Multiple sclerosis mimics: Diagnostic error and management decisions

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Mitchell Wallin, MD
Paralyzed Veterans Summit, Washington Harbor, MD
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Disclosures

• Dr. Rinker and Dr. Wallin have nothing to disclose relevant to the topics discussed in this talk
Learning objectives

1. Describe the current diagnostic criteria for multiple sclerosis (MS) and identify its interpretation in the clinical setting.

2. Recognize common and uncommon mimics of MS, especially those that may affect the spinal cord.

3. Through case discussions, explain how MS may present and evolve over time. Identify useful evaluation tools to identify patients with MS and those with a non-MS diagnosis.
Spectrum of diagnostic certainty

- Symptom-based
  - Bipolar disease
  - Depression
  - Fibromyalgia
  - Irritable bowel disease

- Criteria-based
  - Parkinson’s Disease
  - Alzheimer’s

- Tissue/lab based
  - SLE
  - Rheumatoid arthritis
  - Myasthenia gravis
  - NMO
  - Cancer

Multiple sclerosis

Confirmatory testing not available

Confirmatory testing available
Evolution of diagnostic criteria

- First consensus clinical definitions
- CSF as diagnostic study

Clinical-histological era

- Charcot
- Marburg
- Allison and Millar
- Broman
- Schumacher
- McAlpine, etc.
- Poser

MRI era

Disease severity

1860s 1950s 1960s 1980s 2000s

Complete affected population
# 2010 Revised McDonald MS Diagnostic Criteria

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT)*

<table>
<thead>
<tr>
<th>CLINICAL (ATTACKS)</th>
<th>LESIONS</th>
<th>ADDITIONAL CRITERIA TO MAKE DX</th>
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<tr>
<td>2 or more</td>
<td>Objective clinical evidence of ≥ 2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack</td>
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Implications of expanded diagnostic criteria

• Pros
  – Better grasp of disease natural history and spectrum of severity
  – Earlier diagnosis and treatment
  – Improved long-term prognosis (?)
  – Benefits in clinical research design

• Cons
  – False positives
  – Substitution of criteria over judgment (overuse of MRI)
  – Iatrogenic harm
Local women among many misdiagnosed with MS, lawsuit says

Dr. Gary Wise said his Vail practice while involved in disciplinary proceedings with the Colorado Medical Board. Two local women may be among many who say they were misdiagnosed with multiple sclerosis.

Singing River Hospital discontinues relationship with neurologist

Updated on November 18, 2016 at 3:17 PM, Posted on November 18, 2016 at 1:10 PM

Singing River Hospital (file photo/GulfLive.com)

By TYLER CARTER, tcarter@gal.com

PASCAGOULA, Miss. -- While circumstances remain unclear about a sudden parting of ways between Singing River Hospital and a neurologist whose office abruptly closed, the hospital said it relates to treatment of patients with Multiple Sclerosis.
Consequences of misdiagnosis

For the patient:
• Medical
• Psychological
• Economic
• Social

For the clinician & society:
• Medicolegal
• Reputation
• Economic
Case: MB

• 29 year old female sought neurologic consultation for headaches
• Headaches accompanied at times by blurry vision, difficulty reading, and slowed verbal expression
• Subsequent headaches accompanied by periodic left-sided weakness which resolved within days (no residual, stereotyped pattern)
• Patient also under care of mental health; treatments included lithium, anticonvulsants, ECT
Diagnosed by outside MD with MS

2009

- Diagnosis made based on MRI abnormalities
- MS treatments including interferon beta-1b, natalizumab, and fingolimod initiated and stopped over 7 years
- Discussion underway to begin alemtuzumab
- Polypharmacy and concern over diagnosis led her to a second opinion
MB: Additional workup

• MR C spine: normal
• MR T spine: normal
• CSF: glucose 71, protein 39, WBC 3
  – MS profile: IgG index 0.47, no CSF-unique bands
  – Normal CSF cultures, CSF ACE
• Lab work: normal rheumatology panel, B12, HIV, TFTs
MB: Subsequent clinical course

- Undiagnosed with MS 2016
- Suicide attempt several weeks after undiagnosis
The contemporary spectrum of MS misdiagnosis: a multicenter study

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Contributors to MS misdiagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Inappropriate application to MS diagnostic criteria of neurologic symptoms atypical for a demyelinating attack</td>
<td>72 (65)</td>
</tr>
<tr>
<td>Inappropriate application to diagnostic criteria of a historical episode of neurologic dysfunction without corroborating objective evidence of a lesion (on neurologic examination, evoked potentials, or imaging)</td>
<td>53 (48)</td>
</tr>
<tr>
<td>Overreliance on the presence of MRI abnormalities meeting DIS to confirm a diagnosis of MS in a patient with &quot;nonspecific neurologic symptoms&quot;</td>
<td>66 (60)</td>
</tr>
<tr>
<td>Erroneous determination of juxtacortical or periventricular lesion location to fulfill DIS</td>
<td>36 (33)</td>
</tr>
<tr>
<td>Erroneous determination of DIT because of variability of MRI slice orientation (i.e., MRIs performed on different scanners leading to the appearance of new lesions)</td>
<td>13 (12)</td>
</tr>
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</table>

Abbreviations: DIS = dissemination in space; DIT = dissemination in time; MS = multiple sclerosis.

