Multiple Sclerosis: Clinical Features & Laboratory Evaluation

Nicole E Stanley, MD
Anatomic and Clinical Pathology, PGY-3
Learning Objectives

- Discuss the epidemiology, etiology, pathophysiology, and risk factors for Multiple Sclerosis (MS)

- Describe the clinical manifestations, differential diagnosis, and clinical and laboratory evaluation of MS

- Describe the clinical course, management, and monitoring of patients with MS
In 2013, a 34 yo woman presented with 4 days of blurred vision and 7/10 pain in her left eye.

2 episodes in the previous few years of numbness and tingling in left hand.
- Resolved spontaneously.

Otherwise healthy.
- 2 children.
- Grew up in Canada, moved to Utah in 2007.
- Former smoker, infrequent drinker.

Case Presentation
Learning Objectives

- Discuss the epidemiology, etiology, pathophysiology, and risk factors for Multiple Sclerosis (MS)

- Describe the clinical manifestations, differential diagnosis, and clinical and laboratory evaluation of MS

- Describe the clinical course, management, and monitoring of patients with MS
Multiple Sclerosis Definition

- Immune-mediated demyelinating disorder of the central nervous system (CNS)
- Multiple distinct episodes of neurologic symptoms associated with multiple distinct lesions in the white matter of the CNS
- Heterogeneous disorder with variable clinical and pathologic features
- Episodic, then chronic and progressive
**Nerve Conduction Basics**

- **Neuron**
  - Electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals

- **Oligodendrocyte**
  - CNS support cell that insulates neurons by creating the myelin sheath
Nerve Conduction Basics

- Myelin sheath
  - Oligodendrocyte cellular processes that wrap around neuronal axon
  - Defines “white matter”
    - 70% fat
    - 30% protein
  - Increases conduction speed and reduces ion leakage
Nerve Conduction Basics

- Impulse Conduction
  - Ion movement excites the cell membrane
  - Impulse travels down length of axon to transmit signal to target

- Saltatory Conduction
  - Ion movement occurs between myelin segments
  - Myelin sheath allows the impulse to jump down the axon, increasing speed
Demyelination

- Damage to the myelin sheath
  - Infection
  - Autoimmune process
  - Genetic
  - Metabolic derangement

- Slows or even stops impulse conduction
  - Neurologic symptoms

- Eventual damage to neuronal axon
MS Epidemiology

- Most common demyelinating disorder
  - Second most frequent CNS cause of permanent disability in young adults

- 1-25/10,000 globally
  - 1/1000 in US and Europe

- Females > Males
  - 2-3:1

- Mean onset in 20’s-30’s
  - Onset in women is earlier than in men

- Geographic distribution
  - More prevalent further from the equator
MS Etiology

- Poorly understood

- Thought to be a combination of:
  - Genetic predisposition
  - Autoimmunity
  - Environmental exposure

- Alternate theories
  - Genetic defect of oligodendrocytes
  - Reaction to chronic viral infection
Genetics

- Not a heritable disease
- Still a genetic link
  - 30% concordance rate in monozygotic twins
  - 2-5% increased risk in siblings
  - 10% increased risk if both parents are affected
- Over 100 polymorphisms associated with MS
- Strongest association with variants in the major histocompatibility complex (MHC)
  - HLA-DRB1*15:01 (DR15)
  - HLA-DQB1*06:02 (DQ6)
    - T-cell activation and regulation

[Diagram of HLA MHC Complex]
Genetics

- Not a heritable disease
- Still a genetic link
  - 30% concordance rate in monozygotic twins
  - 2-5% increased risk in siblings
  - 10% increased risk if both parents are affected
- Over 100 polymorphisms associated with MS
- Strongest association with variants in the major histocompatibility complex (MHC)
  - HLA-DRB1*15:01 (DR15)
  - HLA-DQB1*06:02 (DQ6)
  - T-cell activation and regulation
Autoimmunity

