MS ECHO:
White Spots on the Brain:
Common MS Mimics

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Conflicts of Interest

• Dr. McCarthy has no conflicts of interest to disclose
Objectives

• Review imaging criteria for MS diagnosis
• Review common alternatives to MS diagnosis for “White Spots on the Brain”
• Discuss cases of non-demyelinating diagnosis based on MRI “Red-Flag” criteria
What is not discussed today

- Clinical criteria or clinical RED-FLAGs for MS diagnosis
- Variants of MS and other demyelinating disorders
How common are “White Spots” or Unidentified Bright Objects (UBOs)?

Prevalence of White Matter Lesions in Asymptomatic Patients¹,²

- **11%** by age 40
- **84%** by age 70

¹ Cutrer and Black, Headache 2006.
MS Radiographic Diagnostic Criteria

1) Dissemination in Space
   2+ lesions in 2+ locations
   including periventricular, juxtacortical, infratentorial and spinal cord
   AND

2) Dissemination in Time
   New T2 lesion on follow-up  OR  Asymptomatic
   enhancing lesion and non-enhancing T2 lesion
   AND

3) ...??...
1) **Dissemination in Space**
   2+ lesions in 2+ locations
   including periventricular, juxtacortical, infratentorial and spinal cord

   **AND**

2) **Dissemination in Time**
   New T2 lesion on follow-up  OR  Asymptomatic enhancing lesion and non-enhancing T2 lesion

   **AND**

3) “No other diagnosis better explains the patient’s findings”

*Polman et. al. Ann Neurol 2011*
How can we be sure of the diagnosis of MS vs. Not-MS?
What Makes “White Spots” More Likely Multiple Sclerosis

Ovoid Lesions >3mm
Many Lesions (>=9) or Enhancing Lesions
Juxtacortical Lesions
(and infratentorial and spinal lesions)

Haselink. Top Mag Reson Imaging. 2006
What Makes “White Spots” More Likely Multiple Sclerosis

Corpus Callosum Involvement

Haselink. Top Mag Reson Imaging. 2006
What Makes “White Spots” More Likely Multiple Sclerosis

Perpendicular lesions to the Corpus Callosum (“Dawson’s Fingers”)
What Makes “White Spots” More Likely Multiple Sclerosis

Ovoid Lesions $\geq 3$mm in size$^1$
Many lesions ($\geq 9$) OR enhancing lesions$^1$
Not only periventricular lesions$^1$
Corpus Collosum involvement$^2$
Perpendicular lesions to CC (“Dawson’s Fingers”)$^2$

$^2$Charil et al. Lancet Neuro 2006
## What else could it be?

### Multiple Sclerosis Differential Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Autoimmune</th>
<th>Infectious</th>
<th>Genetic</th>
<th>Other</th>
</tr>
</thead>
</table>
| **Neuro-Specific:** | - Multiple Sclerosis  
- Autoimmune Encephalitis  
- ADEM  
- Susac’s Syndrome  
- Hashimoto’s  
- CLIPPERS | HIV  
Lyme  
Syphilis  
PML  
Tuberculosis  
Neuro-cysticercosis  
Coccidiomycosis  
Cryptococcus  
Brucellosis  
SSPE  
HHV6  
Whipple’s Disease | CADASIL  
MELAS  
Neurofibromatosis  
Porphyria  
Friedrich’s Ataxia  
SCA | Neoplastic  
B12 Deficiency  
Copper Deficiency  
Thiamine Deficiency  
Vascular Malformations  
Medication Toxicity  
Hypoxic Ischemic Conditions  
Migraine Headache |
| **Systemic:** | - SLE  
- APS  
- Sjogren’s  
- Sarcoidosis  
- Behcet disease  
- Celiac disease  
- Paraneoplastic | | | |

**Adult Onset Leukodystrophy:**  
- Adreno-Leukodystrophy  
- Metachromatic  
- Alexander’s Disease  
- Krabbe’s Disease

<table>
<thead>
<tr>
<th></th>
<th>Neuro-Specific:</th>
<th>Infectious:</th>
<th>Genetic:</th>
<th>Other:</th>
</tr>
</thead>
</table>
| **Vascular:** | Stroke  
PAN  
Wegener’s  
Primary CNS Angiitis  
Moya-Moya Disease | | | |
| **Infiltrative:** | Langerhan’s Cell Histiocytosis  
Lymphomatoid Granulomatosis  
Erdheim-Chester Disease  
HLH | | | |
Common Differential Diagnosis of “White Spots” on MRI

- Migraine Headache
- Micro-vascular Disease
- Maco-vascular (Stroke)
- Idiopathic UBOs
Migraine Related T2 Lesions

How often do Migraine patients have UBOs?

