Pediatric MS

What are the distinguishing characteristics?

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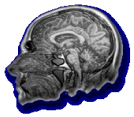

Image Analysis Center

Outline and Focus

- Introduction
- MRI in MS diagnosis
- MRI in MS patient monitoring
- Imaging in a disciplinary setting
- Future perspectives
- Summary and conclusion

MRI=magnetic resonance imaging; MS=multiple sclerosis.

Introduction

- 2-10% of all MS patients have a clinical onset < 18 years
- Definition of MS in children:
  - 13 years – 17 years 11 months
- Overall incidence:
  - 0.6-1.66/100 000 children per year
- Clinical manifestations acquired demyelination:
  - Optic neuritis (22-36%)
  - ADEM (19-24%)
  - Transverse myelitis (3-22%)
  - NMO (2-4%)
- 15-45% conversion rate to definite MS within 5 years

ADEM=acute disseminated encephalomyelitis; NMO=neuromyelitis optica

Waldman A et al. *Lancet Neurol* 2014, 13: 936-948
Krupp LB et al. *Mult Scler* 2013; 19: 1261-67

Introduction

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MRI criteria for pediatric MS

Table 4 Comparison of classification accuracy of published and proposed MRI criteria for MS applied to patients with CDMS at second attack compared to OND controls

	KIDMUS[16]	McDonald[2]	Current
	All of:	At least three of:	At least two of:
	≥1 lesion perpendicular to long axis of corpus callosum	≥9 T2 lesions or ≥1 gadolinium enhancing	≥5 T2 lesions
	Presence of solely discrete lesions	≥3 periventricular	≥2 periventricular
		≥1 juxtacortical	≥1 brainstem
		≥1 infratentorial (or spinal)	
Accuracy statistics			
Sensitivity*	47% (62%)	76% (76%)	85%† (90%)
Specificity	100%	100%	98%
Positive predictive value	100%	100%	97%
Negative predictive value	71%	85%	90%
Area under receiver operating characteristic curve‡	0.74 (0.62–0.85)	0.87 (0.78–0.96)	0.92 (0.84–0.99)
Difference from proposed criteria§	$p < 0.001$	$p = 0.125$	N/A

Callen DJA et al. *Neurology* 2009, 72: 961-67

2010 IP Diagnostic 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 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.

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

IP=International Panel

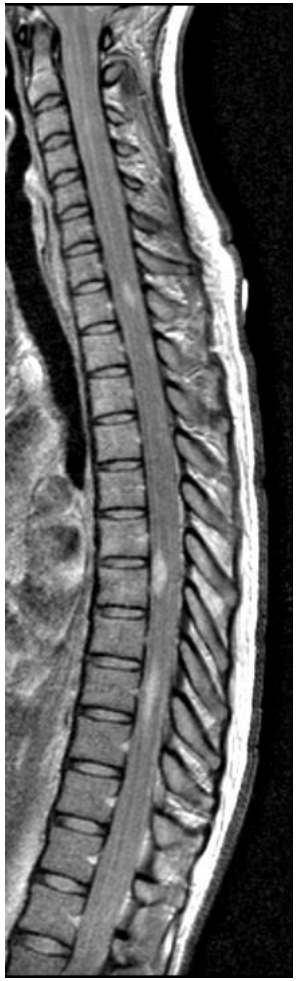
2010 IP Diagnostic criteria

- Can be applied in pediatric populations
- Sensitivity 100%, specificity 86%, PPV 59%, NPV 100%
- <u>Frequency of spinal cord lesions is undereported:</u>
  - SC imaging not performed routinely
  - SC lesions often clinically silent
  - Frequently longitudinally extensive
  - SC lesion can improve the diagnostic performance