"Undiagnosing" multiple sclerosis

Table 2 Patients misdiagnosed with multiple sclerosis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. (%)</th>
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<tr>
<td>Evaluated a misdiagnosed patient within last year</td>
<td></td>
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<tr>
<td>Yes</td>
<td>116 (95.1)</td>
</tr>
<tr>
<td>No</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>No. seen within last year</td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>30 (25.9)</td>
</tr>
<tr>
<td>3-5</td>
<td>46 (39.7)</td>
</tr>
<tr>
<td>6-10</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>≥10</td>
<td>20 (17.2)</td>
</tr>
<tr>
<td>Estimated on DMT</td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>6 (5.2)</td>
</tr>
<tr>
<td>1-25%</td>
<td>35 (30.2)</td>
</tr>
<tr>
<td>26-50%</td>
<td>28 (24.1)</td>
</tr>
<tr>
<td>51-75%</td>
<td>17 (14.7)</td>
</tr>
<tr>
<td>≥75%</td>
<td>30 (25.9)</td>
</tr>
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Abbreviation: DMT = disease-modifying therapy.
# 2010 Revised McDonald MS Diagnostic Criteria

**Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space (DIS) and time (DIT)**

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The expanding list of “better explanations”

- Inflammatory diseases (NMO, CLIPPERS, anti-MOG, anti-GAD encephalitis)
- Genetic conditions (CADASIL, CARASIL, HSP)
- Vasculitides
- Infectious diseases (Lyme, HTLV 1,2)
- Paroxysmal disorders (migraine)
Revised McDonald criteria (2016?)

• First effort to roll back the reach of prior McDonald criteria
• Elevated importance of CSF analysis
• Applied correctly, they should increase specificity at expense of sensitivity
• Vigilance towards incorporating history remains
Reasons for revising McDonald Criteria

- New data on the relationship of MS and neuromyelitis optica spectrum disorders (NMOSD);
- Recognition that MS is frequently misdiagnosed;
- New data showing utility of cerebrospinal fluid (CSF) in diagnosis and the need to emphasize its value;
- Need for better performance of the criteria in special populations (ie, pediatric, Asian, and Latin American persons),
- Identification of subsets of patients with a high likelihood of MS but in whom the 2010 criteria are not diagnostic; and
- Recently revised criteria from MAGNIMS (MAGNetic Imaging In MS).

Paraphrased from CMSC 2017, New Orleans, LA
Guidelines for clinicians

• Remember the importance of the neurologic history in recognizing a typical demyelinating event
• Choose therapies in proportion to one’s confidence of the diagnosis
• Reserve the right to change one’s mind
Acute and Subacute Myelopathies

MULTIPLE SCLEROSIS MIMICS
Acute & Subacute Myelopathies

- Signs & Symptoms
- Clinical course
- Diagnostic Testing
- Differential Diagnosis
- Case study
Clinical Signs of an Acute Myelopathy

- **Strongly suggestive:**
  - Sensory level on torso (pin or cool touch)
  - Spinal tract specific sensory symptoms
  - Bladder retention

- **Consistent but not diagnostic**
  - Uni- or bilateral upper motor neuron signs
  - Hyporeflexia
  - Radicular sensory loss in arms or legs
Clinical Signs of an Acute Myelopathy

• Consider Alternative Diagnosis
  – Spasms (vs. spasticity)
  – Paratonic rigidity
  – Dystonia
  – Cognitive impairment
  – Dysarthria and dysphagia
Acute and Subacute Myelopathy
Clinical Anatomical Syndromes

• Complete
• Brown-Séquard hemicord syndrome
• Anterior cord syndrome
• Posterior cord syndrome
• Central
• Conus medullaris
• Cauda equine
• Tractopathies
Utility of Laboratory Testing in Evaluation of Myelopathy
(adapted from Schamlstieg & Weinshenker, 2010)

<table>
<thead>
<tr>
<th>Test Used to Evaluate For:</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSF Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral PCR</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Cytology</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>IgG Index</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Blood Studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMO IgG</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Antinuclear &amp; anticardiolpin Abs</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Angiotensin converting enzyme</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>EMG Testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelopathy with peripheral neuropathy</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
**Figure 2** Differential diagnosis of acute myelopathy: Time course and MRI findings

*Relapses upon withdrawal of corticosteroids/immunosuppression. **MRI may be normal.*

