Multiple Sclerosis: Clinical Features & Laboratory Evaluation

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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

Case Presentation

- 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

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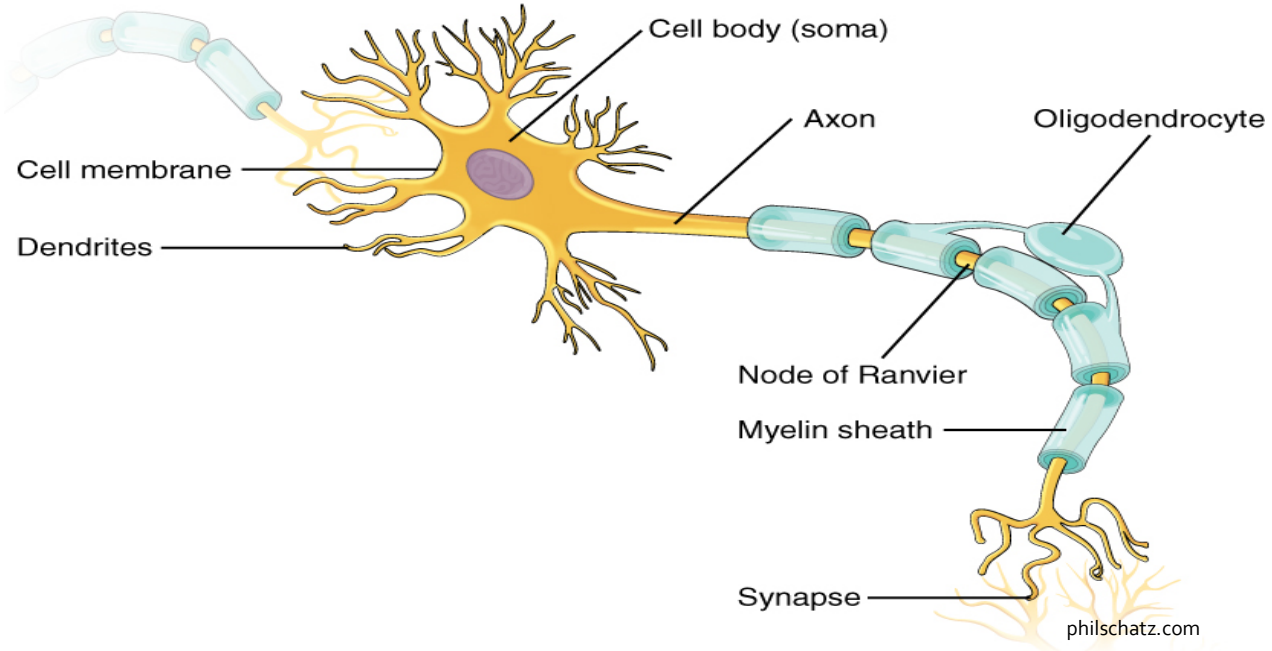
Multiple Sclerosis Definition

- 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

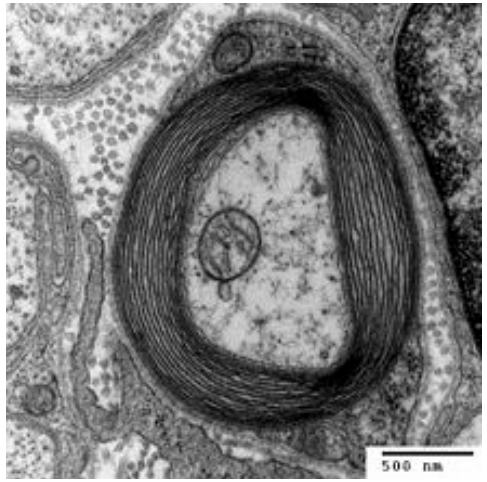
- Neuron
  - Electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals

- Oligodendrocyte
  - CNS support cell that insulates neurons by creating the myelin sheath