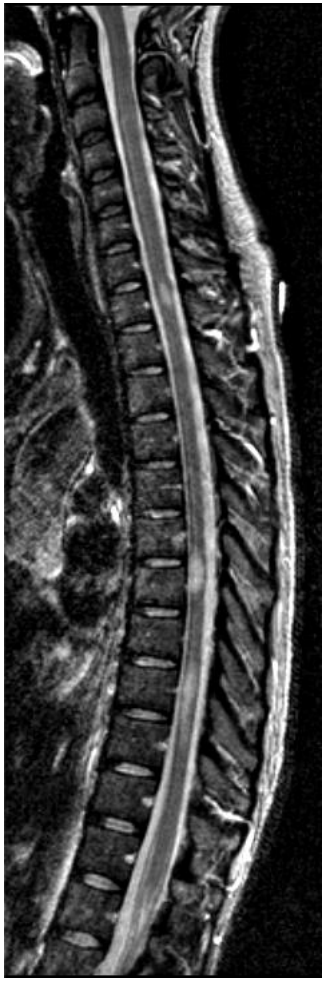
PPV=positive predictive value; NPV=negative predictive value

Sakada Y et al. *Ann Neurol* 2012, 72:211-232
Waldman AT et al. J Child Neurol 2011; 26: 675-82
Hummel HM et al. *Mult Scler* 2013; 19: 1330-35