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>T2 hyperintense signal &lt; 3 vertebral segments in length</th>
<th>T2 hyperintense signal ≥ 3 vertebral segments in length</th>
</tr>
</thead>
</table>
| ![Graph](image1) | • Idiopathic/parainfectious TM  
• MS-associated TM  
• Spinal cord infarct | • Idiopathic/parainfectious TM  
• NMO spectrum disorder*  
• ADEM  
• Spinal cord infarct  
• Paraneoplastic myelitis (often tract specific)  
• Myelitis due to SD* |
| ![Graph](image2) | • Cord compression  
• Chronic infection**  
(HIV, HTLV, syphilis, etc.)  
• Intrinsic cord tumor  
• Sarcoidosis* | • DAVF  
• Sarcoidosis*  
• Cord compression  
• Intrinsic cord tumor  
• SCD**  
• Copper deficiency** |
| ![Graph](image3) | • MS  
• Sarcoidosis* | • NMO  
• Sarcoidosis*  
• Myelitis due to SD* |

Schmalstieg, Neurology 2010
Utility of Imaging Testing in Evaluation of Myelopathy
(adapted from Schamlstieg & Weinshenker, 2010)

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</thead>
<tbody>
<tr>
<td>Imaging Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal MRI</td>
<td>r/o structural lesion</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Brain MRI</td>
<td>MS</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CT Myelogram</td>
<td>r/o cord compression</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Spinal Angiogram</td>
<td>AV malformation</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Spinal CT</td>
<td>r/o structural lesion in vertebral axis</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
MRI of representative cases of acute and subacute myelopathies

Schmalstieg, Neurology 2010
Acute & Subacute Myelopathies
Differential Diagnosis

• Compression: traumatic, neoplastic, degenerative
• Vascular: anterior spinal artery occlusion, AVF
• Infectious: transverse myelitis (viral-HIV & HTLVI/II; bact: TB, Lyme, syphilis, fungal, parasitic-NCC)
• Developmental: syrinx
• Metabolic/Toxic: B12, folate or copper deficiency, nitrous oxide
• Inflammatory: SLE, NMO, MS
• Genetic: Friedrich’s ataxia, adrenomyeloneuropathy, SCA
• Other: r/o myelopathy mimics: CIDP, plexopathy, neuromuscular disease
Case Study

• 37 year-old AA female physical therapy student with subacute bilateral leg and right-arm weakness over 6 weeks.

• Worsening pain and sensory loss noted in both legs and right arm

• PE significant for moderate asymmetric paraparesis R>L 3-4/5, RUE paresis, brisk LE DTRs with ext Babinski reflexes, T3-4 sensory level & gait ataxia
Case: Cervical Spine MRI

Axial T1 with Gd

Axial T1 with Gd
Case: Cervical Spine MRI

Sagittal T2

Sagittal STIR
Case: Brain MRI

Axial T2 FLAIR
Case: Lab Testing

• Serum: Lyme EIA equivocal, FANA + speckled 1:320, B12 190 pg/ml, HIV & HTLV I-II neg, ESR 12, cbc nl, chem panel nl, ua nl

• CSF: glucose 56 mg/dl, protein 41 mg/dl, wbc: 4.0/cmm, rbc 1.0/cmm, IgG index 0.74, no OCB, negative VDRL, negative bacterial and fungal cx,

• NMO Ab: positive
NMO Spectrum Disorders Core Clinical Characteristics
(Wingerchuk, Neurology 2015)

- Optic neuritis
- Acute myelitis
- Area postrema syndrome
- Acute brain stem syndrome
- Symptomatic narcolepsy or acute diencephalic clinical syndrome with typical MRI lesions
- Symptomatic diencephalic MRI lesions
Diagnostic Criteria for NMO Spectrum Disorder in Adults
(Wingerchuk, Neurology 2015)

• Diagnostic criteria for NMOSD with AQP4-IgG
  – At least 1 core clinical characteristic
  – Positive AQP4-IgG (cell-based assay)
  – Exclusion of alternate diagnoses

• Diagnostic criteria for NMOSD without AQP4-IgG
  – At least 2 core clinical characteristics occurring as a result of 1 or more attacks & meeting all the following:
    • At least 1 core clinical characteristic: ON, acute myelitis with LETM or area postrema syndrome
    • Dissemination in space
    • Exclude alternative diagnoses
Neuroimaging Patterns of NMO Spectrum Disorder

(Wingerchuk, 2017)
Approach to “Myelopathy”
Question to ask with normal imaging studies

• Has a compressive cause been missed?
• Is it really a myelopathy?
• Is there a cerebral cause for the syndrome?
• Is it an acute presentation of a chronic condition?
• Is the image quality adequate?
• Were the images taken too early or late?
• Is it a functional disorder?
Questions?