- Autoreactive lymphocytes, self-directed antibodies
- MS patients are at increased risk for other autoimmune diseases
- DR15 and DQ6 variants also implicated in type 1 diabetes and lupus
- Immune suppression is mainstay of treatment
Infectious stimulation of immune system as MS trigger

Molecular mimicry
- Viral elements similar in structure or sequence to self-antigens
- Immune cells respond to virus but also cross-react with self-antigens
No specific link between MS and any one virus

Epstein-Barr Virus (EBV)
- Infectious mononucleosis
- EBV seropositivity is ~100% in MS patients
- ~85-90% in general population
- Children with MS are much more likely to be EBV positive than healthy peers

Varicella Zoster Virus (VZV)
- Chicken pox, shingles
- VZV DNA in CSF of MS patients with acute relapse
- No VZV DNA in CSF of MS patients in remission
Environment: Vaccination

- Controversial
  - Several vaccine studies show no association

- Hepatitis B Virus (HBV) vaccine
  - Several studies have shown no association

- Tetanus vaccine
  - Possible negative association with MS risk

- Human Papillomavirus (HPV) vaccine?
MS frequency highest in Northern latitudes
  - European white > Asian, African, Native American

Migration studies
  - Individuals keep the risk of region where they spent their pre-pubertal years

2010 review: prevalence > incidence increases with geographic latitude
  - Confounded by healthcare access and quality, increased survival

Adapted from multiplesclerosis.net
Exposure to sunlight may be protective

Proposed explanation for geographic differences

Effects of ultraviolet radiation or vitamin D

High serum vitamin D inversely related with
- Risk of developing MS
- Risk of disease progression
Environment: Other Risks

- Smoking
  - No similar link with smokeless tobacco use
- Childhood obesity
- Gastrointestinal microbiome
- Birth month
  - Gestational/neonatal environment?
Blood brain barrier (BBB) compromised (virus? bacteria?)

- T-cells enter tissue and attack myelin
- Other immune cells, cytokines, destructive proteins arrive
- Nerve conduction disrupted by chemical disruption, myelin loss
- Oligodendrocytes attempt to remyelinate, astrocytes arrive to repair damage
- BBB repaired, “trapping” inflammatory cells

Remyelination less effective over time, leading to axonal damage, scarring, and atrophy
Distinct glassy, grey-tan, firm plaques in white matter
  - Less obvious in grey matter

Multifocal (Multiple) scars (Sclerosis)

Plaques frequently found:
  - Around ventricles
  - Optic nerve
  - Corpus callosum
  - Brainstem (pons)
  - Cerebellum
  - Spinal cord

Brain atrophy over time
Pathologic Features: Micro

- Plaques have:
  - Pale brain tissue
  - Sharp borders with surrounding normal tissue
  - Perivascular chronic inflammation
    - Macrophages
    - Lymphocytes
  - Interstitial macrophages
  - Large stellate reactive astrocytes
Pathologic Features: Micro

Plaques, atrophy

Normal

Axonal Preservation

MS

Axonal Damage
Learning Objectives

- Discuss the epidemiology, etiology, pathophysiology, and risk factors for Multiple Sclerosis (MS)

- Describe the clinical manifestations, differential diagnosis, and clinical and laboratory evaluation of MS

- Describe the clinical course, management, and monitoring of patients with MS
Clinical Manifestations

- **Acute**
  - Unilateral optic neuritis
    - Pain, temporary vision loss
  - Double vision
  - Numbness/tingling
  - Weakness, clumsiness
  - Gait/balance problems
  - Vertigo
  - Urinary incontinence
  - Lhermitte sign
    - Shock sensations caused by neck flexion
  - Uhthoff sign
    - Worsening of symptoms with heat

- **Chronic**
  - Progressive paralysis
  - Sensory loss
  - Aphasia
  - Spasticity
  - Rigidity
  - Involuntary movements
  - Fatigue
  - Seizures
  - Chronic pain
  - Depression
  - Cognitive dysfunction
**Differential Diagnosis**