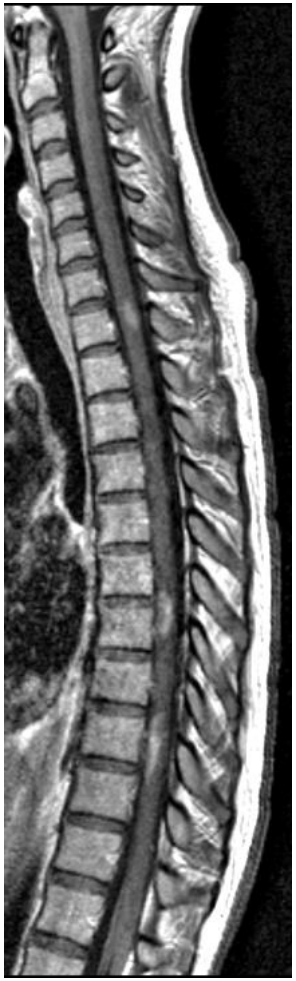
Spinal cord MRI in adult MS



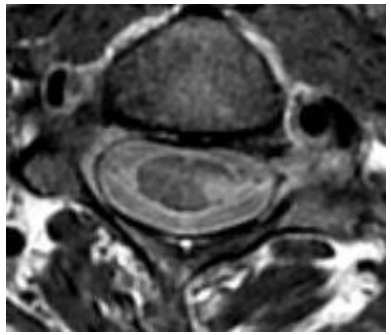
PD

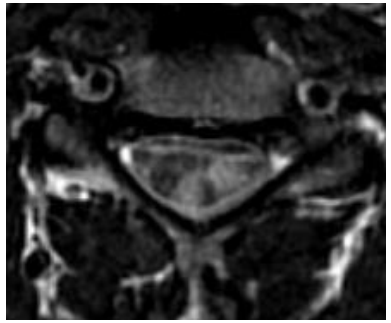


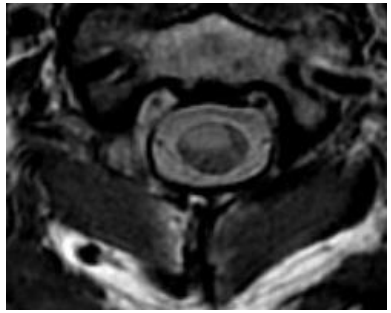
T2



T1 +Gd

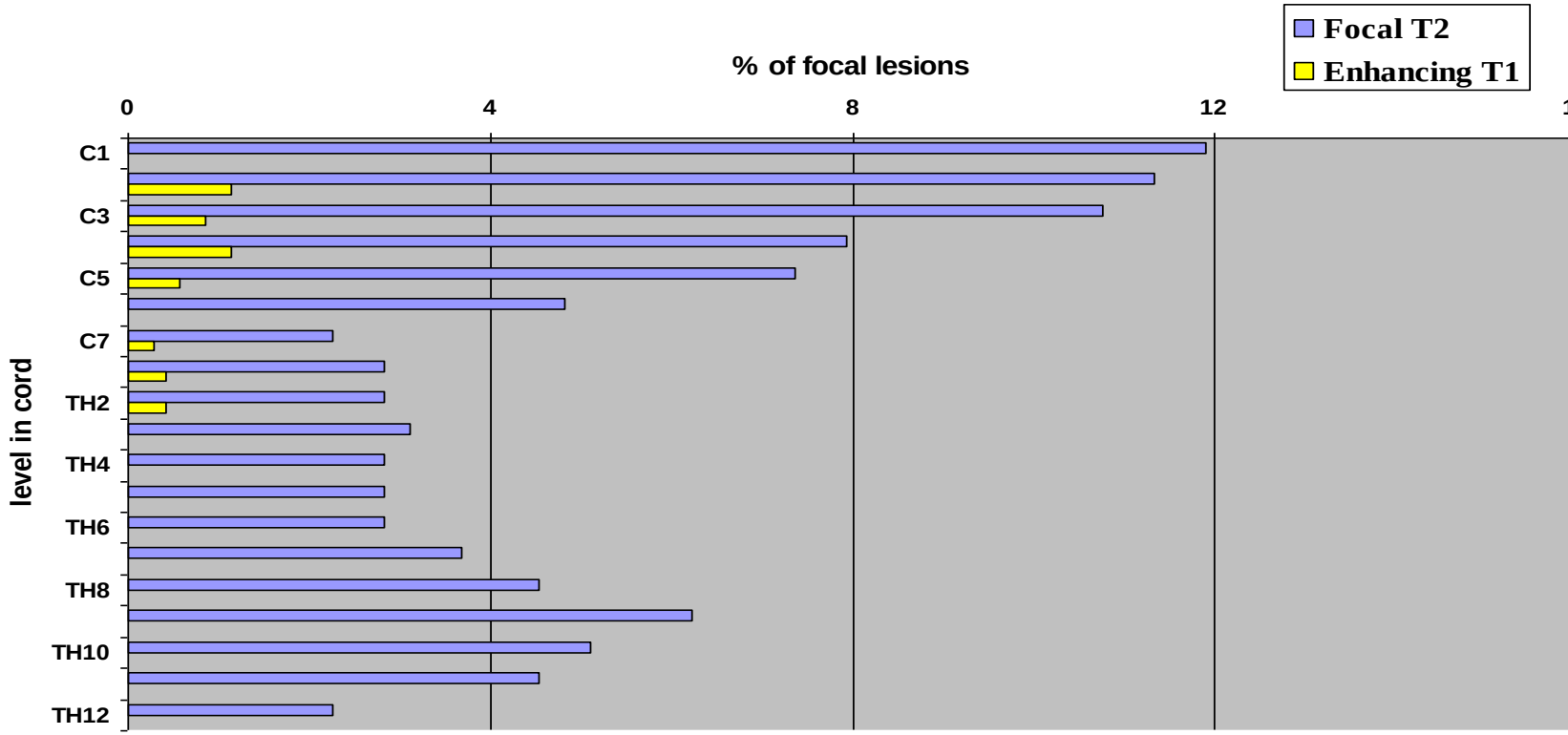




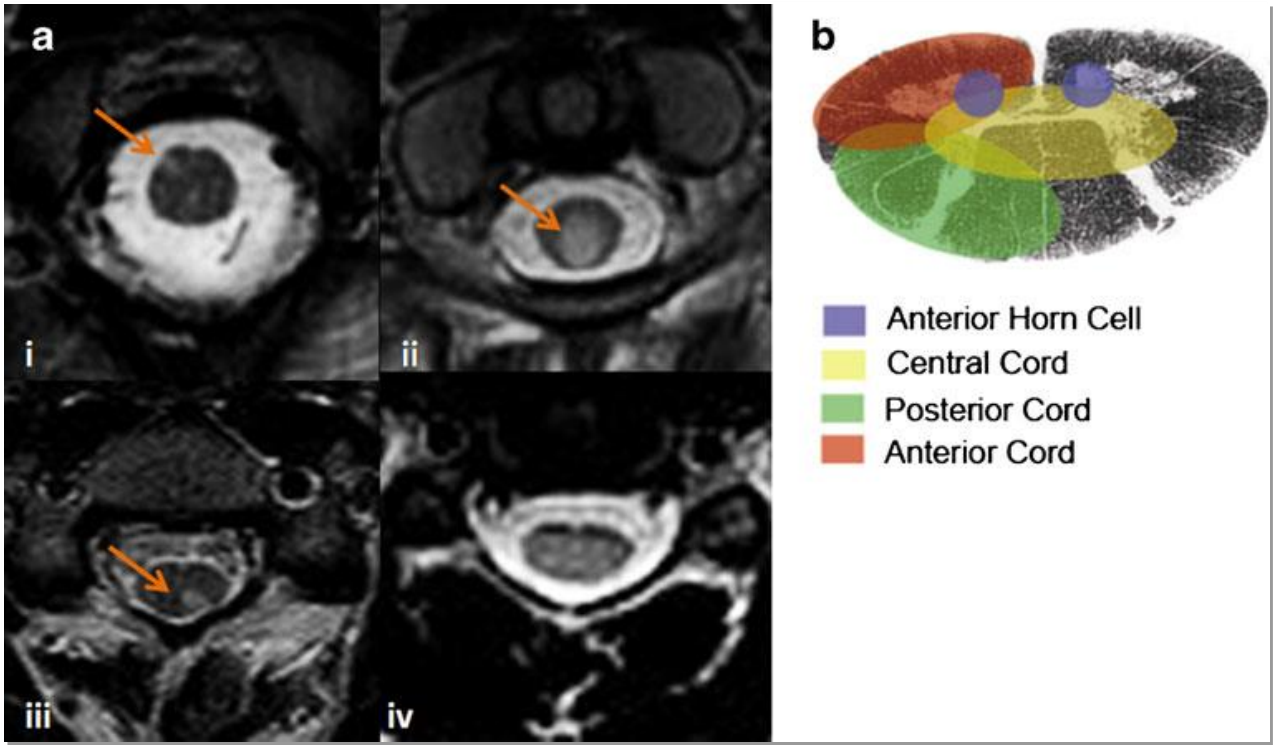


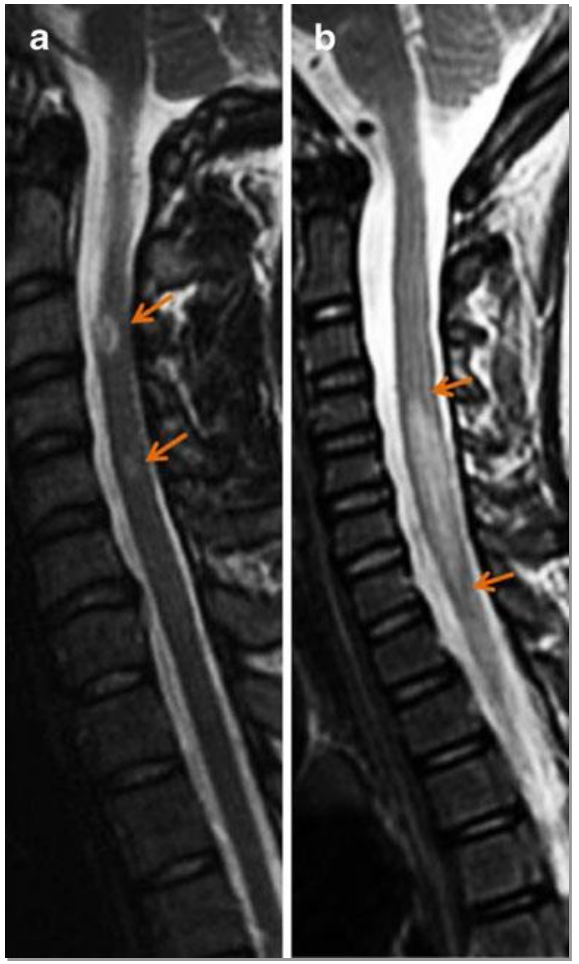
Spinal cord MRI in adult MS

Lesion distribution



Spinal cord MRI in pediatric MS





Verhey LM et al. *Neuroradiology* 2010, 52: 1153-62

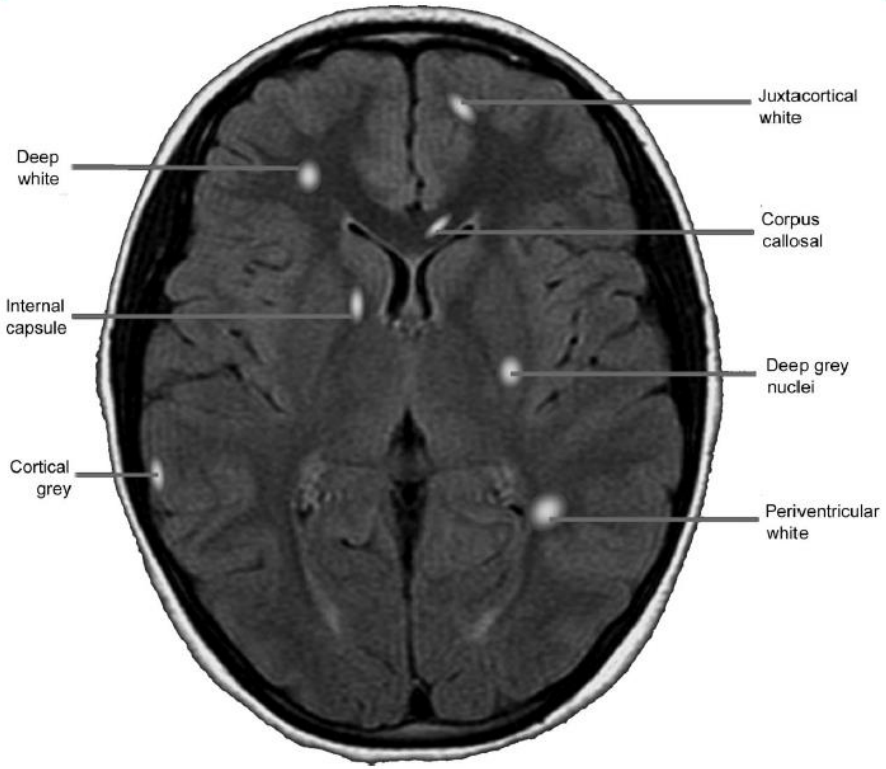
Spinal cord MRI in pediatric MS

	Summary statistics
