoms • MS patients with repeated isolated optic nerve relapses

CIS=clinically isolated syndrome, MS=multiple sclerosis, NMOSD=neuromyelitis optica spectrum disorders

Wattjes et al (under review): International 2020 MAGNIMS-CMSC-NAIMS consensus guidelines on the use of MRI in multiple sclerosis

Summary

- The MAGNIMS/NAIMS/CMSC recommendations are intended to provide practical guidance on the effective use of SC and optic nerve MRI in MS clinical practice
- SC MRI (to detect lesions) is clinically useful in the diagnosis of MS, and as a predictive tool in MS
- SC MRI is useful for disease monitoring only in limited situations
- There is a standardized recommended SC MRI protocol that can optimize SC lesion detection and scan time
- Optic nerve MRIs are not routinely recommended, but can be useful in specific situations for diagnosis and monitoring in MS

Thank you
for your attention!