Multiple Sclerosis

Misdiagnosis & Differential Diagnosis

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Acknowledgment:

- Thank you to Dr. Andrew Solomon for sharing his slides on MS Misdiagnosis.
MS DIAGNOSIS

• We still lack a highly specific biomarker for MS.

• MS remains a clinical diagnosis.

• Diagnostic criteria apply to **typical** demyelinating presentations.

• Objective findings, not just historical reports, are needed.

• Although early diagnosis and treatment is important it is equally important to avoid **MISDIAGNOSIS**.
MS MISDIAGNOSIS: Historical Perspective

• 1950’s-1970’s: Case Reports
• 1984: 13%
• 1985: 9-12%
• 1988: 6%
• 1997: 35%

• 2005: 67% of new consults did NOT have MS
  – Having MS (or possible MS) was very dependent on the presenting symptoms.
    – Typical Symptoms: 71%
    – Possible Symptoms: 27%
    – Atypical Symptoms: 0%

Murray & Murray, CMAJ, 1984
Herndon & Brooks, Semin Neurol, 1985
Engell, Acta Neurol Scand, 1988
Poser, Lancet, 1997
Carmosino et al., Arch Neurol, 2005
MS MISDIAGNOSIS
Contemporary Perspective: 2012

- Cross-sectional, internet-based survey of MS specialists
- 242 invited
- Response rate 50%
- 83% responders spent > 50% of their clinical time in MS
- 65% completed a fellowship in MS or neuroimmunology

Solomon et al., Neurology 2012
MS MISDIAGNOSIS: 2012

Survey Question:

“Have you ever evaluated a patient who carried a diagnosis of MS (given by another provider) for longer than a year who, after your neurologic exam and review of lab data, you strongly felt did NOT in fact have MS?”

<table>
<thead>
<tr>
<th>Evaluated a misdiagnosed patient within last year</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>116 (95.1)</td>
</tr>
<tr>
<td>No</td>
<td>6 (4.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. seen within last year</th>
<th></th>
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<tbody>
<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>
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<tr>
<td>≥10</td>
<td>20 (17.2)</td>
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</tbody>
</table>

Solomon et al., Neurology 2012
MS MISDIAGNOSIS: 2012

Survey Question:

“The most likely alternative diagnosis in patients you have seen with a longstanding misdiagnosis (i.e., greater than 1 year) of MS have been.”

NSWMA= nonspecific white matter abnormalities
SVID= small vessel ischemic disease

Solomon et al., Neurology 2012
MS MISDIAGNOSIS
Contemporary Perspective: 2016

- Prospective multicenter study of 110 misdiagnosed patients encountered clinically from Aug 2014- Sept 2015
- Sites: Mayo Clinic, University of Vermont, Washington University in St. Louis, Oregon Health Sciences University
- 85% women, 15% men,
- Mean age 49 ± 11 years (range from 21-77)
- 46% “definite” misdiagnosis
- 54% probable misdiagnosis

Solomon et al., Neurology 2016
Who gave the misdiagnosis?

- 24%: neurologist with MS fellowship training or practice focus
- 32%: neurologist without such training or focus
- 3%: non-neurologist
- 42%: physician with unknown training

Solomon et al., Neurology 2016
What was misdiagnosed?

66% of misdiagnosis accounted for by 5 diagnoses.

1. **Migraine**: 22%
2. **Fibromyalgia**: 15%
3. **Nonspecific** or non-localizing symptoms with **abnormal MRI**: 12%
4. **Conversion** or **psychogenic** disorder: 11%
5. **Neuromyelitis optica** spectrum disorder: 6%

Solomon et al., Neurology 2016
Duration of Misdiagnosis

- <1 year: 15%
- 1-2 years: 24%
- 3-9 years: 29%
- ≥ 10 years: 33%
### MS MISDIAGNOSIS 2016

**DMT exposure**

- 70% of misdiagnosed were given DMTs
- 36% given >1 DMT

<table>
<thead>
<tr>
<th>Immunomodulatory therapies received by patients with misdiagnosis</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a or interferon beta-1b</td>
<td>58 (53)</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>44 (40)</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1 (1)</td>
</tr>
<tr>
<td>IV immunoglobulin</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Repository corticotropin injection</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Solomon et al., Neurology 2016
Duration of DMT

