Multiple Sclerosis (MS): Diagnosis and Evaluation

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MS: Diagnosis and Evaluation:
LEARNING OBJECTIVES

- Identify and appropriately utilize diagnostic criteria for multiple sclerosis (MS)
- Recognize common presenting sign & symptoms of MS
- Accurately interpret diagnostic studies in the evaluation of MS
- Differentiate imaging findings of MS from that of other common neurologic disorders
- Outline the initial evaluation of a patient with suspected MS
MULTIPLE SCLEROSIS (MS): Myelin

- CNS: Oligodendrocytes
- Composition
  - 40% water
  - Remaining 60%:
    - 70 – 80% lipids
    - 20 – 30% protein
- Function
  - Increases conduction velocity
- Demyelination
  - Loss of myelin
- Dysmyelination
  - Defective structure & function of myelin
MULTIPLE SCLEROSIS:
Defined

- Autoimmune, T-cell mediated destruction of myelin sheath (white matter) within the central nervous system
- Characteristic pattern of inflammatory demyelinating plaques
- Dissemination in space & time
- Early within the course it is predominately an inflammatory disease
- Later within the course it is predominately a neurodegenerative disease
MULTIPLE SCLEROSIS: Pathophysiology

Genetic Predisposition

- No particular gene identified
- 20% - 30% in identical twins
- 2% - 5% in same sex fraternal twins
- MS Susceptible genes
  - HLA-DRB1*1501
  - IL7Ra polymorphism
MULTIPLE SCLEROSIS: Pathophysiology

- Vitamin D
- Infectious agents
- Hormonal effects
- Smoking
- Hygiene hypothesis
- Salt
- Obesity

Environmental Factors
MULTIPLE SCLEROSIS: Pathophysiology

Genetic Predisposition

Environmental Factors

Immune dysregulation

Multiple Sclerosis
MULTIPLE SCLEROSIS: Pathologic Hallmarks

**MS “Plaques”**

- Focal areas of myelin loss within the Central Nervous System (CNS)

- Common locations:
  - Optic nerves
  - Cerebral white matter
  - Cerebellum
  - Brainstem
  - Spinal cord
MULTIPLE SCLEROSIS: Pathologic Hallmarks

- **Inflammation**
- **Demyelination**
  - Slow, disordered, arrested nerve conduction
- **Axonal injury**
  - Axonal loss is the major determinant of progressive, long term, and permanent disability in MS
- **Neurodegeneration**
Cortical Demyelination & Diffuse White Matter Injury in MS

- Demyelinated lesions in the white matter
- Cortical demyelination
- Demyelinated lesions in the deep gray matter
- Inflammatory infiltrates in the brain
- Inflammatory infiltrates in the meninges

*MS is NOT just a myelin disorder!*
Natural History of Multiple Sclerosis
MULTIPLE SCLEROSIS: Prognosis

- No definite prognosis
- Highly variable and unpredictable disease
- Favorable prognostic factors
  - Early visual or sensory symptoms
  - Onset before age 40, female, relapsing forms
- Unfavorable prognostic factors
  - Early cerebellar or motor symptoms
  - Onset after age 40, male, progressive forms
MULTIPLE SCLEROSIS: Variants

RELAPSING-REMITTING MS

SECONDARY PROGRESSIVE MS

PRIMARY PROGRESSIVE MS

RELAPSING PROGRESSIVE MS

% nl

TIME

% nl

TIME

% nl

TIME

% nl

TIME
MULTIPLE SCLEROSIS: Epidemiology

- ~ 450,000 cases in U.S.
- Phenotypically heterogeneous
- Female > male 4:1
- Most cases occur between ages 15 & 45
- Latitude
MULTIPLE SCLEROSIS: Differential Diagnosis

- Multiple diseases mimic the clinical presentation and radiologic findings of multiple sclerosis
  - Inflammatory
  - Infectious
  - Vascular
  - Dysmyelinating diseases
  - Other demyelinating diseases

- Other diagnoses should be considered and potentially excluded in the evaluation and workup of patients with possible multiple sclerosis
MULTIPLE SCLEROSIS: Differential Diagnosis

- **Inflammatory**
  - Systemic Lupus Erythematosus (SLE)
  - Sjogren syndrome
  - Behcet disease
  - Sarcoidosis

