MRI as a Measure of MS Disease Activity and Therapy

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Why Use MRI?

- Direct and Non-invasive Monitoring of Pathology \textit{in vivo}
- Greater “Activity” per Time Compared to Clinical Measures
Relapsing-remitting

Secondary-progressive

Preclinical

Disability

Relapses and Impairment

MRI Activity

Clinical Threshold

Time
Relapses = Acute Inflammatory Lesions = Gadolinium Enhancement

New Inflammatory MS Lesions Have Blood-Brain Barrier Leakage Seen as Gd-enhancing Lesions

Relapses = Acute Inflammatory Lesions = Gadolinium Enhancement

Acute Optic Neuritis: >95% Optic Neuritis Cases Show Gadolinium-enhancement

Hickman et al. J Neurol 2004
Why Use MRI?

- Direct and Non-invasive Monitoring of Pathology *in vivo*
- Greater “Activity” per Time Compared to Clinical Measures
- Some Relationship to Clinical Measures, Especially Over Long Intervals
Time

Relapsing
- remitting

Secondary
- progressive

Preclinical

Relapsing-remitting

Secondary-progressive

MRI Activity

MRI Burden of Disease

Measures of Brain Volume

Disability

Time

Relapses and Impairment

Measures of Brain Volume

MRI Activity

MRI Burden of Disease
Histopathologic Correlates of Black Holes

*T1 Hypointensity Directly Correlates to Degree of Axonal Loss*

Van Waesberghe et al. Ann Neurol
McDonald MRI Criteria 2001

Gd-enhancing  
T2-hyperintense  
Infratentorial

Juxtacortical  
Periventricular  
Spinal Cord

McDonald et al. Ann Neurol 2001
MRI in Monitoring the Clinical Course and Treatment Outcome
MRI in Monitoring the Clinical Course and Treatment Outcome

- **Relapses:**
  - New T2/Gd-enhancing Lesions

- **Disability:**
  - T2 Number/Volume
  - Atrophy
  - Optical Coherence Tomography

- **Repair/ Remyelination**
  - MTR: Remyelination
MRI in Monitoring the Clinical Course and Treatment Outcome

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Relapses = Acute Inflammatory Lesions = Gadolinium Enhancement

New Inflammatory MS Lesions Have Blood-Brain Barrier Leakage Seen as Gd-enhancing Lesions

Clinical Course in MS

- **Relapsing-remitting**
  - Disability over time

- **Primary-progressive**
  - Disability over time

- **Secondary-progressive**
  - Disability over time

- **Progressive-relapsing**
  - Disability over time

*Lublin et al. Neurology 1996*
McDonald MRI Criteria for MS in Patients with Single Clinical Episode

Dissemination in Space – Three of the Following:

- One Gd-enhancing lesion or 9 hyperintense lesions if no Gd-enhancing lesion
- At least 1 infratentorial lesions
- At least 1 juxtacortical lesions
- Three or more periventricular lesion

- Spinal cord lesion equivalent to brain infratentorial lesion
- Gd+ cord lesions equivalent to Gd+ brain lesion
- T2 cord lesions can contribute to total R2 lesion count

Polman et al. Ann Neurol 2005
McDonald MRI Criteria for MS in Patients with Single Clinical Episode

Two Ways to Show Dissemination in Time:

- Gd-enhancing lesion at least 3 months after onset of attack, not at the site of initial clinical event
- New T2 lesion at any time compared to MRI done at least 30 days after onset of initial clinical event

Polman et al. Ann Neurol 2005
Application of New Diagnostic Criteria

Polman et al. Ann Neurol 2005
2005 McDonald Criteria: CIS patients with two scans analysed for MRI dissemination in space (DIS) and time (DIT)

Conversion free survival predicted by 2005 criteria

Hazard ratios compared to neither DIS nor DIT adjusted for gender, site, type of CIS and treatment

Magnims Collaboration (282 patients)
MRI in Monitoring the Clinical Course and Treatment Outcome

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Presence of MRI Lesions Predict the Development of MS

ONTT: Optic Neuritis Treatment Trial

*Number of lesions present at baseline

The exact relationship between MRI findings and the clinical status of patients is unknown

Arch Neurol 1993
Predictive Value of Baseline MRI in Monosymptomatic Patients: 10 Year Follow-up