Of those < 40 years old without CVD

– 29.4% vs. 11.2% of age-matched controls\(^1\)
– Typically periventricular or frontal
– No correlation with frequency/severity of HA

Igarashi et al. Cephalalgia 1991
### How to differentiate Micro-Vascular Disease from Multiple Sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Micro-Vascular Disease</th>
<th>Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td>Increases with age</td>
<td>Rare onset &gt;50 years old</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Increased lesions over time</td>
<td>Increased lesions over time</td>
</tr>
<tr>
<td><strong>Corpus Callosum</strong></td>
<td>Spares</td>
<td>Typically Involved</td>
</tr>
<tr>
<td><strong>Juxtacortical U-fibers</strong></td>
<td>Spares</td>
<td>Commonly Involved</td>
</tr>
<tr>
<td><strong>Hemorrhages</strong></td>
<td>Possible</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Restricted Diffusion</strong></td>
<td>Lacunar infarcts</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Symptom Onset</strong></td>
<td>Abrupt (Stroke)</td>
<td>Subacute</td>
</tr>
<tr>
<td><strong>Cardiovascular Disease Risk Factors</strong></td>
<td>High correlation</td>
<td>Slight correlation</td>
</tr>
<tr>
<td><strong>White matter involvement</strong></td>
<td>Fairly symmetric</td>
<td>Asymmetric</td>
</tr>
</tbody>
</table>
Frequency of Alternative Diagnosis in an MS Specialty Clinic

754 consecutive patients referred to an MS Center in the Netherlands:

67 % - MS or Probable MS (52% Definite, 15% Probable MS)
23 % - No Certain Diagnosis
7.7 % - Other Neurologic Disease
  • 2.2 % Ischemic Cerebrovascular Disease
  • 0.5 % Vasculitis
  • 0.4 % Multi-System Atrophy
1.3% - Other Demyelinating Disease

Nielsen et al. Ann Neurol 2005
Alternative “Red-Flag” Diagnosis

Many diseases fit the MS Diagnostic Criteria of dissemination in time and space. We must exclude “no better explanation”.

1Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease:

Red Flags

- Sparing of corpus callosum and cerebellum
- No enhancement
- Slight T1 hypointensity
- Areas of restricted diffusion
- Micro-hemorrhages

Haselink. Top Mag Reson Imaging. 2006

Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease: Micro-vascular Disease

Red Flags¹

- Sparing of corpus callosum and cerebellum
- No enhancement
- Slight T1 hypointensity
- Areas of restricted diffusion
- Micro-hemorrhages

¹Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease:

Red Flags\(^1\)
- Persistent enhancement
- All lesions enhance
- Meningeal enhancement
- Hydrocephalus

\(^1\)Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease: Neuro-Sarcoidosis

Red Flags\(^1\)
- Persistent enhancement
- All lesions enhance
- Meningeal enhancement
- Hydrocephalus

1Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease:

Red Flags$^1$
- Spare Corpus Callosum
- Spare juxtacortical U-fibers

Haselink. Top Mag Reson Imaging. 2006
Non-MS White Matter Disease: Hypoxia-Ischemia

Red Flags\(^1\)
- Spare Corpus Callosum
- Spare juxtacortical U-fibers

Haselink. Top Mag Reson Imaging. 2006
\(^1\)Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease:

Red Flags$^1$:
- Lacunar strokes and micro-hemorrhages
- Sparing Corpus Callosum
- Temporal pole and External capsule involvement

Schmahmann et al. Ann NY Acad Sci 2008

$^1$Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease: 
CADASIL

Red Flags\(^1\):
- Lacunar strokes and hemorrhages
- Sparing Corpus Callosum
- Temporal pole and External capsule involvement

\(^1\)Charil et al. Lancet Neuro 2006
Schmahmann et al. Ann NY Acad Sci 2008
Non-MS White Matter Disease:

Red Flags:\(^1\):
- Meningeal enhancement
- Brainstem Atrophy
- Infiltrating Brainstem Lesions

Zandi et al. J Neurol Neurosurg Psychiatry, 2007
Lee et al. Clinical Radiology, 2001

