Multiple Sclerosis

- Definition:
  - MS is an inflammatory demyelinating disease of the central nervous system of unknown etiology
- The most common CNS demyelinating disease
- The most common cause of non-traumatic neurologic disability in young adults

Epidemiology

- 250,000 to 400,000 affected in the US
- 57.8 per 100,000 prevalence in the US
- Frequency much higher in temperate zones, north and south of the equator, rare in the tropics – environmental component
- Women affected 2-3 times the rate of men

History

- 14th century:
  - “Blessed Lidwina of Schneider”, the earliest account of the disease, affecting a Dutch nun
- 1838,1845:
  - Carswell and Cruveiller publish the first pathologic descriptions
- 1868:
  - Charcot publishes the first comprehensive tretise on the clinical features and pathology of MS

Worldwide Prevalence of MS

Potential Triggers for MS

- Infectious agent
- Genetic predisposition
- Abnormal immunologic response
- Environmental factors
  - MS
Etiology

- The cause of MS is not known
- Best hypothesis:
  - MS is an autoimmune disease that occurs in genetically susceptible persons following an environmental exposure
- Experimental allergic encephalomyelitis (EAE):
  - animal model for MS

Genetics

- MS is polygenic resulting in susceptibility to the disease
  - 1st degree relations of MS patients have 20 fold increased risk
  - Monozygotic twins have 20-40% risk
  - Dizygotic twins have 3-4% risk
- HLA class II region on short arm of chromosome 6 associated with increased risk of MS

Immunopathogenesis of MS

- Autoreactive T cells directed against CNS targets (e.g., myelin)
  - Hypothesis:
    - Common viruses may trigger acute immune-mediated demyelination through molecular mimicry
    - cross reactivity between virus proteins and myelin

- Activation:
  - T cells activated in the periphery
  - requires antigen presentation within the major histocompatibility complex on the surface of an antigen-presenting cell
  - macrophage
  - dendritic cell
  - T cells bind to antigens
  - Adhesion:
    - activated T cells bind to BBB

- Attraction:
  - chemokine gradients may attract T cells that express chemokine receptors

- Invasion:
  - disruption of BBB enables T cells to invade the CNS

- Reactivation:
  - T cells reactivate in the CNS when they encounter local antigen-presenting cells
    - microglia
    - macrophages

Precipitating Factors

- Viral or bacterial infection may precipitate exacerbations
- Pregnancy
  - risk of exacerbation decreases by 2/3 in 3rd trimester
  - risk of exacerbation increases post partum, occurring in 20-40% of such patients
  - overall, pregnancy may have little long term effect on the disease
Pathology

- CNS demyelination with relative axonal sparing
  - MS plaque develops in stages
- Lymphocytes and macrophages migrate across blood brain barrier into perivascular space
  - perivascular plaque distribution, Dawson's fingers
- Diffuse parenchymal infiltration by inflammatory cells, edema, and demyelination of white matter by lipid laden macrophages

Pathology

- Astrocyte hyperplasia and accumulation of lipid laden macrophages
- Plaques enlarge and coalesce, periventricular distribution becomes less apparent
- Axonal sparing is relative but occurs in almost all lesions
- Gray matter inflammatory reaction is much less pronounced, due to less myelin in these areas
- Oligodendrocyte proliferation and remyelination may occur

Pathophysiology

- Inflammatory demyelination causes conduction delay along axons
- Conduction may improve as edema resolves and remyelination occurs

Diagnosis

- Symptoms and signs disseminated in time and space in the CNS
  - clinically definite MS (CDMS)
- No one single test is diagnostic
- McDonald Criteria, 2001

Symptoms and Signs

- Visual
- Motor
- Sensory
- Coordination
- Pain
- Cognition
- Psychiatric
- Fatigue
- Bowel, Bladder, Sexual Dysfunction
### Vision
- 30% MS patients present with visual symptoms
  - Optic neuritis
    - mononuclear (usually) visual loss
    - develops over hours to days
    - pain on eye movement in 90%
    - associated with loss of color perception and visual field (scotoma)
    - afferent pupillary defect (Marcus Gunn pupil)
    - 2/3 Retrobulbar; 1/3 papillitis