<table>
<thead>
<tr>
<th>Asymptomatic lesions detected on MRI at baseline</th>
<th>0</th>
<th>1</th>
<th>2-3</th>
<th>4-10</th>
<th>&gt;10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>27</td>
<td>3</td>
<td>16</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Progression to CDMS</td>
<td>3 (11%)</td>
<td>1</td>
<td>14 (87%)</td>
<td>13 (87%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>EDSS &gt; 3</td>
<td>0</td>
<td>0</td>
<td>5 (31%)</td>
<td>4 (27%)</td>
<td>14 (75%)</td>
</tr>
<tr>
<td>EDSS &gt; 5.5</td>
<td>1</td>
<td>0</td>
<td>2 (13%)</td>
<td>3 (20%)</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

Correlation between EDSS and lesion number
0-5 yrs $r = 0.45$, $p = <0.0001$  
5-10 yrs $r = 0.29$, $p = 0.03$

O’Riordan et al. Brain
Number of Asymptomatic MRI Lesions At Baseline Predict Long Term Disability

Brex et al. NEJM 2002
## 20 Year CIS Follow-up (91 patients)

<table>
<thead>
<tr>
<th></th>
<th>Abnormal scan (Baseline)</th>
<th>Normal scan (Baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>60</td>
<td>31</td>
</tr>
<tr>
<td><strong>Number of patients who developed CDMS</strong></td>
<td>52 (87%)</td>
<td>6 (19%)</td>
</tr>
<tr>
<td><strong>EDSS≤3 (CDMS only)</strong></td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td><strong>EDSS≥6 (CDMS only)</strong></td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fisniku et al. 2008*
Baseline Lesion Number and Disability at 20 Years

<table>
<thead>
<tr>
<th></th>
<th>No. of brain T2 lesions at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 N=31</td>
</tr>
<tr>
<td></td>
<td>1-3 N=19</td>
</tr>
<tr>
<td></td>
<td>4-9 N=14</td>
</tr>
<tr>
<td></td>
<td>10+ N=27</td>
</tr>
<tr>
<td>CIS at 20 years</td>
<td>25 (81%)</td>
</tr>
<tr>
<td>CDMS at 20 years</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>EDSS ≥ 3 at 20 years</td>
<td>6 (19%)</td>
</tr>
<tr>
<td></td>
<td>17 (89%)</td>
</tr>
<tr>
<td></td>
<td>13 (93%)</td>
</tr>
<tr>
<td></td>
<td>22 (81%)</td>
</tr>
<tr>
<td>EDSS ≥ 6 at 20 years</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>9 (47%)</td>
</tr>
<tr>
<td></td>
<td>9 (64%)</td>
</tr>
<tr>
<td></td>
<td>19 (70%)</td>
</tr>
</tbody>
</table>

Fisniku et al. 2008
# Prognostic Value of T2 Lesion Volume in CIS: Five Year Follow-up

<table>
<thead>
<tr>
<th>MRI at presentation</th>
<th>Conversion to CDMS</th>
<th>EDSS &gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2/32 (6%)</td>
<td>0/32</td>
</tr>
<tr>
<td>Abn &lt;1.23 cc</td>
<td>17/31 (55%)</td>
<td>7/31 (32%)</td>
</tr>
<tr>
<td>Abn &gt;1.23 cc</td>
<td>19/21 (90%)</td>
<td>11/21 (52%)</td>
</tr>
</tbody>
</table>

*Filippi et al. Neurology*
The Importance of T2 Lesion Volume in Monitoring Disability Over the Long Term
Annulised T2 Lesion Volume Rate of Change in SPMS vs RR MS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Lesion growth</th>
<th>Bootstrap 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>31</td>
<td>0.7 cc/year</td>
<td>0.6, 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SPMS</td>
<td>18</td>
<td>2.2 cc/year</td>
<td>1.3, 3.1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Multilevel Gradient Analysis of Difference of Lesion Growth (SPMS-RRMS): +1.5 cc/year
MRI in Monitoring the Clinical Course and Treatment Outcome

- Relapses:
  - New T2/Gd-enhancing Lesions

- Disability:
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- Repair/ Remyelination
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Brain Atrophy in MS

1. Measures Global Consequences of Pathological Events (Lesions and Normal Appearing Tissue)
2. Axonal Loss is Likely to be Major Cause of Atrophy (45% of White Matter Bulk is Axons; 25% is Myelin)
3. But Tissue Volumes Are Influenced by Loss or Gain of Tissue Water, Glial or Vascular Elements
4. More Severe in SPMS
5. Sensitive and Reproducible Tools are Available to Measure Atrophy
Sample Sizes for Placebo Controlled Trial in RRMS Using Brain Atrophy as Primary Outcome Measure

