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**MRI in multiple sclerosis**

**MRI in MS**

- Conventional MRI lesions
  - T2, T1, gad
- Atrophy of the CNS in MS
  - MRI assessment
- Recent MRI advances in MS

**Brain lesions – Morphology Matters**

- Typical of MS: Oval/ovoid/>5mm
- Ischemia: Punctate/linear/small

**Sagittal FLAIR – Morphology Matters**

- Typical of MS: Perivenular

**Brain Lesions – Location Matters**

- Typical of MS

**MS T2 Lesions: Pathology**

- Non-specific
  - Demyelination
  - Remyelination
  - Inflammation
  - Edema
  - Axonal loss
  - Tract degeneration
- Limited sensitivity
Clinical Correlations of T2 Lesions

- In cross-sectional studies:
  - mild correlation with clinical status
- Better longitudinal predictive value for:
  - disease progression in established MS
  - development of brain atrophy
  - conversion from CIS to RRMS
- Probably a brain reserve/threshold effect

MRI may predict clinical progression in MS


MRI gadolinium enhancement in MS

- Active BBB disruption
- Passage of T cells into the CNS
- 5–10x more frequent than relapses
- Predictive of relapses, but lessens in SPMS
- Window 2-8 wk; mean 3 wk

Cotton et al., Neurology 2003;60:640-646

MS & Gadolinium: Optimization

T1-non  T1-gad immediate T1-gad 5-min delay

Gadolinium MRI in MS

The Open Ring Sign

-52 y.o. MS patient in relapse
Evolution of T1-hypointense Lesions

Baseline
T1 non-contrast

T1 post-gadolinium

1 month
2 month

Bakshi et al., NeuroRx 2005;2:277-303

Persistent T1 black holes in MS

baseline
12 months


MRI of acute spinal MS

FSE-T2
T1-gad

Bakshi et al., Neurology 2004;63(Suppl 5):S3-S11

MRI of acute spinal MS

FSE-T2
T1-gad

Bakshi et al., Neurology 2004;63(Suppl 5):S3-S11

Non MS Acute Myelitis

T2

T2

Bakshi et al., Eur J Neuro 1998; 5:35-48

Acute Optic Neuritis
Enhanced fatsuppressed MRI

T1-non
T1-gad

Bakshi & Ketonen, Baker/Joynt's Clinical Neurology, 2004
MRI findings in MS

Differential diagnosis

- Related inflammatory/demyelination
  - Devic, Balo
  - Acute disseminated encephalomyelitis
- Vascular ischemic disease, vasculitis
- Autoimmune/collagen vascular disease
- Aging, perivascular spaces
- Infection, sarcoid
- Trauma, toxin, metabolic

Fatal ADEM: 51 yo W post-URI

Fatal ADEM: 51 yo W post-URI

Cerebral autosomal dominant arteriopathy with subcortical infarcts & leukoencephalopathy (CADASIL)

Benign or MS?

Lupus Cerebritis
**Sjögren’s syndrome**

Morgen et al., *Semin Arthritis Rheum* 2004;34:623-30

**LYME OF THE BRAIN**

- Lesions difficult to distinguish from MS


**Whipple’s Disease**

Duprez et al., *AJNR* 17:1589, 1996

**Vitamin B₁₂ deficiency**

Pre-Rx

8 wk

4 yr

Stoparčević et al., *Neurology* 1997

**Brain atrophy in MS**

Neema et al., *Neurotherapeutics* 2007;4:602-617

**Brain Atrophy in MS**

*MRI over 7 years in an untreated patient*

The MS Collaborative Research Group
Serial FLAIR-MRI: findings?

3/00
EDSS 1.0
BPF 0.88

9/01
EDSS 4.0
BPF 0.84

Gray vs. white matter atrophy in MS

GM vs. WM Brain Atrophy

Sanfilipo et al., Neuroimage 2005;26:1068–77

Regional brain atrophy in MS: 3T MRI
Early RRMS vs. normal controls

Voxel-based morphometry study from 3T MRI scans
Caudate and thalamus were the only GM structures showing atrophy in MS

Thalamic atrophy related to cognition in MS

Houtchens et al., Neurology 2007;69:1213-23
Comparison of the reconstructed brain cortical surface. Significant thinning (< 2 mm) is shown in green, while red represents cortical areas > 2 mm. Marked cortical thinning is seen in various areas including the sensorimotor cortex (arrow) in MS.