- **Cerebrovascular**
  - Stroke
  - Vasculitis
- **Infectious**
  - HIV
  - HSV
  - VZV
  - Tertiary syphilis
  - Lyme disease
  - Tuberculosis
  - Rubella
- **Neoplastic**
  - Primary CNS tumors
  - CNS lymphoma
- **Primary neurologic**
  - Migraine
  - Amyotrophic lateral sclerosis
  - Huntington disease
  - Guillain-Barre
- **Metabolic**
  - Vitamin B12 deficiency
  - Copper deficiency
  - Zinc toxicity
  - Wilson disease
- **Primary eye**
  - Retinal detachment
  - Glaucoma
- **Psychiatric**
  - Somatization
  - Conversion disorder
- **Autoimmune**
  - Rheumatoid arthritis
  - Sjogren syndrome
  - SLE
  - Antiphospholipid syndrome
- **Genetic**
  - Hereditary spastic paraparesis
  - Porphyrias
  - Mitochondrial diseases
- **Drug**
  - Alcohol
  - Cocaine
  - Chemotherapies
Diagnosis

- Primarily a clinical diagnosis supported by imaging and laboratory findings

- 2010 McDonald Diagnostic Criteria
  - ≥ 2 attacks AND clinical evidence of ≥ 2 lesions
  - ≥ 2 attacks AND MRI evidence of ≥ 2 lesions
  - Combination
    - 1 year of progressive disability AND two of the following:
      - ≥ 1 brain lesion
      - ≥ 2 spinal cord lesions
      - CSF oligoclonal bands
Clinical Evaluation: Imaging

- Active lesions
  - Gadolinium enhanced MRI
  - Ill-defined, irregular large lesions
  - Blood brain barrier damage
    - Enhancement diminishes 30-40 days following steroid treatment

- Chronic lesions
  - Smaller, ovoid lesions with sharp borders

- Absence of lesions does not exclude diagnosis
Clinical Evaluation: Imaging

- Active lesions
  - Gadolinium enhanced MRI
  - Ill-defined, irregular large lesions
  - Blood brain barrier damage
  - Enhancement diminishes 30-40 days following steroid treatment

- Chronic lesions
  - Smaller, ovoid lesions with sharp borders
  - Absence of lesions does not
Active lesions
- Gadolinium enhanced MRI
- Ill-defined, irregular large lesions
- Blood brain barrier damage
  - Enhancement diminishes 30-40 days following steroid treatment

Chronic lesions
- Smaller, ovoid lesions with sharp borders

Absence of lesions does not exclude diagnosis
Clinical Evaluation: Evoked Potentials

- Electrical events generated in the CNS by external stimulation of a sensory organ, used to detect subclinical CNS deficits
  - Pinpoint lesions in sites not easily visualized by MRI
  - Establish multifocality

- Sensory, auditory, and visual evoked potentials
Laboratory Evaluation

- CSF Oligoclonal bands **ESSENTIAL**
- CSF IgG Index
- CSF IgG synthesis rate **SUPPORTIVE**
- CSF Cell count
- CSF Myelin basic protein **LESSER ROLE**
- CSF Anti-MBP antibodies
- CSF Kappa free light chains **FUTURE**
Lumbar Puncture

- Medical procedure in which a needle is inserted into the spinal canal to collect CSF, usually for diagnostic testing
  - “LP” or “Spinal Tap”
  - Considerations
    - Small volume collection
    - “Clean” vs “bloody” tap
    - Painful, difficult procedure
Oligoclonal Band Detection

- **Oligoclonal bands**
  - Bands produced by immunofixation of oligoclonal immunoglobulins (IgG)
  - IgG antibodies produced by clonally expanded B-cell populations
  - Present in CSF of 95-100% of MS patients

- Gold standard laboratory test for MS
  - High sensitivity ~90-95%
  - High specificity ~85-90%
Oligoclonal Band Detection

- **Isoelectric focusing on agarose gel**
  - Sample proteins travel through a continuous pH gradient under an electric field
  - Stop at (separated by) isoelectric point