Number of lesions per patient, median (IQR, range)	1 (1, 1–6)
Number of children with, *n* (%)	
Focal lesions	23 (64)
Longitudinally extensive lesions	3 (8)
Both	3 (8)
Number of children with lesions in each region, *n* (%)	
Cervical	11 (31)
Thoracic	9 (25)
Cervical and thoracic	9 (25)
Lumbar	0
Number of children with gadolinium enhancing lesions, *n* (%)[a]	5 (31)
Number of lesions detected in 36 children, *n* (%)	60 (100)
Number of focal lesions, *n* (%)	54 (90)
Number of longitudinally extensive lesions, *n* (%)	6 (10)
Number of lesions in each region, *n* (%)	
Cervical	30 (50)
Thoracic	27 (45)
Cervical and thoracic	3 (5)
Lumbar	0
Number of lesions in each intramedullary axial location, *n* (%)[b]	
Posterior	34 (77)
Central	26 (59)
Anterior	18 (41)
Complete	8 (18)
Anterior Horn Cells	0
Central gray matter	0

Verhey LM et al. *Neuroradiology* 2010, 52: 1153-62

Brain MRI lesions in pediatric MS

Figure Axial T2-weighted image at the level of the decussation of the genu of the corpus callosum showing representative examples for most of the location categories assessed



Infratentorial lesions and size categories are not displayed.