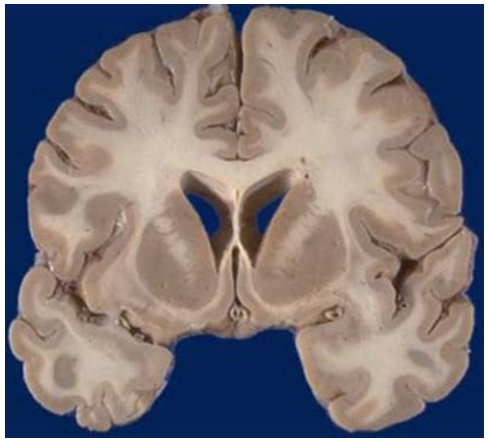


Nerve Conduction Basics

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



Electron Microscopy Facility, Trinity College



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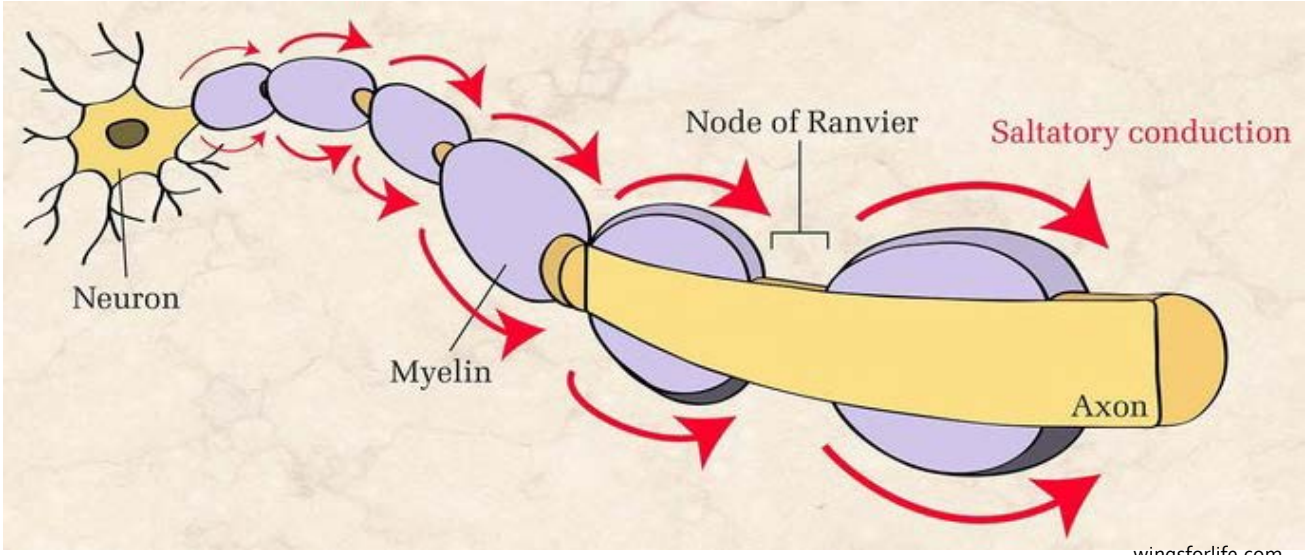
Nerve Conduction Basics