- **Immunofixation with IgG antiserum**
  - Sample IgG binds to anti-IgG antibodies
  - Precipitate out, visualized as bands

- **Serum and CSF analyzed in parallel**
  - Distinguish between IgG produced in CSF vs serum IgG
  - ≥ 2 bands in CSF not in serum
Oligoclonal Band Detection

- Oligoclonal band detection in CSF and serum

No bands: Negative
Identical bands: Negative
Identical bands: Negative
≥2 bands in CSF, none in serum: Positive
≥2 bands in CSF, few/different in serum: Positive

Adapted from multiple-sclerosis-research.blogspot.com
IgG Index

- Uses measurements of albumin and IgG in CSF and serum to:
  - Detect/correct for damage to BBB
    - Increased concentration of albumin in CSF
  - Detect IgG production in CSF
    - CSF IgG:albumin ratio compared to serum IgG:albumin ratio
IgG Index: CSF Albumin Quotient

- **Albumin**
  - Not produced or metabolized in CSF
  - Increased concentration indicates BBB breakdown

- **Nephelometry**
  - Anti-albumin antibodies added to specimen
  - Light beam passed through specimen
  - Albumin:antibody complexes cause light to scatter
  - Intensity of scattered light proportional to concentration
IgG Index: CSF Albumin Quotient

- Serum and CSF analyzed in parallel

\[ Q\text{Alb} = \frac{\text{Albumin CSF (mg/dL)}}{\text{Albumin Serum (g/dL)}} \]

- \( Q\text{Alb} \times 1000 = \text{Albumin Index} \)
  - < 9 – intact BBB
  - 9-14 – slight impairment
  - 14-30 – moderate impairment
  - > 30 – severe impairment

- Caveat:
  - Traumatic LP (“bloody” tap)
IgG Index: CSF IgG Quotient

- CSF IgG measured by nephelometry
- Serum and CSF analyzed in parallel

\[
Q_{IgG} = \frac{\text{IgG CSF (mg/dL)}}{\text{IgG Serum (g/dL)}}
\]
IgG Index

\[
\text{IgG Index} = \frac{\text{QIgG}}{\text{QA1b}} = \frac{\text{IgG CSF (mg/dL)/IgG Serum (g/dL)}}{\text{Albumin CSF (mg/dL)/Albumin Serum (g/dL)}}
\]

- Increased CSF ratio compared to that of serum indicates IgG production in the CSF
  - > 0.7 – abnormal

- Sensitivity 90% (>95% when oligoclonal bands are positive)
- Specificity 80%
If BBB is damaged, permeability to albumin should be proportional to that of IgG

Corrects for IgG in CSF due to serum leakage

Estimates amount of IgG being produced in CSF per day

- Uses constants representing

\[
\left[ \frac{\text{IgG}}{\text{CSF}} - \frac{\text{IgG serum}}{369} \right] - \left( \frac{\text{Alb}}{\text{CSF}} - \frac{\text{Alb serum}}{230} \right) \times \frac{\text{IgG serum (0.43)}}{\text{Alb serum}} \times 5
\]
If BBB is damaged, permeability to albumin should be proportional to that of IgG

- Corrects for IgG in CSF due to serum leakage
- Estimates amount of IgG being produced in CSF per day
  - Uses constants representing

\[
\left[ \frac{\text{IgG}_{\text{CSF}} - \frac{\text{IgG}_{\text{serum}}}{369}}{\left( \frac{\text{Alb}_{\text{CSF}} - \frac{\text{Alb}_{\text{serum}}}{230}}{\text{Alb}_{\text{serum}}} \right) \times \frac{\text{IgG}_{\text{serum}}(0.43)}{\text{Alb}_{\text{serum}}}} \right] \times 5
\]

