Clinical Guidelines:
Ongoing Monitoring of MS Patients with MRI

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- Participated in scientific advisory boards for Biogen, Novartis, and Genzyme
- Received research support from Biogen and Novartis (paid directly to the institution)
Outline

- Introduction
- Baseline studies for patients with clinically isolated syndrome (CIS) and/or suspected multiple sclerosis (MS)
- Timing of follow-up brain MRI for patients with CIS and/or suspected MS (evidence of dissemination in time)
- Timing of brain MRI for patients with established MS
- Timing of brain MRI for progressive multifocal leukoencephalopathy (PML) surveillance
- Clinical requisition and radiology report
- Conclusions

Introduction

- The 2010 revised McDonald diagnostic criteria for MS allows for an earlier diagnosis of MS after a single CIS attack
- New MRI activity occurs more frequently than new clinical relapses
- MRI is increasingly being used to assess for subclinical disease activity and to monitor response to therapy
- Early MRI activity (contrast enhancing lesions and T2 lesions) is associated with future disability
- Consensus guidelines for monitoring CIS (low and high risk) and established MS are needed
**Evolution of MS**

<table>
<thead>
<tr>
<th>Preclinical RIS</th>
<th>CIS</th>
<th>Relapsing-Remitting</th>
<th>Secondary Progressive Primary Progressive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ???</td>
<td></td>
<td>Age ~10–40</td>
<td>Age ~&gt;40</td>
</tr>
</tbody>
</table>

- **Clinical Course**
- **Brain Volume**
- **Lesion Load**
- **Contrast enhancing/new MS lesions**

**Inflammation/Response to Current Therapy**

**Neurodegeneration?**

**Mitochondrial Dysfunction vs Compartmentalized IR**

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**Recommended Baseline Studies for CIS and/or Suspected MS**

- **Brain MRI protocol with gadolinium**

- **Spinal cord MRI if transverse myelitis (PTM vs. LETM), insufficient features on brain MRI to support diagnosis of MS, or age >40 with non-specific brain MRI findings**

- **A cervical spine MRI performed with baseline brain MRI in patients with or without transverse myelitis may help reduce the number of subsequent MRIs**

- **Orbital MRI if severe optic neuritis with poor recovery**

*PTM= partial transverse myelitis; LETM= longitudinally extensive transverse myelitis
Traboulsee A, et al. AJNR 2015 (in press).*
**Recommended Timing of a Follow-Up Brain MRI for CIS and/or Suspected MS**

- **Low risk CIS** (i.e., normal brain MRI) or uncertain clinical syndrome with suspicious brain MRI features or incidental MRI findings (i.e., RIS): 12-24 months

- **High risk CIS** (i.e., ≥2 ovoid lesions on first MRI): 6-12 months

- Low and high risk CIS: at the time of development of new symptoms consistent with demyelination

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**Low-Risk and High-Risk CIS**

- **Brain MRI with suspicious lesions?**
  - **NO**
  - **YES**

  **Low-risk CIS**
  - Watchful waiting
  - Recommend close monitoring with serial MRIs

  **High-risk CIS**
  - Strongly consider initiation of MS disease-modifying treatment

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RIS= radiologically isolated syndrome

## Risk of MS after CIS

<table>
<thead>
<tr>
<th>Study</th>
<th>MS risk with normal brain MRI</th>
<th>MS risk with abnormal brain MRI</th>
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</thead>
<tbody>
<tr>
<td>Optic Neuritis Treatment Trial&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>• 1.6% at 5 years</td>
<td>1 or more lesions:</td>
</tr>
<tr>
<td></td>
<td>• 2.3% at 10 years</td>
<td>• 4.2% at 5 years</td>
</tr>
<tr>
<td></td>
<td>• 2.5% at 25 years</td>
<td>• 5.6% at 10 years</td>
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<tr>
<td></td>
<td></td>
<td>• 7.2% at 15 years (60% with 1 lesion, 68% with 2 lesions, 78% with &gt;3 lesions)</td>
</tr>
<tr>
<td>Any CIS, London cohort&lt;sup&gt;5-8&lt;/sup&gt;</td>
<td>• 3% at 5 years</td>
<td>3 or more lesions:</td>
</tr>
<tr>
<td></td>
<td>• 11% at 10 years</td>
<td>• 65% at 5 years (54% with 1-3 lesions, 85% with 5 or more lesions)</td>
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<tr>
<td></td>
<td>• 19% at 14 years</td>
<td>• 83% at 10 years</td>
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<tr>
<td></td>
<td>• 21% at 20 years</td>
<td>• 88% at 14 years</td>
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<tr>
<td></td>
<td></td>
<td>• 82% at 20 years</td>
</tr>
<tr>
<td>Acute Transverse Myelitis&lt;sup&gt;9-11&lt;/sup&gt;</td>
<td>• 26% at 3 years</td>
<td>At least 1 brain lesion:</td>
</tr>
<tr>
<td></td>
<td>• 29% at 5 years</td>
<td>• 54% at 3 years</td>
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<tr>
<td></td>
<td></td>
<td>• 92% at 8 years (if OCBs present)</td>
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## Radiologically Isolated Syndrome: 5-year Risk for an Initial Clinical Event