- 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



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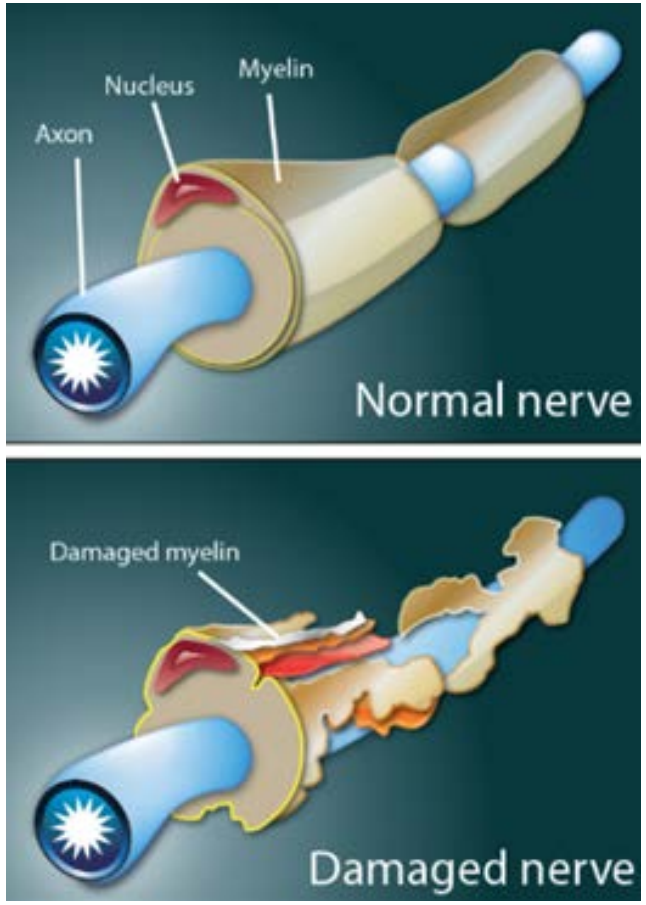
Demyelination



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- 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

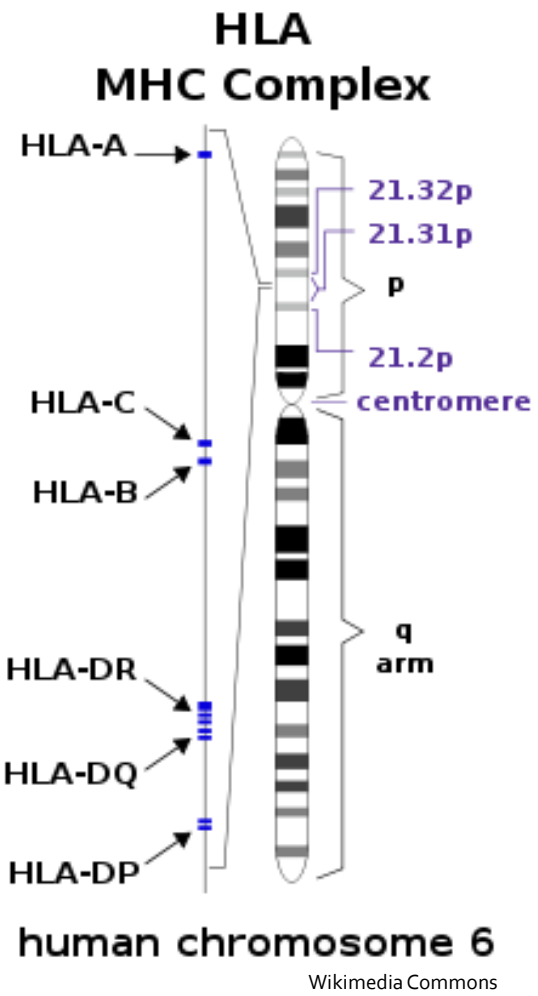
- Most common demyelinating disorder
  - Second most frequent CNS cause of permanent disability in young adults
- 1-25/10,000 globally
  - 1/1000 in US and Europe
- Females > Males
  - 2-3:1
- Mean onset in 20's-30's
  - Onset in women is earlier than in men
- Geographic distribution
  - More prevalent 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 histocompatability complex (MHC)
  - HLA-DRB1*15:01 (DR15)
  - HLA-DQB1*06:02 (DQ6)
    - T-cell activation and regulation