### Ocular Motor Syndromes
- Internuclear ophthalmoplegia (INO), often bilateral later in the course of MS
- Nystagmus
- Impaired pursuit
- Ocular dysmetria

### Motor
- Weakness:
  - one or more extremities
- Bilateral weakness suggests myelitis (spinal cord inflammation), usually lower extremities
- Spasticity (increased tone), especially of lower extremities – may cause spastic gait
- Hyperreflexia and ankle clonus
- Extensor plantar signs

### Sensory
- 1/3 have sensory disturbance as the initial symptom
  - the majority develop sensory symptoms during the course of the disease
- Symptoms vary
  - tingling
  - numbness
  - burning
  - electrical

### Sensory
- A sensory level defines spinal cord involvement, as in myelitis
- Lhermitte’s phenomenon:
  - an electric tingling sensation down the back or into the arms and legs, precipitated by neck flexing, and indicative of cervical spinal cord disease

### Coordination
- Imbalance and incoordination
- Cerebellar dysfunction especially in upper extremities
- Gait ataxia
- Nystagmus
- Scanning dysarthria (impaired prosody)
Pain
- Pain is common
- May be due to sensory disturbances or due to muscle spasticity
- Trigeminal neuralgia may occur
- A band-like tightness about the abdomen or thorax is common

Cognition
- 50% of MS patients show cognitive impairment in the course of the disease
- May affect short term memory, concentration, attention, and processing
- Dementia is uncommon

Psychiatric
- Depression is common
  - 50% have at least one episode of major depression
- 10% have pseudobulbar affect:
  - inappropriate laughing or weeping
- Bipolar disorder is more common in MS

Fatigue
- May be the most common symptom
- Fatigue may worsen with heat

Bowel, Bladder, Sexual Dysfunction
- Bladder dysfunction is common
  - urinary urgency
  - incontinence
  - urinary retention
- Constipation is common
  - fecal incontinence is rare
- Sexual dysfunction occurs in 50-75%

Clinical Pattern
- 85% present with relapsing remitting MS (RRMS)
- Secondary progressive MS (SPMS) develops 10 to 20 years after initial symptoms
  - relapses may still occur
- 10-15% have primary progressive MS (PPMS), steady decline
  - more likely to be men over age 40
- 6% have progressive-relapsing MS (PRMS), steady decline following initial attack, punctuated by further relapses
Progression of Untreated MS

- Relapsing forms
- Subclinical mono-symptomatic
- Relapsing-remitting Secondary Progressive
- Initial demyelinating event
- Clinically definite MS

Variants
- Marburg's disease
- Neuromyelitis optica (Devic's disease)
- Acute disseminated encephalomyelitis (ADEM)
- Acute necrotizing hemorrhagic encephalopathy (ANHE)
- "Tumefactive" MS

MRI
- Brain MRI is abnormal in 95% of CDMS patients
- Hyperintense T2/FLAIR white matter foci,
  - typically periventricular
  - typically ovoid or round
  - often perpendicular to lateral ventricles
    (Dawson's fingers)

- Often affect corpus callosum
- Often juxtacortical (gray-white matter junction)
- Often affect spinal cord, cervical 2x more common than thoracic
- May enhance on T1W contrast images
- T1W hypodensities may be seen in similar distribution
- Cerebral atrophy develops later in the course of MS

Clinically Isolated Syndrome
- Presenting as 1st symptom or sign
- Brain MRI consistent with MS
- Diagnosis established as previously described

MRI
- Gd enhancement
- T2 lesion
- Brain atrophy (shrinkage)
- Spinal cord lesion

Gd = gadolinium.