3-9 years: 29%

≥ 10 years: 29%

MS MISDIAGNOSIS
Contemporary Perspective: 2016

Solomon et al., Neurology 2016
MS MISDIAGNOSIS
Contemporary Perspective: 2016

Contributors to Misdiagnoses

“Inappropriate application to MS diagnostic criteria of neurological symptoms atypical for a demyelinating attack” 65%

“Overreliance on the presence of MRI abnormalities meeting DIS to confirm a diagnosis of MS in a patient with nonspecific neurological symptoms” 60%

Solomon et al., Neurology 2016
MS MISDIAGNOSIS
Contemporary Perspective: 2016

Contributors to Misdiagnoses

“Inappropriate application to diagnostic criteria of a historical episode of neurological dysfunction without corroborating objective evidence of a lesion”
48%

“Erroneous determination of juxtacortical or periventricular lesion location to fulfill Dissemination in Space”
33%

Solomon et al., Neurology 2016
Misdiagnosis carries risks and causes harms.

- Adverse effects of DMTs
- Disability/Damage from untreated alternative diagnoses
- Psychosocial harm
- Financial costs
- Confounding of clinical trials
SUMMARY OF MS MISDIAGNOSIS

• MS remains a clinical diagnosis.
• Diagnostic criteria are meant to apply to patients presenting with a **typical** demyelinating syndrome.
• Historical events need objective evidence to count towards diagnosis.

• **MISDIAGNOSIS** is…
  – Common
  – Often longstanding
  – Harmful
  – Often avoidable
AVOIDING MISDIAGNOSIS

• Apply diagnostic criteria appropriately
• Don’t be afraid to question the “longstanding”
• Don’t be compelled to give a diagnosis if the case is not clear
• Look out for RED FLAGS
• Consider a broad differential diagnosis
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical</th>
<th>Laboratory</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Acute relapsing or chronic progressive</td>
<td>OCBs often present in CSF (79–90%)</td>
<td>Periventricular and juxtacortical lesions ± enhancement</td>
</tr>
<tr>
<td></td>
<td>Isolated CNS involvement</td>
<td></td>
<td>Typically well-demarcated ovoid lesions</td>
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<td></td>
<td></td>
<td></td>
<td>May see T1 hypointensities (“black holes”)</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>Acute relapsing</td>
<td>NMO IgG positive (56–73%)</td>
<td>Spinal lesions usually ≤ 2 vertebral segments, often only with partial cross-sectional involvement of the spinal cord</td>
</tr>
<tr>
<td></td>
<td>Recurrent optic neuritis or myelitis</td>
<td></td>
<td>Typically few cerebral lesions, which may be periventricular, especially in the caudate nucleus</td>
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<tr>
<td></td>
<td>Refractory nausea or hiccups</td>
<td></td>
<td>Longitudinally extensive spinal cord lesions usually ≥ 3 vertebral segments in length</td>
</tr>
<tr>
<td>Acute disseminated encephalomyelitis</td>
<td>Subacute menophasic</td>
<td>Typically OCBs absent in CSF</td>
<td>Diffuse or multi-lesion enhancement</td>
</tr>
<tr>
<td></td>
<td>Post-infectious or post-vaccination</td>
<td>May be anti-MOG Ab positive in pediatric population</td>
<td>Lesions frequently have indistinct lesion borders</td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td>Acute relapsing or chronic progressive</td>
<td>Anti-SSA/SSB positive (50–60%)</td>
<td>Spinal cord lesions often longitudinally extensive (≥ 3 vertebral segments in length)</td>
</tr>
<tr>
<td></td>
<td>Sjö syndrome</td>
<td>NMO IgG positive in some patients</td>
<td></td>
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<tr>
<td></td>
<td>Rarer OCBs present in CSF</td>
<td>Rarely OCBs present in CSF</td>
<td></td>
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<tr>
<td>Systemic lupus erythematosus</td>
<td>Acute or chronic progressive</td>
<td>Positive ANA, anti-dsDNA Ab, anti-Sm Ab, anti-SmRNP Ab, anti-Ab, anti-histone Ab, and/or anti-phospholipid Abs</td>
<td>Restricted diffusion or diffusion weighted imaging consistent with ischemic infarcts</td>
</tr>
<tr>
<td></td>
<td>Other organ system involvement</td>
<td></td>
<td>Cortical atrophy in chronic cases</td>
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<tr>
<td>Neurosarcoïdosis</td>
<td>Variable neurologic presentation</td>
<td>± ACE (&lt;50%)</td>
<td>Nodular meningeal enhancement</td>
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<tr>
<td></td>
<td>Uveitis</td>
<td></td>
<td>Spinal cord lesions often longitudinally extensive</td>
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<tr>
<td></td>
<td>Lung or skin involvement</td>
<td></td>
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<tr>
<td>Neuropathy Behcet’s disease</td>
<td>Acute or chronic progressive</td>
<td>HLA-B51 positive in Japanese and Turkish population (70%)</td>
<td>Unilateral or bilateral upper brainstem lesions extending into basal ganglia and thalamus</td>
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<tr>
<td></td>
<td>Meningoencephalitis</td>
<td></td>
<td>Spinal cord lesions often longitudinally extensive</td>
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<td>Cerebral venous thrombosis</td>
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<td>Oral and genital ulcers</td>
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<td></td>
<td>Positive pathergy test</td>
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<tr>
<td>Primary CNS Vasculitis</td>
<td>Stroke or transient ischemic attack like episodes in multiple vascular distributions</td>
<td>None</td>
<td>Restricted diffusion or diffusion weighted imaging consistent with ischemic infarcts</td>
</tr>
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<td></td>
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<td>Conventional angiography may reveal vessel wall irregularities (50–60%)</td>
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</tbody>
</table>