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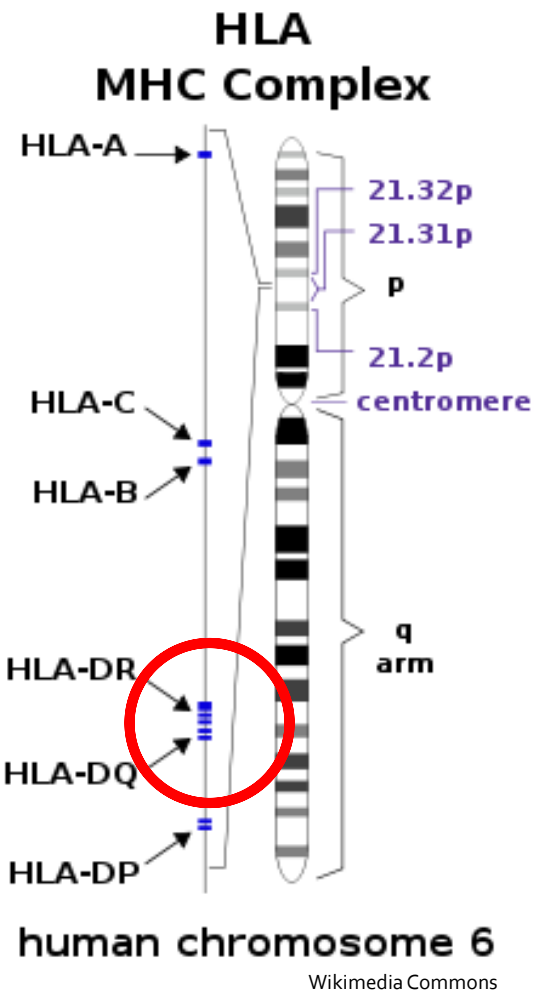

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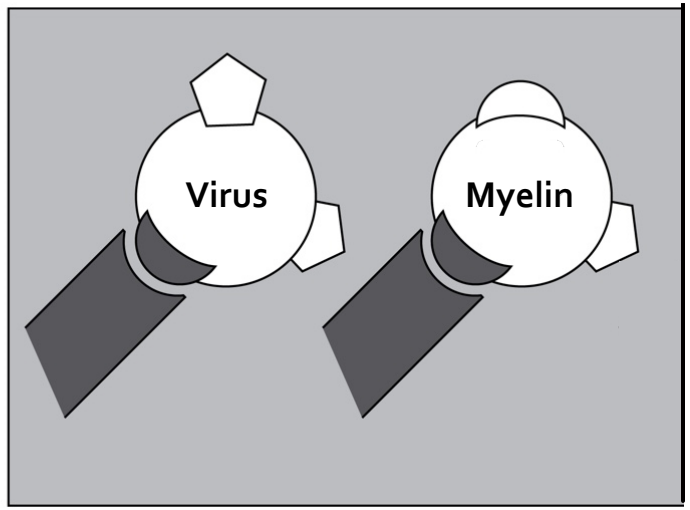
Autoimmunity

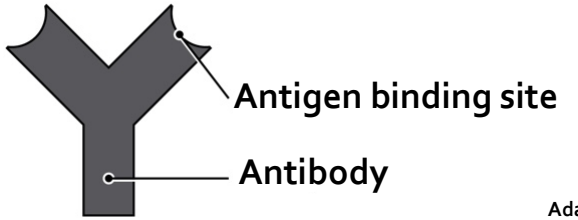
- Autoreactive lymphocytes, self-directed antibodies
- MS patients are at increased risk for other autoimmune diseases
- DR15 and DQ6 variants also implicated in type 1 diabetes and lupus
- Immune suppression is mainstay of treatment