MRI, magnetic resonance imaging
Atrophy or Shrinkage

MS can cause permanent loss of brain tissue (atrophy or shrinkage)

MRI FLAIR Sequence

Paraclinical Testing

- CSF by Lumbar Puncture
  - increased lymphocytes, usually <50 cell/mm³
  - increased total protein, usually <100 mg/dl
  - oligoclonal bands (OCB) present in 80-90% CDMS patients; not pathognomonic
  - IgG index often increased
  - myelin basic protein often increased but not specific

MRI Sagittal FLAIR Sequence

Paraclinical Testing

- Evoked Potentials
  - visual evoked potentials (VEP) are most sensitive
  - somatosensory evoked potentials (SSEP) measure posterior column function to the cortex
  - brainstem auditory evoked potentials (BAEP) are not a measure of auditory function

Differential Diagnosis

- Vascular:
  - small vessel arteriopathy
  - vasculitis
  - AVM
- Structural:
  - skull base anomaly
  - tumor
Differential Diagnosis

- **Degenerative:**
  - motor neuron disease
  - spinocerebellar degeneration
- **Genetic:**
  - leukodystrophies
- **Infection:**
  - HTLV-1, HIV myelopathy
  - HIV-related cerebritis
  - Lyme disease

- **Other:**
  - ADEM
  - cobalamin (B12) deficiency
  - sarcoid
  - Sjogren’s syndrome
  - nonspecific MRI
- **Psychiatric disorder**

MRI Differential Diagnosis

- Diseases that mimic Multiple Sclerosis on MRI
  - ADEM
  - small vessel disease
  - CADASIL
  - sarcoidosis
  - Vasculitis
  - Migraine
  - Age related changes
  - Organic aciduria
  - Histiocytosis
  - HTLV-1
  - Lyme disease
  - Leukodystrophies
  - Mitochondrial disease
  - Lupus
  - Behcet’s disease
  - HIV

Disease Modifying Therapies

- **Beta Interferons**
  - naturally occurring cytokines with immunomodulatory and antiviral properties
  - mechanisms of action, modulation of:
    - major histocompatibility complex expression
    - suppressor T-cell function
    - adhesion molecules
    - matrix metaloproteinases

- Interferon beta 1a
  - Avonex IM
  - Rebif SQ
- Interferon beta 1b
  - Betaseron SQ
  - reduce relapses by 1/3 and MRI lesions by 50-80% compared to placebo

- side effects:
  - fever
  - chills
  - muscle aches
  - malaise
  - depression
  - worsening of spasticity
  - transaminase elevation (Rebif)
  - neutralizing antibodies (NAB)
**Disease Modifying Therapies**

- **Glatiramer acetate (Copaxone)**
  - polypeptide
  - mechanism:
    - designed to mimic MBP
  - reduces relapses by 1/3 and MRI lesions by 1/3 compared to placebo
  - side effects:
    - flushing
    - chest tightness
    - dyspnea
  - NAB do not develop
  - SQ

- **Natalizumab (Tysabri)**
  - recombinant humanized IgG4 kappa monoclonal antibody
  - mechanism:
    - binding of alpha 4-integrin with vascular cell adhesion molecules (VCAM-1) on the blood brain barrier initiates leukocyte adhesion and migration across the BBB
    - natalizumab, a selective adhesion molecule (SAM) inhibitor, blocks adhesion, preventing migration across the BBB
  - reduces relapses by 2/3 and reduces MRI lesions compared to placebo
  - 1 year data of planned 2 year study
  - side effects:
    - hypersensitivity reaction
    - anaphylaxis
    - headache
    - arthralgia
    - fatigue
    - infection
    - NAB may develop
  - IV

- **Mitoxantrone (Novantrone)**
  - anthracenedione antineoplastic agent
  - reduces treated relapses by 67% compared to placebo
  - cardiotoxicity limits lifetime cumulative dose 120-140 mg/m² (2-3 years)
  - potential leukemia
  - IV
  - for worsening forms of relapsing MS and SPMS

**Other Disease Modifying Therapies**

- **Lack FDA approval**
  - IVIG
  - methotrexate
  - azathioprine
  - cyclophosphamide

