MR imaging of chronic inflammation in multiple sclerosis

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Funding: Intramural Research Program of NINDS, NIH
NMSS grant award #FG 2093-A-1
MS treatments reduce the number of new enhancing lesions
MR imaging biomarkers of inflammation

- Acute inflammation
  - BBB opening
- Chronic inflammation
  - BBB closed

- Plaque-level
- Leptomeninges
Pathological staging of MS lesions

- Active
  - MRI Gadolinium-enhancing lesions
- Relapsing MS
  - No or low disability
- Progressive MS
  - Disability accrual
- Disease duration, years
- Percent of plaques
- Early active
- Late active
- Smoldering
- Inactive
- Shadow

adapted from Frischer et al., Ann Neurol 2015
Susceptibility-based 7T MRI

LFB-PAS
Myelin

DAB-Turnbull
Iron

adapted from Dal-Bianco et al., Acta Neuropathol 2016

Chronic active

Chronic inactive
Paramagnetic rim on susceptibility-based 7T MRI

Postcontrast T1-MPRAGE

7T Phase 200 μm resolution

Absinta et al., Ann Neurol 2013
Absinta et al., JCI 2016
### Transition to persistent chronic inflammation

<table>
<thead>
<tr>
<th></th>
<th>Centrifugal Baseline</th>
<th>Centripetal Month 1</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Month 18</th>
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<tbody>
<tr>
<td><strong>Postcontrast T1-MPRAGE</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td><strong>7T Phase</strong></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
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Absinta et al., JCI 2016
Different scenarios of lesion evolution and propensity to repair @ 7T MRI

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>In vivo BBB breakdown</th>
<th>In vivo BBB restored</th>
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<tbody>
<tr>
<td>A. Centrifugal lesion</td>
<td></td>
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<tr>
<td>B. Transient rim following shift from centrifugal to centripetal lesion</td>
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<tr>
<td>C. Persistent rim following shift from centrifugal to centripetal lesion</td>
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LEGEND

- Centrifugal DCE pattern
- Centripetal DCE pattern
- Paramagnetic rim
- Lesion volume
- Lesion T1-hypointensity

Absinta et al., JCI 2016
MS lesions with vs. without rim: dichotomy in longitudinal evolution

Adjusted log lesion volume

Patient age

7T MRI
rim @7T
no rim @7T
Take-home messages

✧ Chronic active lesions can be seen on high-resolution MRI

✧ In newly forming MS lesions, chronic inflammation develops within the first 3 months and marks the failure of early lesion repair.
MR imaging of chronic inflammation in multiple sclerosis

Chronic inflammation

- Plaque-level
- Leptomeningeal compartment
Focal leptomeningeal enhancement (LME) on postcontrast 3D T2-FLAIR

299 MS patients
>> progressive MS cases

MS cases with vs. without LME:
↑ disability, age, disease duration
↓ brain and cortical volumes

No association of LME with:
• enhancing WM lesions
• total WM lesion volume
• disease-modifying treatments

Absinta, Vuolo et al., Neurology 2015
LME discloses leptomeningeal inflammation

- Leptomeningeal inflammatory infiltrate (lymphocytes and monocytes)
- Subpial cortical demyelination

Absinta, Vuolo et al., Neurology 2015
Figure 3: Odds ratios of leptomeningeal enhancement in disease groups compared to healthy controls.

- OIND
- HTLV
- HIV
- NIND
- 299 MS

254 patients

HTLV = human T-lymphotropic virus; MS = multiple sclerosis; NIND = noninflammatory/infectious neurologic diseases; OIND = other inflammatory/infectious neurologic diseases.
Take-home messages

✧ Blood-meningeal barrier impairment due to meningeal inflammation can be visualized on high-res MRI

✧ LME and susceptibility rim are novel imaging biomarkers for chronic inflammation and might help patient selection and stratification

✧ Current disease-modifying treatments are not completely effective on chronic inflammation--> new therapeutic targets
Acknowledgments

Daniel S. Reich’s lab, NINDS, NIH
Govind Nair, Pascal Sati, Matthew Schindler, Eric Beck, Nick Luciano, Nate Lee, Seung Kwon Ha, Jennifer Lefeuvre, Roger Depaz, Kevin Terashima, Kartiga Selvaganesan, Manori De Alwis

Neuroimmunology Clinic, NINDS, NIH
Irene Cortese, Joan Ohayon, Francis Andrada and all clinical fellows

7T FMRIIF staff, NIH

Our patients and their families for their willingness to participate in organ donation for biomedical research

MS
National Multiple Sclerosis Society

NIH National Institute of Neurological Disorders and Stroke