Environment: Viral infection

- 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

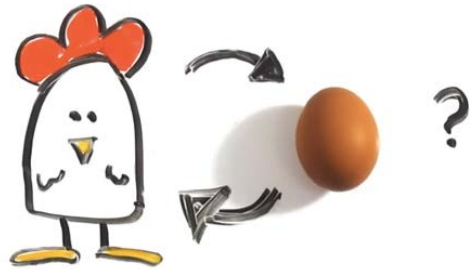




Adapted from amymyersmd.com

Environment: Viral infection

- 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



theblaze.com

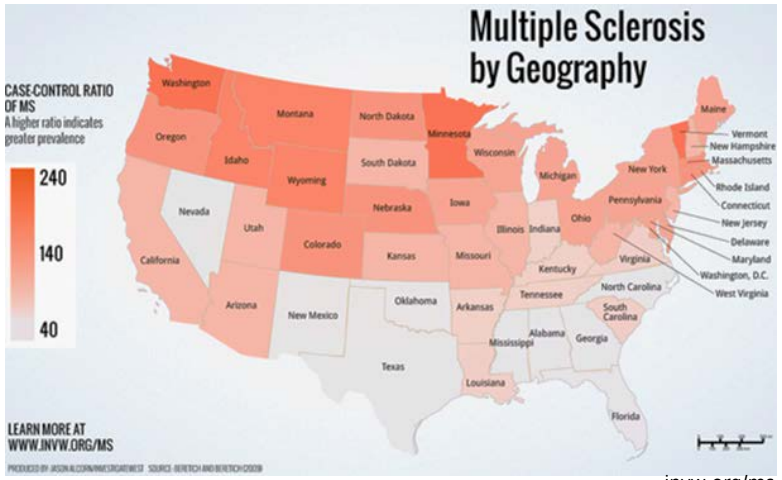
Environment: Vaccination

- 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?