Normal serum:CSF IgG
CSF IgG Synthesis Rate

- If BBB is damaged, permeability to albumin should be proportional to that of IgG
- Corrects for IgG in CSF due to serum leakage
- Estimates amount of IgG being produced in CSF per day
  - Uses constants representing

\[
\left[ \frac{\text{IgG}_{\text{CSF}} - \frac{\text{IgG}_{\text{serum}}}{369}}{\text{Alb}_{\text{CSF}} - \frac{\text{Alb}_{\text{serum}}}{230}} \right] \times \frac{\text{IgG}_{\text{serum}} (0.43)}{\text{Alb}_{\text{serum}}} \times 5
\]

Normal serum:CSF albumin
If BBB is damaged, permeability to albumin should be proportional to that of IgG

Corrects for IgG in CSF due to serum leakage

Estimates amount of IgG being produced in CSF per day

- Uses constants representing

\[
\text{IgG:albumin molecular weight ratio} = 0.43
\]

\[
\left[ \frac{\text{IgG}}{369} - \left( \frac{\text{IgG serum}}{230} \right) \times \frac{\text{IgG serum}}{\text{Alb serum}} \right] \times 5
\]
If BBB is damaged, permeability to albumin should be proportional to that of IgG

Corrects for IgG in CSF due to serum leakage

Estimates amount of IgG being produced in CSF per day
  - Uses constants representing daily CSF production (dL)
CSF IgG Synthesis Rate

- > 8 mg/d indicates increased CSF IgG production
  - 90% of MS patients
  - 4% of normal individuals

- Sensitivity 85-90%
- Specificity 80%
CSF Cell Count

- White Blood Cells
  - normal < 5 cells/μL
  - MS 15 - 50 cells/μL
  - > 50 cells/μL, consider another etiology

- Differential: primarily lymphocytes
  - T-cells
  - Other cell types, consider another etiology
Myelin Basic Protein (MBP)
- Presence in CSF can indicate active demyelination
- Increases during acute exacerbations

Chemiluminescent sandwich-type immunoassay
- Relative light output units directly proportional to MBP concentrations

>5.5 ng/mL is abnormal
CSF Kappa Free Light Chains

- Plasma B-cells secrete excess free light chains in CSF
  - Elevation may occur earlier than IgG

- Measured by nephelometry
  - Calculated similarly to IgG index/synthesis rate

- Comparison with oligoclonal band detection
  - Similar sensitivity in MS: 90-95%
  - Improved sensitivity in CIS ("early MS"): 80% vs 70%
  - Less technically demanding and time consuming
  - Rater-independent
Case Presentation

- Physical Exam: central vision defect
- MRI: Enhancement of left optic nerve
  - Possible spinal cord lesion, unable to characterize definitively
- Oligoclonal band detection: Positive (3 bands)
- Increased IgG Index: 0.74
- Increased IgG synthesis rate: 8.7 mg/d
- CSF cell count: 23 cells/μL (22 lymphs, 1 mono)
- Does she meet McDonald diagnostic criteria?
Case Presentation

- Physical Exam: central vision defect
- MRI: Enhancement of left optic nerve
  - Possible spinal cord lesion, unable to characterize definitively
- Oligoclonal band detection: Positive (3 bands)
  - Increased IgG Index: 0.74
  - Increased IgG synthesis rate: 8.7 mg/d
  - CSF cell count: 23 cells/μL (22 lymphs, 1 mono)
- Does she meet McDonald diagnostic criteria?
  - Yes! (≥ 2 attacks AND clinical evidence of ≥ 2 lesions)
Learning Objectives

- Discuss the epidemiology, etiology, pathophysiology, and risk factors for Multiple Sclerosis (MS)

- Describe the clinical manifestations, differential diagnosis, and clinical and laboratory evaluation of MS

- Describe the clinical course, management, and monitoring of patients with MS
Clinical Course

- Four MS Types
  - Clinically Isolated Syndrome
  - Relapsing-Remitting MS
  - Secondary Progressive MS
  - Primary Progressive MS
Clinical Course: Clinically Isolated Syndrome

- One attack of symptoms compatible with MS but does not yet fulfill diagnostic criteria
  - Lasts ≥ 24h with full or partial resolution
  - Not due to other cause
  - 20-60% risk of progression to MS