- **Infectious**
  - Lyme disease
  - HTLV-1
  - HIV
  - Neurosyphilis
  - Progressive Multifocal Leukoencephalopathy

- **Vascular**
  - Antiphospholipid Syndrome
  - Ischemic stroke
  - CADASIL

- **Other demyelinating diseases**
  - Neuromyelitis Optica (NMO)
  - Acute Demyelinating Encephalomyelitis (ADEM)

- **Disease of myelin**
  - Leukodystrophies

- **Miscellaneous**
  - B12 & copper deficiency
  - Migraine
MULTIPLE SCLEROSIS: Diagnosis

- **Clinical diagnosis** based on combination of clinical presentation & results of diagnostic testing
  - Hinges on clinical and/or radiologic demonstration of *dissemination in time* AND *space*
    - Dissemination in time = multiple attacks
    - Dissemination in space = multiple areas of CNS involvement
      - Includes optic nerves, cerebral white matter, cerebellum, brainstem, spinal cord
# MULTIPLE SCLEROSIS: Diagnosis

## 2010 McDonald criteria for MS

<table>
<thead>
<tr>
<th>Attacks</th>
<th>Lesions</th>
<th>Additional requirements for MS diagnosis</th>
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<tbody>
<tr>
<td>2 or more</td>
<td>2 or more</td>
<td>None</td>
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<tr>
<td>2 or more</td>
<td>1</td>
<td>Dissemination in space demonstrated by MRI or further attack</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Dissemination in time demonstrated by MRI or further attack</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Dissemination in space and time demonstrated by MRI or further attack</td>
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</table>
| 0 Insidious neurological progression suggestive of MS | 1 year of progression and 2 of the following:  
  - Positive brain MRI  
  - Positive spinal cord MRI  
  - Positive CSF |
MUTIPLE SCLEROSIS: Typical Clinical Presentations

- Subacute onset (hours – days), persistent
- Partial spontaneous recovery within weeks
- Clinically isolated syndrome (CIS)
  - Optic neuritis
  - Brainstem or cerebellar syndrome (e.g., INO, 6th nerve palsy, ataxia, gaze-evoked nystagmus, vertigo)
  - Spinal cord syndrome
    - Partial transverse myelitis
    - Sensory (e.g., L’hermitte phenomenon)
MULTIPLE SCLEROSIS: Diagnostic Evaluation

- Complete history
- Comprehensive neurologic exam
- MRI w/ & w/o Gadolinium
  - Brain & optic nerves
  - Cervical & thoracic spine
- Serologic testing to exclude MS mimickers*
- Cerebrospinal fluid (CSF)*
  - Cells & protein → normal or mild ↑
  - Oligoclonal bands
  - IgG index and synthesis ↑
- OCTs, SSEPs, VEPs, BAEPs*
MULTIPLE SCLEROSIS: Typical Imaging Features

Brain lesions:
- Periventricular
  - Ovoid, well circumscribed, homogenous, radial orientation away from ventricles (Dawson’s fingers)
- Juxtacortical (uncommon in microvascular disease)
- Infratentorial
  - Floor of 4th ventricle, superficial pons (microvascular disease is more central)
- Involvement of paracentral corpus callosum
- Lack of vascular pattern
- T1 “black holes,” open ring sign w/ Gd

Patchy spinal cord lesions (dorsolateral)
MRI BRAIN: Normal
MRI BRAIN: Multiple Sclerosis

T2 FLAIR AXIAL
MRI BRAIN: Multiple Sclerosis

T2 FLAIR SAGITTAL
MRI BRAIN: Multiple Sclerosis

T2 FLAIR
MRI SPINE: Multiple Sclerosis

Sagittal T2
MRI BRAIN: Post-Contrast Enhancement

T2 FLAIR

T1 + Gad
MRI ORBITS:
Post-Contrast Enhancement

T1 + Gad
MRI SPINE:
Post-Contrast Enhancement

T2

T1 + Gad
Biologic Biomarkers: CSF IgG Index and Synthesis

- Cerebrospinal fluid IgG Index and Synthesis rate
  - Compares CSF IgG:albumin ratio to serum IgG:albumin ratio
  - Elevated levels represent *intrathecal* B-cell mediated response
  - Index Range (at OUMC): 0.0 - 0.7
  - Synthesis Range (at OUMC): 0.0 - 3.3 mg/24 hrs