<table>
<thead>
<tr>
<th>Trial duration</th>
<th>Measurement method</th>
<th>Treatment effect size (% reduction in atrophy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>1 year</td>
<td>BVD</td>
<td>3051</td>
</tr>
<tr>
<td></td>
<td>BBSI</td>
<td>314</td>
</tr>
<tr>
<td></td>
<td>SIENA</td>
<td>191</td>
</tr>
<tr>
<td></td>
<td>VE</td>
<td>269</td>
</tr>
<tr>
<td>2 years</td>
<td>BVD</td>
<td>763</td>
</tr>
<tr>
<td></td>
<td>BBSI</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>SIENA</td>
<td>123</td>
</tr>
<tr>
<td></td>
<td>VE</td>
<td>140</td>
</tr>
<tr>
<td>3 years</td>
<td>BVD</td>
<td>339</td>
</tr>
<tr>
<td></td>
<td>BBSI</td>
<td>128</td>
</tr>
<tr>
<td></td>
<td>SIENA</td>
<td>111</td>
</tr>
<tr>
<td></td>
<td>VE</td>
<td>114</td>
</tr>
</tbody>
</table>

Anderson et al. J Neurol 2008
Retinal Nerve Fibre Layer Imaging
Optical Coherence Tomography (OCT)

- Cross-sectional Imaging of Internal Tissue Microstructure by Measuring the Echo Time Delay of Backscattered Infrared Light
- Analogous to Ultrasound Imaging
Group OCT Data in Optic Neuritis vs Control

Tril et al. Ann Neurol 2005
Correlation of Inter-ocular Differences in FLAIR Optic Nerve Area and OCT RNFL Thickness Following Optic Neuritis

Mean 33% decrease in affected nerve

\[ R = 0.66, \ p < 0.001 \]

Mean 30% decrease in affected nerve
MRI in Monitoring the Clinical Course and Treatment Outcome

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Postmortem Studies of MTR and Myelin

- Post-mortem study of MTR in fresh brain slices from 20 patients with MS compared with axonal density and myelin content
- Remyelinated lesions have higher MTR than demyelinated lesions
- MTR correlated with myelin loss but not with axonal density

<table>
<thead>
<tr>
<th></th>
<th>MTR Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal appearing white matter</td>
<td>34.0 (±2.9)</td>
</tr>
<tr>
<td>Remyelinated lesions</td>
<td>30.0 (±2.9)*</td>
</tr>
<tr>
<td>Demyelinated lesions</td>
<td>23.8 (±4.3)*</td>
</tr>
</tbody>
</table>

Schmierer et al. Ann Neurol 2005
Remyelination (MTR) Can be Studied in the Brain or Optic Nerve

Central field VEP latency shorter by 6.1 ms (95% CI 1.5, 10.7, p = 0.012) per 1 pu rise in time-averaged diseased optic nerve MTR

Hickman et al 2004
Evaluating the Therapeutic Response

- Patient ➔ Self Report
- Physician ➔ Global Impression
- More Objective Data:
  - Clinical Features: Relapses and Disability
  - Biomarkers
  - MRI Metrics
MRI Assessment of Response to Therapy

- New Gd-enhancing lesions
- New T2 lesions
- Enlarging T2 lesions (BOD)
- New T1 hypointense lesions
- Enlarging T1 hypointense lesions
- Increased atrophy
MRI Burden Of Disease (Median)
4-Treatment Group, Years 1-4

Change in BOD, years 1-4 (%)

Plc/Rebif 22 mcg tiw: 9.7
Plc/Rebif 44 mcg tiw: 7.2
Rebif 22 mcg tiw: 3.4
Rebif 44 mcg tiw: -6.2

p = 0.003
p = 0.009

PRISMS Study Group. Neurology 2001
Monitoring of Treatment Outcome ub Patients Using Rebif 44 tiw from the start

Median % Change in BOD (PRISMS Long Term Follow Up population)

* Rebif 44 tiw vs Placebo/Rebif p=0.002
Conclusions

MRI is Useful in MS Because:

- Assessment of Pathology
- Sensitivity in detecting clinical activity
- Correlation with relapses
- Correlation with EDSS
- Predictive value
- Treatment effect