- Radiographically Isolated Syndrome (RIS)
  - Incidental MRI findings compatible with MS but without symptoms
  - Not due to other disease process
  - Estimated 30% risk of progression to MS (limited data)

Adapted from Neurology 1996; 46(4):907-911
80-90% of patients, initially

Discrete attacks separated by periods of return to near-normal function

Most will enter a secondary progressive phase

Complete resolution between attacks, even 15 years from onset, is referred to as benign MS
Clinical Course: Secondary Progressive

- 60-70% of initial relapsing-remitting MS cases
- Progressive neurologic decline without definite periods of remission
- Transition usually 10-20 years after disease onset
- Distinction is usually made retrospectively

Adapted from Neurology 1996; 46(4):907-911
Clinical Course: Primary Progressive

- 10% of MS patients at onset
- Progressive neurologic decline from the start
- Occasional plateaus, minor improvement, and acute worsening of symptoms
- Later mean age of onset at 40
- More even sex distribution
- Worse prognosis

A rapidly progressive course, with significant deficits in multiple neurologic systems, shortly after onset is referred to as **malignant MS**

Adapted from Neurology 1996; 46(4):907-911
Management: Acute Exacerbations

- Steroid therapy
  - Immune suppression
  - IV methylprednisolone
  - Oral prednisone

- Plasma exchange if not responsive to steroids
  - Removal of antibodies from blood

- Symptom management
Management: Relapsing-Remitting

- **Disease modifying therapies (DMT)**
  - Reduce relapse rate
  - Slow plaque accumulation
  - Immunosuppression, liver toxicity, birth defects

- **Natalizumab** (humanized monoclonal antibody)
  - Interferes with T-cell migration into CNS

- **Glatiramer acetate** (amino acid polymer resembling MBP)
  - Shifts T-cell population from proinflammatory to regulatory
  - Acts as a decoy, attracting autoimmune T-cells away from myelin

- **Teriflunomide**
  - Disrupts interaction between T-cells and antigen presenting cells
Management: Progressive

- Therapies are limited

- Primary progressive
  - **Ocrelizumab** (human monoclonal antibody)
    - Targets CD20, depleting B-cell population
    - Only DMT with good evidence of efficacy

- Secondary progressive
  - **Siponimod** (sphingosine 1-phosphate receptor modulator)
    - Interferes with lymphocyte migration into CNS

- Symptom management
Monitoring

- Brain MRI every 12 months
- Assessment using Expanded Disability Status Scale (EDSS) every 3 months
  - Movement, sensation, vision, cognition, brainstem and bowel/bladder function
- Limited laboratory role in monitoring disease activity
  - Therapy
    - IFN-β neutralizing antibody
    - Natalizumab antibodies
    - Side effects
      - CBC
      - LFT
Case Presentation

- Placed on natalizumab therapy at diagnosis
- Initial symptoms resolved
- 2 additional episodes of numbness and tingling in both hands
- Mild permanent sensory loss in left hand, mild chronic fatigue
- Most recent MRI 2017: left optic nerve and spinal cord lesions
- EDSS score 2018: 2.0
Case Presentation

- Placed on natalizumab therapy at diagnosis
- Initial symptoms resolved
- 2 additional episodes of numbness and tingling in left hand
- Mild permanent sensory loss in hand, mild chronic fatigue
- Most recent MRI 2017: optic nerve and spinal cord lesions
- EDSS score 2018: 2.0
Summary

- MS is a chronic, immune-mediated, heterogeneous neurologic disorder with variable clinical and pathologic findings
  - Etiology and pathogenetic mechanism poorly understood

- Clinical diagnosis, supported by imaging and laboratory findings
  - Very few findings are specific to MS

- Therapy based on immunosuppression and immunomodulation
Thank You!

- For listening!
- Jonathan Genzen, MD
- Elizabeth Frank, PhD
- Anu Maharjan, PhD
- Carmen Gherasim, PhD
- Timothy Hanley, MD, PhD
- Mary Offe

Adapted from sciencenotes.org
ARUP Consult


References