MS Misdiagnosis—An Analysis From Case Studies

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A handful of patience is worth more than a barrel full of brains.

Dutch Proverb
Causes of Misdiagnosis

- **Diagnosis momentum**
  - Diagnosis even on insufficient evidence becomes fixed in a doctor’s mind
- **Framing effects**
  - Being swayed by subtle wording or focusing on certain aspects of a case more than others
- **Satisfaction of search**
  - Stopping when you find a satisfying diagnosis
- **Confirmation bias (anchoring)**
  - Dismissing material that does not fit with your diagnostic impression
- **Attribution error**
  - Failing to consider a diagnosis that does not fit the prototype
- **Representativeness error**
  - Failing to consider possibilities that contradict the prototype and base rate of disease
  - Failing to account for base rates (“If you hear hoof beats, think horses, not zebras”)
- **Availability heuristic**
  - Diagnosing based on the ease of recalling past experience
- **Blind obedience**
  - Showing undue deference to authority or technology

Schumacher Criteria for MS (1965)

- Designed for therapeutic trials
- **Six criteria**
  - Age between 10 and 50 years
  - Objective abnormalities on neurological exam
  - Two or more separate lesions in the CNS
  - Predominantly involve the white matter
  - 2 episodes separated by >1 mo, lasting >24 hours, or progression over 6 months’ time
  - No better explanation for the disorder

Diagnostic Criteria—Revised 2010

Clinical Presentation

- ≥2 clinical attacks; and
- Clinical evidence of ≥2 lesions
  or
- Clinical evidence of 1 lesion with history of prior attack
- ≥2 clinical attacks; and
- Clinical evidence of 1 lesion
- 1 clinical attack; and
- Clinical evidence of ≥2 lesions
- 1 clinical attack; and
- Clinical evidence of 1 lesion (CIS)
- Vertebral neurological presentation suggestive of MS (PPMS)

None, but must be consistent with MS

Dissemination in Space (DIS)

Additional clinical attack implicating a different CNS site; or
≥1 T2 lesion in at least 2 of the following areas: periventricular, juxtacortical, infratentorial, spinal cord

Dissemination in Time (DIT)

Second clinical attack; or
New T2 and/or Gd+ lesion on follow-up MRI, referencing a baseline scan, irrespective of the timing of the baseline scan
Simultaneous presence of asymptomatic Gd+ and Gd- lesions at any time

1 year of disease progression plus 2 of:
DIS in the brain; or
DIS in the spinal cord (≥2 T2 lesions); or
Progressive CIS

Two-fold Importance of Correctly Diagnosing MS

- Treating the real underlying etiology
- Illness may be associated with significant morbidity or mortality in the absence of treatment
- Avoid the use of potentially harmful MS therapies

The Importance of Initiating DMD Early

[Graph showing benefit study results]

The Potential Risk of MS Therapy

- 41-year-old woman with numbness and burning of right extremities
- Previous history of migraine and numbness in her right hand
- 1 tone of right ext and 1 reflexes
- VA OS 20/100
- MRI with 4 small T2 hyperintensities of corona radiata
- CSF normal
- Treated with IFN-β1a 30 µg IM weekly; IVMP x 3
- April 2002—ultimately started natalizumab as part of SENTINEL trial
- November 2004—new coordination problems and decline thereafter

Primary Differential Diagnosis of MS

- **Inflammatory**
  - Neuromyelitis optica
  - Acute disseminated encephalomyelitis
  - Sarcoidosis
  - SJL
  - Diagnosis syndrome
  - MS
  - Behcet's syndrome
  - Sjogren's syndrome
  - Systemic lupus erythematosus
  - Chronic demyelinating polyneuropathy
- **Vascular**
  - Migraine variants
  - CEDAS
  - Brainstem's disease
  - Small vessel disease of HBP and DM
  - Diabetes mellitus
- **Neoplastic**
  - Metastatic brain disease
  - Glioma
  - Primary CNS Lymphoma
- **Infectious illness**
  - Lyme disease
  - Neurosyphilis
  - Toxoplasmosis
  - HTLV-1 myelopathy
  - PML
  - HSV
- **Metabolic disorders**
  - Vitamin B12 deficiency
  - Adrenoleukodystrophy and adrenomyeloneuropathy
  - Mitochondrial disorders
  - Metachromatic leukodystrophy
  - Fabry disease
  - Krabbe disease
  - Adult polycystic kidney disease
  - Adrenoleukodystrophy and adrenomyeloneuropathy
  - Mitochondrial disorders
  - Metachromatic leukodystrophy
- **Mechanical**
  - Cervical spondylosis
  - Arnold-Chiari malformation
  - Spinal AVM and dural fistula
  - Syringomyelia

Changes in Ascertainment of MS

- North American Research Committee on MS registry
- Correlated time to diagnosis from symptom onset with year of onset
- The later the date of diagnosis, the sooner the diagnosis was established
- Ascertainment time is very brief
- False-negative attribution of MS is likely to be very rare

Overdiagnosis of MS

- 281 patients referred to University of Colorado with possible MS
  - 33% diagnosed with MS or possible MS by McDonald Criteria
  - 31.5% had other neurological disease
  - 22.5% had a psychiatric disorder
  - 12.5% had no clear diagnosis
- 63% referred for clinical features; 37% referred for MRI abnormalities
  - 46% of those with clinical disease had MS
  - 11% of those with MRI abnormalities had MS


Overdiagnosis of MS (cont)

- 29 studies were reviewed for accuracy of diagnosis on the basis of MRI findings
- Only 2 studies conducted patient follow-up for >10 years
- Even with large number of lesions that were non-predictive
  - >8 lesions on MRI—likelihood ratio, 2.0
  - >10 lesions on MRI—likelihood ratio, 3.0
- Absence of lesions is of limited utility in ruling out MS
  - Likelihood ratio for negative test was 0.1–0.5
- Use of MRI at the time of a single attack leads to overdiagnosis


Overdiagnosis of MS (cont)

Most common diagnostic error—
The result of uncritical reliance on MRI and hasty workup
Red Flags for Diagnosing MS

- Clinical Features
  - Onset after age 60 or before adolescence
  - Family history of a similar disease
  - Early cognitive signs
  - Cortical signs
  - Progressive course from onset in a young person
  - Presence of symptoms not attributable to CNS

(Rudick RA et al. Arch Neurol. 1986;43:578-583.)

Red Flags for Diagnosing MS (cont)

- MRI Features
  - Symmetric lesions
  - Peripheral white matter lesions rather than periventricular lesions
  - Lack of ovoid lesions
  - Lack of involvement of the inner corpus callosum
  - Areas of mass effect
  - Longitudinally extensive spinal cord lesions

(Charil A et al. Lancet Neurol. 2006;5:841-852.)

Differential Diagnosis of MS—Consensus Approach

- Identified 36 major, 32 intermediate, and 11 minor red flags
- 4 categories
  - Clinical, laboratory and imaging features "classic" for MS
  - Features compatible with MS but alternative diagnosis possible
  - Clinical and/or paraclinical red flags point to alternative diagnosis
  - Coexistence of MS and another superimposed disorder

(Reprinted with permission from Miller DH et al. Mult Scler. 2008;14:1157-1174.)
"In the last analysis, we see only what we are ready to see, what we have been taught to see. We eliminate and ignore everything that is not a part of our prejudices."

Jean-Martin Charcot
1825–1893