- Often present in other conditions such as Lyme disease, syphilis, SSPE, fungal infections, Sjogren’s syndrome
Biologic Biomarkers: CSF Myelin Basic Protein

- Cerebrospinal fluid myelin basic protein (MBP)
  - Represents myelin destruction and breakdown within the CNS

- Acceptable lab ranges
  - Normal: < 4 ng/ml
  - Chronic or recovery phase: ~ 4-8 ng/ml
  - Acute myelin breakdown: > 9 ng/ml

- Levels can be used clinically…
  - To follow the activity of demyelination
  - Assist in the diagnosis of the 10% of MS patients who never form CSF OCB’s
Biologic Biomarkers: Serum Autoantibodies

- Serum myelin basic protein autoantibodies (Anti-MBP Antibodies)
- Serum myelin oligodendrocyte glycoprotein autoantibodies (Anti-MOG Antibodies)
- Well characterized in animal mouse models (i.e., experimental autoimmune encephalomyelitis [EAE])
- Clinical utility is unknown and does not follow a predictable pattern (i.e., repeatable experimental pattern). .yet.
PROPOSED EVALUATION OF PATIENT WITH SUSPECTED MULTIPLE SCLEROSIS:

- Complete history assessing for typical clinical presentations of multiple sclerosis with dissemination in space AND time
- MRI neuroaxis with and without Gadolinium
  - Includes brain, cervical & thoracic spine, and orbits (if history consistent with optic neuritis)
- Referral to neuro
CASE:

- 28-year-old, right-handed woman
- Previously healthy
- CC: 3-day history blurry vision, desaturation of colors, & right eye pain, worse with eye movement
- Exam:
  - VA 20/400 OD, 20/20 OS
  - Right relative afferent pupillary defect (RAPD)
  - Swollen right optic disc
  - Brisk reflexes throughout

Next step(s) in management?
CASE: Continued...

- Admitted to inpatient neurology service
- Started on IV Solumedrol 1G daily X 5 days
- MRI brain, cervical and thoracic spine normal
- MRI orbits as shown
- LP with 7 oligoclonal bands, normal IgG synthesis & index

Diagnosis?
CASE: Continued...

- 2 month outpatient follow-up
- No new symptoms
- MRI brain w/ and w/o Gadolinium repeated
Continued…..

**Diagnosis?**

- **T2 FLAIR**
- **T1 + Gad**
MULTIPLE SCLEROSIS: Treatment

- Acute exacerbations
  - Decrease inflammation
  - IV Steroids (Optic neuritis treatment trial)

- Chronic management
  - Immunomodulation *(see next slide)*
    - Alter the disease course
    - Decrease relapse rate
    - Slow progression of disability
    - MRI stabilization
  - Symptomatic treatment
MULTIPLE SCLEROSIS: Treatment

- Immunomodulation is accomplished via disease modifying therapies (DMTs)
  - First line
    - Injectables: interferons, glatiramare acetate
    - Oral agents: fingolimod, teriflunomide, dimethyl fumarate*
  - Second line
    - Monoclonal antibodies: natalizumab*, alemtuzumab, daclizumab, ocrelizumab
    - Mitoxantrone (secondary progressive MS)
    - Cytotoxic agents (i.e., mycophenolate mofetil, azathioprine)
MULTIPLE SCLEROSIS: Symptomatic Treatment

- Spasticity
- Fatigue
- Urinary dysfunction
- Constipation
- Sexual dysfunction
- Depression
- Pain
- Heat intolerance
MULTIPLE SCLEROSIS: Exacerbation vs. Pseudo-exacerbation

**Exacerbation**
- Immune mediated attack on CNS → development of **new lesions**
- New or worsening neurological deficit (previously stable for 30 days) that persists longer than 24 hours
- Contrast enhancement on MRI

**Pseudo-exacerbation**
- “Uhthoff phenomenon”
- **Reactivation of prior lesions** → worsening of symptoms
- Occurs in the setting of provoking etiology (e.g., heat exposure, fever, dehydration, infection, overexertion, etc.)
- No contrast enhancement

*Relapses are associated with increased disability and decreased quality of life*
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