CNS central nervous system, OCB oligoclonal bands, CSF cerebrospinal fluid, NMO neuromyelitis optica, MOG myelin oligodendrocyte glycoprotein, ANA anti-nuclear antibody, dsDNA double-stranded DNA, snRNP sn ribonucleoprotein, Ab antibody, ACE angiotensin converting enzyme.

Stangel et al., Nat Rev Neuro 2015
Brownlee et al., Lancet 2017
Eckstein et al., J Neurol, 2012
MS RED FLAGS

Patient Characteristics

• Extremes of age:
  – Childhood onset (<15)
  – Late onset (>50)

• Very prominent family history

Miller et al., MSJ, 2008
Siva, Neuro Clin, 2018
MS RED FLAGS

Clinical Presentation

- Hyperacute onset
- Fulminant or rapidly progressive course
- Cortical signs
- Constitutional symptoms
- Extrapyramidal symptoms
- Seizures
- Stereotyped symptoms
- Atypical response to steroids

Miller et al., MSJ, 2008
Toledano et al., Curr Neurol Neurosci Rep, 2015
Siva, Neuro Clin, 2018
MS RED FLAGS

CSF Analysis

• Pleocytosis > 50
• Prominent neutrophils or eosinophils
• Marked protein elevation >100
• Normal immunoprofile
  – No oligoclonal bands (OCB’s)
  – Normal IgG index
  – Normal IgG synthesis rate
MS RED FLAGS

Imaging Findings

- Punctate lesions (<3 mm)
- Subcortical predominance with minimal juxtacortical or periventricular lesions
- Absence of corpus callosum involvement
- Symmetrical and/or confluent lesions (especially early)
- Mass effect
- Hemorrhages or microbleeds
- Persistent gadolinium enhancement
- Lack of enhancement on any studies
- No observed evolution over time
- Calcifications on Head CT

Miller et al., MSJ, 2008
Siva, Neuro Clin, 2018
MISDIAGNOSES/DIFFERENTIAL DIAGNOSIS SUMMARY

• Apply diagnostic criteria to typical presentations only
• Rely on objective data whenever possible
• Look out for RED FLAGS
• Don’t be afraid to question the longstanding

• Some cases (even your own) may require de-diagnosis

MS
National Multiple Sclerosis Society
Thanks for your time!

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