The AS method is highly reproducible (n=60)

\[
\text{COV} = \left( \frac{\text{SD}}{\text{mean}} \right) \times 100\%
\]

<table>
<thead>
<tr>
<th>Method</th>
<th>Intra-Observer</th>
<th>Inter-Observer</th>
</tr>
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<tbody>
<tr>
<td>Losseff method C2-3</td>
<td>2.15 %</td>
<td>7.95 %</td>
</tr>
<tr>
<td>AS method C2-3</td>
<td>0.59 %</td>
<td>1.36 %</td>
</tr>
<tr>
<td>AS method C2-C5</td>
<td>0.44 %</td>
<td>1.07 %</td>
</tr>
</tbody>
</table>

Spinal cord atrophy in SP MS

\[ p < 0.001^* \]
\[ (*\text{SP vs. NC or RR}) \]

<table>
<thead>
<tr>
<th>Normal controls</th>
<th>RR</th>
<th>SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean C2-C5 normalized area (mm²)</td>
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</table>

Whole spinal cord volume

Operator time = 5 minutes

Kim et al. Eur J Radiol (in revision)

Uncoupling of brain & cord MS damage

<table>
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<tr>
<th>Spinal cord MRI Measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume measures*</td>
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<tr>
<td>Lesion measures</td>
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<tr>
<td></td>
</tr>
<tr>
<td>C2-C3</td>
</tr>
<tr>
<td>Caudal</td>
</tr>
<tr>
<td>Thoracic</td>
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<tr>
<td>Thoracic</td>
<td></td>
</tr>
<tr>
<td>Whole cord</td>
<td></td>
</tr>
</tbody>
</table>

*SP = status post; RR = relapsing-remitting; RR = relapsing-remitting; RR = relapsing-remitting; RR = relapsing-remitting.
**Gray matter hypometabolism in MS**

- MS (n=25) vs. NL
- 9% whole brain hypometabolism
- Across all 20 ROIs
  - Cerebral cortex
  - Basal ganglia
  - Thalamus
- Range 3%-18%

Bakshi et al., J Neuroimaging 1998; 8:228-234

**Cortical Lesions in MS**

- FLAIR
- T2WI

Bakshi et al., Arch Neurol, 2001; 58:742

**Double Inversion Recovery MRI**

Cortical lesions in MS

- T2
- FLAIR
- DIR

Guerts et al., Radiology 2005; 236:254–260

**Subtraction Imaging**

Baseline Follow-up Subtraction

Duan et al., AJNR 2008; 29:340-6

**MS Cortical lesions: Neuropathology**

- Type I
  - WM + Cortex
- Type II
  - Cortex, perivascular
- Type III/IV
  - Pial/subpial

Peterson et al., Ann Neurol 2001; 50:389–400

- Orange=cortical plaque
- Green=WM plaque
- Blue=deep GM plaque

Kutzelnigg et al., Brain 2005; 128:2705–2712
T2 hypointensity in gray matter

Bakshi et al., Arch Neurol 2002;59:62-68

T2 hypointensity and disability

Follow-up scan: T2 intensity putamen 0.51; thalamus 0.48
Follow-up scan: T2 intensity putamen 0.42; thalamus 0.44

Neema et al., J Neuroimaging 2009;19:3-8

T2 hypointensity and disability

46 y.o. stable MS
49 y.o. progressive MS

EDSS 2 ➔ 1.5 (3.2y)
Follow-up scan: T2 intensity putamen 0.51; thalamus 0.48

EDSS 1 ➔ 3.5 (3.5y)
Follow-up scan: T2 intensity putamen 0.42; thalamus 0.44

Neema et al., J Neuroimaging 2009;19:3-8

MRI T1 shortening in MS lesions

• Cause?
  • Iron or other metal
  • Calcium
  • Melanin
  • Free radicals
  • Lipid-laden macrophages
  • Proteinaceous substance

Janardhan et al., Radiology 2007;244:823-31

MRI T1 shortening in MS lesions

• Cause?
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Janardhan et al., Radiology 2007;244:823-31

Thalamic atrophy is related to WM damage in MS

DGM area | WM region | P-value
--- | --- | ---
Left thalamus | Central peduncle | 0.01
Right caudate | External capsule | 0.01
Right thalamus | Posterior corona radiata | 0.02
Right thalamus | External capsule | 0.04
Right thalamus | Cingulum | 0.01
Right thalamus | Superior longitudinal fasciculus | 0.03

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Evolution of WM tract damage over 1y