Table 2 Summary of mean lesion counts for location and size variables for patients with MS at second attack and OND controls

Category	MS patients, attack 2, n = 34	OND controls, n = 45	t Score	Significance (p)	Effect size*
Location					
Deep white matter	15.85 ± 14.08	1.33 ± 3.19	5.90	<0.001†	1.4
Juxtacortical white matter	13.65 ± 26.54	0.47 ± 1.25	2.89	0.007	0.7
Periventricular white matter	5.85 ± 5.57	0.2 ± 0.46	5.91	<0.001†	1.4
Corpus callosal	2.32 ± 2.79	0.16 ± 0.42	4.49	<0.001†	1.1
Internal capsule	1 ± 1.56	0.04 ± 0.3	3.53	0.001†	0.9
Cortical grey matter	6.09 ± 12.42	0.11 ± 0.32	2.81	0.008	0.7
Deep grey nuclei	2.62 ± 3.46	0.2 ± 0.81	4.00	0.001†	1.0
Brainstem	3.26 ± 3.33	0	5.71	<0.001†	1.4
Cerebellar	1.53 ± 1.99	0.02 ± 0.15	4.41	<0.001†	1.1
Supratentorial	39.29 ± 46.56	2.24 ± 5.17	4.62	<0.001†	1.1
Infratentorial	4.26 ± 4.53	0.02 ± 0.15	5.46	<0.001†	1.3
Total lesions	43.56 ± 49.57	2.27 ± 5.17	4.84	<0.001†	1.2
Spinal lesions	4/7†	0/3‡	—	—	—
Gadolinium-enhancing lesions	9/16†	0/4‡	—	—	—
Black holes	13/28†	5/41‡	—	—	—
Size					
Small§	32.85 ± 37.96	1.96 ± 4.34	4.72	<0.001†	1.1
Medium¶	7.94 ± 10.21	0.27 ± 1.36	4.36	<0.001†	1.1
Large‖	2.76 ± 4.08	0.04 ± 0.21	3.88	<0.001†	0.9

Callen DJA et al. *Neurology* 2009, 72: 961-67

MRI features of pediatric MS and DDx

	Frequent MRI findings	Common MRI features	Features that suggest alternative diagnoses[28]
MS*	• >1 periventricular T2 lesion(s) • Periventricular lesions oriented perpendicular to corpus callosum • >1 T1 hypointense lesion • Gadolinium-positive and gadolinium-negative lesions • Low thalamic volume	• Juxtacortical lesions • Brainstem or cerebellar lesions • Low global brain volume	• Absence of T2 lesions at baseline • Failure to document T2 lesion accrual • Meningeal gadolinium-positive • Visible cortical lesions on T2 at 1·5 or 3T • Focal cortical volume loss
ADEM	• <2 periventricular lesions • Absence of non-enhancing T1 hypointense lesions	• Diffuse ill-defined multifocal bilateral lesions • LETM (when cord involvement is present)	• Enhancement of all lesions
NMO†	• LETM • Long optic nerve lesions • Diencephalic lesions • Periaqueductal lesions	• Diffuse ill-defined brain lesions • Tumefactive lesions • Chiasmal lesions	• Absence of optic nerve or spinal cord involvement over time • Sole presence of well defined lesions • Focal spinal cord lesions
CRION‡	• Absence of brain or spine involvement • Unilateral or bilateral optic nerve involvement	• Gadolinium-positive optic nerve lesions • Chiasmal lesions	• Expansive lesions of the optic nerve • MRS lactate
CNS vasculitis§	• Meningeal gadolinium-positive • Focal cortical T2 lesions • MRA lesions • Angiographic evidence of vascular beading	• Multifocal T2 lesions • Optic neuritis and cord lesions • Normal or near-normal brain MRI	• Absence of cortical lesions

DDx=differential diagnosis; ADEM=acute disseminated encephalomyelitis; NMO=neuromyelitis optica; MS=multiple sclerosis; T=Tesla; LETM= longitudinally extensive transverse myelitis; CRION=chronic relapsing inflammatory optic neuropathy; MRS=magnetic resonance spectroscopy; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging

Waldman A et al. *Lancet Neurol* 2014, 13: 936-948

Conclusion

- Standardization & harmonization of MRI is crucial
  - Hardware
  - Imaging acquisition
- Multi-center standardization & harmonization
  - Establishement of MS research and care networks
  - Data sharing, multi-center projects
- Try to act according international guidelines
- MS patients care and research should be performed in a multi-disciplinary approach!

Acknowledgment

MS Center Amsterdam

Thank you very much for your attention!