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Management of Multiple Sclerosis, Part 1 of 2: Differential Diagnosis–A Consensus Approach

Supported by an unrestricted educational grant from Pfizer Inc.
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Disclosures

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**Speakers Bureau:** Biogen Idec; EMD Serono, Inc.; Pfizer Inc.; Teva Pharmaceuticals
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Dr. Lublin has disclosed that he may discuss unapproved agents that are in the MS developmental pipeline without any recommendation on their use.
Disclosures of faculty financial relationships and biographical profiles can be found at neuroscienceCME.com/426
The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational uses (any use not approved by the FDA) of products or devices.
Learning Objective

Utilize consensus-based guidelines in determining a more accurate differential diagnosis of MS
To receive CE credits for this activity, participants must complete the post-test and evaluation online at neuroscienceCME.com/test
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Background

2001—International panel convened to develop guidelines for diagnosing multiple sclerosis (MS)
- All modern diagnostic criteria for MS had included the caveat “that there be no better diagnosis”
- Diagnostic criteria for MS designed to provide clinical and paraclinical guidelines for making the diagnosis
- Criteria did not distinguish MS from other diseases that could mimic it

2007—Second panel convened to develop guidelines for the differential diagnosis of MS
- Alternative Diagnosis, (i.e. not inflammatory demyelinating diseases (IDD))
- Clinically Isolating Syndrome (CIS)
- Differentiating MS from other idiopathic inflammatory demyelinating diseases (IIDD)

Objectives

The panel focused on three areas:

- Exclusion of MS mimics
- Diagnosis of common CIS
- Differentiating between MS and non-MS idiopathic inflammatory demyelinating disease

Panel Guidelines

- Diagnostic algorithms for MS differential diagnosis
- Differential diagnosis of patients presenting with demyelinating:
  - Optic neuritis
  - Brain stem syndrome
  - Spinal cord syndrome

Red Flags

Table of 79 “Red Flags”—clinical and MRI

- **Major** red flags—carry more weight; scored highest for concern
  - Examples:
    - Bone Lesions ➔ histiocytosis
    - Lung involvement ➔ sarcoidosis
- **Intermediate** red flags—scored in between major and minor
- **Minor** red flags—less consensus for importance

Red Flags

- Help to exclude nondemyelinating syndromes
- Classic IIDD or alternative diagnosis
- IIDD
  - MS
  - Classical neuromyelitis optica (NMO)
  - Acute disseminated encephalomyelitis (ADEM)
  - Less well classified IIDD, (i.e., Bellows or Marburg)
- Criteria for defining NMO
- Criteria for diagnosing ADEM

Clinically Isolated Syndrome (CIS)

- Term has no pathologic specificity
- Monofocal—involvement of one area of the nervous system
- Multifocal—involvement of multiple areas of the nervous system
- Considered the first episode of an inflammatory demyelinating event
- Exception: CIS type 5—initial event is picked up on an MRI

Methods

- Table of 79 red flags rated independently on scale of 1-5
  - 1-2: Minor
  - 3: Intermediate
  - 4-5: Major
- Major
  - Total score of 24 or greater, no more than one individual with a score of 3
- Minor
  - Total score of 12 or less, no more than one individual with a score of 3
- Intermediate
  - Total score between 13-23, more than one individual with a score of 3
  - Indicated a lack of consensus among the raters

Minor Red Flags

- Minor red flags = think about the diagnostic issue
- Caveat—“no better diagnosis”
  - Are you missing something?
- Make sure you have supporting evidence to confirm diagnosis and exclude minor confounding factors
- Red flags may not alter diagnosis of MS

Types of CIS

5 different types of CIS

- Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion
- Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion
- Type 3 CIS: clinically monofocal, MRI may appear normal; no asymptomatic MRI lesions
- Type 4 CIS: clinically multifocal, MRI may appear normal; no asymptomatic MRI lesions
- Type 5 CIS: no clinical presentation to suggest demyelinating disease, but MRI is suggestive

Monofocal vs. Multifocal CIS

- Difference between monofocal CIS with one or more abnormalities on MRI vs. monofocal CIS with no changes on MRI?
  - MRI useful in guiding diagnostic and prognostic process of CIS
  - Changes on the MRI consistent with IDD more likely to have another attack than those who have normal MRIs
  - Multifocal CIS – raises different issues with differential diagnosis, (i.e. isolated optic neuritis with no changes vs. optic neuritis and corticospinal track dysfunction and many lesions on the MRI)

IDD = inflammatory demyelinating disease

Type 5 CIS

- MRI shows changes in brain that look typical for MS, but no clinical symptoms
- CIS is really MRI isolated
- Need more research to determine diagnosis and prognosis

Classical MS vs. Other Entities

Importance of Nomenclature

- Prognostic implications
- Potential therapeutic implications

**Example 1:** Distinguishing between ADEM vs. first attack of MS
- ADEM occurs more commonly in children
- Considerable overlap between ADEM and MS at time of first attack
- If ADEM—no ongoing therapy
- If MS—treatment for MS at that time reduces risk of further exacerbations

**Example 2:** Classical NMO
- Some similar syndromes within the spectrum that mimics NMO
- Overlaps considerably with MS

Criteria for Diagnosis of NMO

Major criteria

- Episode of optic neuritis
  - In one or both eyes
- Episode of transverse myelitis
  - Clinically complete or incomplete
  - Radiologic evidence of an extensive spinal cord lesion—extending over 3 or more spinal segments
- No evidence for other systemic diseases
  - Sarcoidosis
  - Vasculitis
  - Clinically manifest collagen vascular disorders, (i.e., systemic lupus erythematosus or Sjogren's disease)

Criteria for Diagnosis of NMO

Minor criteria

- Most recent brain MRI should be normal or show abnormalities that don’t fit McDonald diagnostic criteria for MS

  McDonald diagnostic criteria for MS:
  - Integrate data MRI
  - Focus on early diagnosis of patients presenting with CIS suggestive of MS (e.g., unilateral optic neuritis, internuclear ophthalmoplegia, partial myelopathy)

Criteria for Diagnosis of NMO

Minor criteria

- Could be nonspecific brain abnormalities
- Lesions in the dorsal medulla noted as hypothalamic lesions
- Linear periventricular corpus callosum signal abnormalities
  - Not ovoid lesions
  - Not extending into the parancema of the cerebral hemisphere in a Dawson’s finger-like configuration
- Positive test for serum or spinal fluid for the NMO-IGG aquaporin 4 antibodies

Presentation of Myelopathic Syndrome

**MS vs. Non-MS Diagnosis**

- **In MS myelopathy comes on in sub-acute fashion**
  - Hours to days
  - Progressive MS—weeks, months, or years
  - Partial myelopathy—not truly transverse
  - Acute exacerbation—reasonable degree of recovery
  - Longitudinal extent in MS less than 3 vertebral segments

- **In other conditions, (i.e., spinal cord infarct)**
  - Deficit is more rapid
  - More vascular pattern
  - In compressive lesions of the spinal cord—slower onset
  - In NMO—damage to spinal cord more extensive and less likely to recover

Conclusions

“Red Flags” help clinicians to develop a differential diagnosis of MS and other IIDDs
- Help to exclude non-IIDDs

CIS can either be monofocal or multifocal or seen on MRI only

MS must be distinguished from other IIDDs
- NMO
- ADEM

Through the use of differential features and relative red flags, the diagnosis of MS or its mimics is made easier for the practicing clinician

Additional Resources

Visit neuroscienceCME.com/MS for clinical information and certified educational activities on multiple sclerosis