• 25 mildly-disabled MS pts; 9 normal controls; 3T DTI
• Over 1y: Decreasing FA (yellow-red) in WM tracts (overlaid on the green FA skeleton) in MS vs. NC
• Thalamic volume at baseline linked to on-study decreasing FA in the corpus callosum (p<0.05)

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Longitudinal change in MRDSS (n=84)

<table>
<thead>
<tr>
<th>MRI:</th>
<th>Baseline</th>
<th>3 years</th>
<th>Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRDSS</td>
<td>4.8 ± 2.5</td>
<td>5.5 ± 2.3</td>
<td>0.64 ± 0.8</td>
<td>1.5 x 10^{-10}</td>
</tr>
<tr>
<td>BPF</td>
<td>0.83 ± 0.05</td>
<td>0.82 ± 0.05</td>
<td>-0.01 ± 0.02</td>
<td>8.8 x 10^{-5}</td>
</tr>
<tr>
<td>T2</td>
<td>6.9 ± 5.5</td>
<td>7.2 ± 6.2</td>
<td>0.3 ± 2.6</td>
<td>0.31</td>
</tr>
<tr>
<td>T1/T2</td>
<td>0.15 ± 0.2</td>
<td>0.2 ± 0.2</td>
<td>0.06 ± 0.1</td>
<td>1.6 x 10^{-6}</td>
</tr>
</tbody>
</table>

Key: MRDSS=Magnetic Resonance Disease Severity Scale; BPF=brain parenchymal fraction; T2=T2 hyperintense lesion volume; T1=T1 hypointense lesion volume; values are mean±SD

MRI-defined phenotypes in MS

- Type I (low lesions/ mild atrophy)
- Type II (high lesions/ mild atrophy)
- Type III (low lesions/ high atrophy)
- Type IV (high lesions/ high atrophy)

The majority of patients (phenotypes I, II and III) showed clinical-MRI paradox & dissociation between lesions and brain atrophy

MS brain hyperintensities: 1.5T vs. 3T

MS brain hyperintensities: 1.5T vs. 3T

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>1.5T FLAIR</th>
<th>3T FLAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASAT Time</td>
<td>-0.37</td>
<td>0.09</td>
</tr>
<tr>
<td>COWAT Time</td>
<td>-0.28</td>
<td>0.21</td>
</tr>
<tr>
<td>BVMT TL</td>
<td>-0.40</td>
<td>0.06</td>
</tr>
<tr>
<td>BVMT TL</td>
<td>-0.41</td>
<td>0.06</td>
</tr>
<tr>
<td>FLO</td>
<td>-0.31</td>
<td>0.41</td>
</tr>
<tr>
<td>SDMT</td>
<td>-0.49</td>
<td>0.02*</td>
</tr>
<tr>
<td>CVLT TL</td>
<td>-0.32</td>
<td>0.32</td>
</tr>
<tr>
<td>CVLT TL</td>
<td>-0.34</td>
<td>0.03*</td>
</tr>
<tr>
<td>DKEFS</td>
<td>-0.26</td>
<td>0.42</td>
</tr>
<tr>
<td>DKEFS DR</td>
<td>-0.42</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Key: r = Spearman partial correlation coefficient controlling for age and depression. FLAIR = Fluid-attenuated inversion recovery/hyperintense lesion volume; PASAT=Paired Auditory Serial Addition Test; 2 and 3 second delay; COWAT=Controlled Oral Word Association Test; BVMT=Boston Visual Memory Test (BVRT), FLO=Digit Symbol Digit Modalities Test; CVLT=California Verbal Learning Test (TL=total recall, DR=delayed recall), DKEFS=Delayed Recalls, DKEFS=Delay Kaplan McComas test (CS=total confirmed correct recall, DS=total confirmed correct delay), *indicates p<.05 statistical significance.
Detecting MS Spinal Cord Lesions: 1.5T vs. 3T


MS Lesions: 7T

Dr. F. Bagnato

MS Lesions: 8T

Kottil Rommohan et al.

Use of MRI for routine MS care

• Brain MRI
  • T1/T2/FL ax, FL sag, T1-Gd sag/ax
• Spinal cord MRI
  • T1/T2-SE sag, T2-SE ax, T1-Gd sag
• For diagnosis and annually in active patients
• More often in CIS
• Less often in stable patients
• MRS, MTI, DWI not for routine care


Conclusions

• MRI is a powerful tool for diagnosing MS
• MRI is a valuable marker of biologic disease activity and disease severity
• Worsening of MRI findings even if clinically silent probably impacts on long term clinical outcomes
• MRI technology continues to unfold and requires validation

MRI in multiple sclerosis

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