- Retrospective review of 451 RIS cases from 5 countries
- Clinical events occurred in 34% of cases within 5-years of first MRI
- Age <37 years old, male, and spinal cord involvement were most important predictors of symptom onset
- Asymptomatic spine lesions were the strongest predictor of future clinical events

**Recommended Timing of Brain MRI for Established MS**

- No recent prior imaging available (i.e., patient with MS transferring to a new clinic) or poor quality MRI
- Postpartum to establish a new baseline
- Unexpected clinical deterioration
- Reassessment of original diagnosis


**Recommended Timing of Brain MRI for Established MS (Round 2)**

- Prior to starting or switching disease modifying therapy
- Approximately 6 months after switching DMT to establish a new baseline on the new therapy
- Every 1-2 years while on DMT to assess for subclinical disease activity (annually for at least the first few years)

DMT = disease modifying therapy
**One-Year MRI Scan Predicts Clinical Response to Interferon-β in MS**

Patients with *subclinical disease activity* were at greatest risk for disability progression (≥1 point in the EDSS):

⇒ 1 new lesion; HR 15.1
⇒ 2 new lesions; HR 38.8
⇒ 3 or more lesions; HR 44.6

Responders: White
Poor Responders: Checkerboard

HR = hazard ratio.

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**Early MRI Activity on Interferon Predicts Poor Long-Term Outcome**

**ASSURANCE Study**

(15-year follow-up of IM interferon β-1a) — Results:

MRI activity and relapses predicted future disability in patients treated with interferon-β

ASSURANCE = Assessment of Drug Utilization, Early Treatment, and Clinical Outcomes;
IM = intramuscular.
Recommended Timing of Brain MRI for Established MS (Round 3)

- More frequent surveillance may be indicated in aggressive cases or atypical MRI lesions (i.e., tumefactive lesions)

- Fewer MRI scans in later stages of relapsing disease (SPMS), or in PPMS because MRI activity is less and no effective treatment exist

- Routine spinal cord follow-up not required unless:
  1) recurrent transverse myelitis
  2) significant clinical worsening with few changes on brain MRI
  3) rule out alternative cause for progressive myelopathy

SPMS = secondary progressive MS; PPMS = primary progressive MS
Recommended Timing of PML Surveillance Brain MRI While on Nataluzimab

- Serum JC virus antibody negative: every 12 months
- Serum JC virus antibody positive patients and > 18 months on nataluzimab: every 3-6 months
- Any new or worsening symptoms should prompt urgent MRI

**Brain MRI protocol for monitoring patients on disease modifying therapies includes the PML surveillance sequences.**


PML on Axial FLAIR Sequence

**FLAIR = fluid attenuated inversion recovery**
The Clinical Requisition for MRI

- Request the CMSC standardized brain and/or spine MRI protocol
- Indicate purpose of study:
  - Diagnostic study for CIS or MS
  - Treatment monitoring study (indicate if on disease modifying therapy)
  - PML surveillance study (indicate if high or low risk)
  - Unexpected clinical decline
  - Reassessment of diagnosis
- Date and location of most recent MRI study


The Radiology Report

For a diagnostic MS study:
- Number of gadolinium enhancing T1 lesions
- Compare with previous studies for number of new T2 lesions
- Presence/absence of juxtacortical, periventricular, infratentorial or spine lesions
- Report should avoid statements like “McDonald diagnostic criteria met”
- The interpretation should indicate if findings are typical, atypical, or not consistent with MS, and provide a differential diagnosis if appropriate

For a follow-up MS study:
- Number of gadolinium enhancing T1 lesion
- Compare with previous studies for number of new T2 lesions
- Overall T2 lesion burden severity (e.g. mild, moderate, severe)
- Comparison with previous studies for overall worsening of T2 lesion burden and atrophy

**Radiology report should use standardized terminology and MRI studies stored in DICOM format**

Radiology Report for a PML Surveillance Study

- Comparison with previous studies for new T2 lesions and hyperintense lesions on diffusion weighted imaging
- Presence of suspicious features for PML

Conclusions

- MRI is the most sensitive tool currently available for monitoring inflammatory disease activity in MS
- MRI is useful for supporting a diagnosis of MS and can help predict disease modifying therapy treatment response or failure
- Subclinical disease activity needs to be monitored over time especially early on in MS
- If new lesions are present on surveillance scans especially in conjunction with clinical deterioration (relapsing or progressive subtypes) one needs to re-evaluate treatment strategies
- Increased surveillance MRI monitoring recommended in certain circumstances (untreated CIS, JCV antibody positive, unusual lesion type, aggressive MS)