\(^1\)Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease: Neuro-Bechet’s

Red Flags:\footnote{Charil et al. Lancet Neuro 2006}:
- Meningeal enhancement
- Regional Brainstem Atrophy
- Large Infiltrating Brainstem Lesions
- Cerebral Venous Sinus Thrombosis

Zandi et al. J Neurol Neurosurg Psychiatry, 2007
Lee et al. Clinical Radiology, 2001
Non-MS White Matter Disease:

Red Flags¹:
- Symmetric confluent lesions
- Dentate Nucleus Involvement
- Posterior predominance (ALD)
- Anterior predominance (Alexander disease, Metochromatic)

¹Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease: Adult Onset Leukodystrophy (e.g., ALD)

Red Flags\(^1\):
- Symmetric confluent lesions
- Dentate Nucleus Involvement
- Posterior predominance (ALD)
- Anterior predominance (Alexander disease, Metachromatic)

Haselink. Top Mag Reson Imaging. 2006

\(^1\)Charil et al. Lancet Neuro 2006
Non-MS White Matter Disease:

Red Flags
- Punctate T2 lesions
- No enhancement
- No T1 hypointensity
- Subcortical and Periventricular
- No corpus callosum involvement

Cutrer and Black. Headache, 2006
Non-MS White Matter Disease: Migraine-Related UBOs

Red Flags
- Few scattered small T2 lesions
- No enhancement
- No T1 hypointensity
- Subcortical and periventricular only
- No corpus callosum involvement

Charil et al. Lancet Neurol 2006

Cutrer and Black. Headache, 2006
Take-home Points:
“White Spots on the Brain”

- Not always MS
- Dissemination in Time and Space not sufficient for MS diagnosis
- Must be confident in “alternatives less likely” for accurate MS diagnosis
- Look for absence of clinical and radiographic RED-FLAGS for accurate MS diagnosis
Gary Stobbe’s Case

- 33 yo female
- R optic neuritis 2005; B optic neuritis 2006
- Avonex – switched to Rebif after exacerbation
- Depression – switched to Copaxone
- 2008 – off meds for pregnancy; restarted Copaxone but several exacerbations; Betaseron – failed due to SE
- 11/2009 – started Tysabri
Dr. Stobbe’s case (cont.)

- 2009 – 2012 – stable, working full time
- EDSS – 4.0 (unsteady gait, LE weakness, spasticity, LE pain)
- JC Ab positive
- 4/2013 – pregnant, d/c’ed Tysabri
- 12/2013 – delivered healthy baby; pre-emptive pulse steroids administered after delivery
- 1/2014 – increased LE weakness – pulse steroids, Tysabri re-started
- 2/2014 – increased LE weakness, R facial numbness – MRI with new brain and spinal cord lesions (2 very small enhancing lesions, brain and T10-11); EDSS – 7.0
Dr. Stobbe’s case (cont.)

- 2014 – steady improvement; Tysabri continued (infusion #49, 5/2014)
- JC Ab index, 3/2014 – 3.05 (risk 1:117)
- 1/2015 – EDSS – 6.0; returns to work part-time
- 3/2015 – decides to d/c Tysabri – candidate for AHSCT, but insurance disapproves – chooses Gilenya over Lemtrada – monthly pulse steroids as “bridge”
- 6/3/15 – first dose Gilenya
Dr. Stobbe’s case (cont.)

- 6/18/15 – return from 5 day trip to Texas to visit father with ALS – worsening speech, swallow, thinking, and strength
  - UTI – treated; 3 days IV pulse steroids; urine organism resistant, 2nd course of Abx; trial of Ampyra

- 7/7/15 – still cognitive complaints, new R hand weakness, legs weaker; EDSS – 6.5
  - MRI – 3 new enhancing brain lesions, cord stable
Dr. Stobbe’s case (cont.)

- UTI persists – repeat Abx treatment, rest, hydrate, medical leave from work
- 7/19/15 – not improving, leg weakness worse and now having trouble even transferring due to arm weakness, EDSS – 8.0
  - Admitted to UWMC
  - MRI, 7/20 – multiple new enhancing lesions, including cervicomedullary junction, no change in cord
  - Plasma exchange x 7 treatments
  - Strength improving but still not at “pre-Texas baseline”
Dr. Stobbe’s case (cont.)

• What next?
  – Continue Gilenya
  – Switch to Lemtrada
  – Go back to Tysabri
  – Switch to alternative DMT
  – Start off-label immunosuppressant
  – Re-submit for AHSCT