**Experimental**

- IL-12 (interleukin-12)
- IL-2 receptor
- VLA-4 (very late antigen-4)
- phosphodiesterase inhibitors
- novel NSAIDS
- beta adrenergic agonists
- lipid lowering agents
- Schwann cell transplantation
- immunoablation by high dose chemotherapy, followed by autologous stem-cell rescue
Symptomatic Therapy

- **Acute exacerbations:**
  - corticosteroids
  - IV methylprednisolone

- **Spasticity:**
  - baclofen
  - tizanidine
  - diazepam
  - stretching
  - aqua therapy

Symptomatic Therapy

- **Pain:**
  - tricyclic antidepressants
    - amitriptyline
    - nortriptyline
  - anticonvulsants
    - carbamazepine
    - gabapentin
    - topiramate
    - valproate

Symptomatic Therapy

- **Vertigo:**
  - meclizine

- **Fatigue:**
  - amantadine
  - modafinil

- **Urinary urgency:**
  - oxybutinin
  - tolterodine

- **Urinary retention:**
  - catheterization

Symptomatic Therapy

- **Erectile dysfunction:**
  - sildenafil, etc.

- **Psychiatric:**
  - antidepressants
  - anxiolytics
  - counseling

Other CNS Inflammatory Demyelinating Disorders

- Isolated inflammatory demyelinating CNS syndromes
- Neuromyelitis optica
- Acute disseminated encephalomyelitis
- Experimental allergic encephalomyelitis

Isolated Inflammatory Demyelinating CNS Syndromes

- **Region restricted**
- **Most common**
  - Optic neuritis
  - Myelitis
  - Brainstem
Neuromyelitis Optica
Devic's Disease/Syndrome

- Optic neuropathy/neuritis and myelopathy/myelitis
- Inconsistently defined
- Opticospinal MS – East Asia
- Pathology
  - Acute myelitis
    - Inflammation involving several levels
    - Macrophage infiltration
    - Loss of myelin and axons
  - Optic neuritis – similar pathology

Acute Disseminated Encephalomyelitis (ADEM)

- Monophasic CNS inflammatory demyelinating disorder
  - Begins several weeks after antigenic challenge
  - Multifocal or focal deficits
- Pathology: perivenous inflammation, edema, demyelination
  - Overlaps MS
- Clinical
  - HA, fever, myalgia, malaise
  - Neurological symptoms and signs

Experimental Allergic Encephalomyelitis (EAE)

- Antigen specific, T-cell mediated autoimmune disease
  - Acute EAE resembles ADEM
  - Chronic-relapsing EAE resembles MS
- Used to screen for potentially effective treatments for MS

CNS Demyelination
Viral Infections

- Progressice multifocal leukoencephalopathy (PML) – JC papilloma virus
  - Focal neurologic deficits, seizures, cognitive impairment
  - Reactivation of latent virus associated with immunosuppression
- Subacute sclerosing panencephalitis (SSPE) – measles virus
  - Several years after measles infection

CNS Demyelination
Viral Infections

- Human T-cell lymphoma/leukemia virus Type I (HTLV-I) associated myelopathy, tropical spastic paraparesis (HAM-TSP)
  - Slowly progressive spastic paraparesis
  - Demyelination with axonal involvement
- Acute or recurrent myelitits – varicella zoster virus or herpes simplex virus

Leukodystrophies

- Genetic inborn errors of metabolism
  - Demyelination: destruction of normal myelin
  - Dysmyelination: abnormal lipids incorporated into defective myelin
- Subtypes
  - Pelizaeus – Merzbacher syndrome
  - Cockayne’s syndrome
  - Alexander’s syndrome
  - Canavan’s syndrome
  - Krabbe’s syndrome
  - Metachromatic leukodystrophies
  - Peroxisomal leukodystrophies: adrenoleukodystrophy
Summary

- MS is an autoimmune inflammatory demyelinating disease of the CNS
- Most commonly occurs in a relapsing remitting pattern
- Diagnosis is established by symptoms and signs separated in time and space, supplemented by MRI and additional paraclinical testing
- Management focuses on immunomodulatory therapy and symptom specific treatments