Environment: Geographic Distribution

- 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

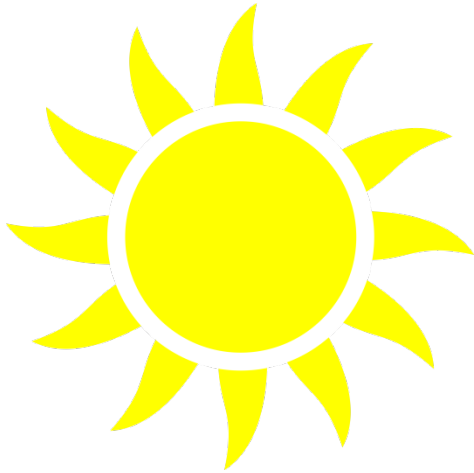
Adapted from multiplesclerosis.net



invw.org/ms

Environment: Sunlight

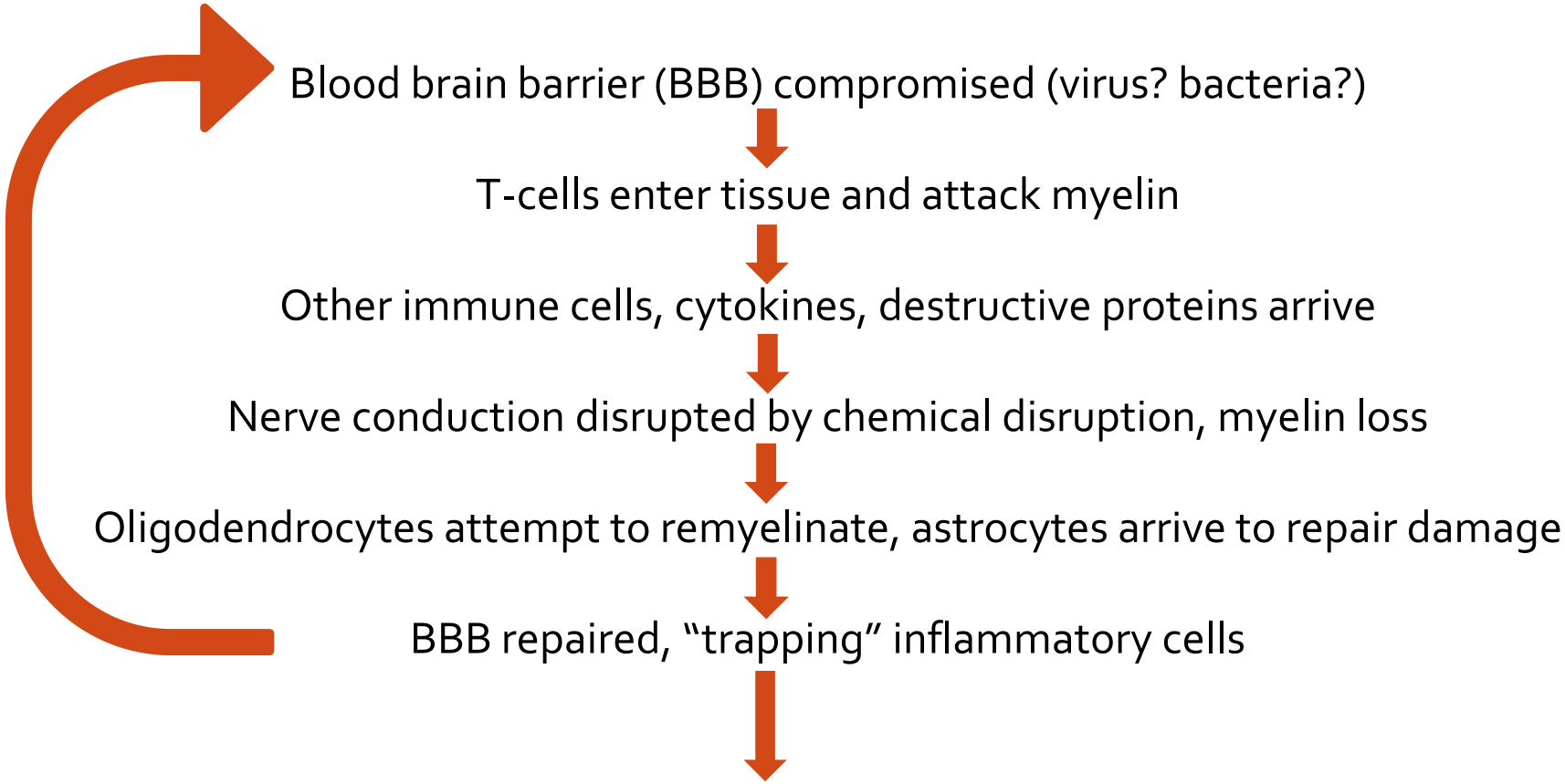
- Exposure to sunlight may be protective
- Proposed explanation for geographic differences
- Effects of ultraviolet radiation or vitamin D
- High serum vitamin D inversely related with
  - Risk of developing MS
  - Risk of disease progression



Environment: Other Risks

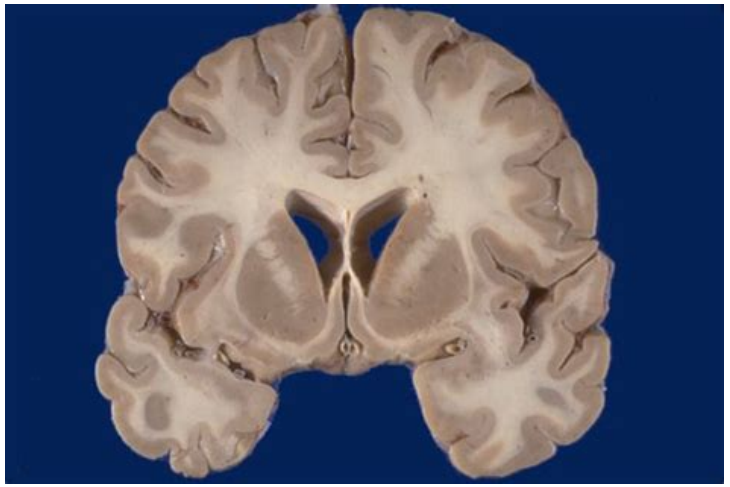
- Smoking
  - No similar link with smokeless tobacco use
- Childhood obesity
- Gastrointestinal microbiome
- Birth month
  - Gestational/neonatal environment?

Pathophysiology

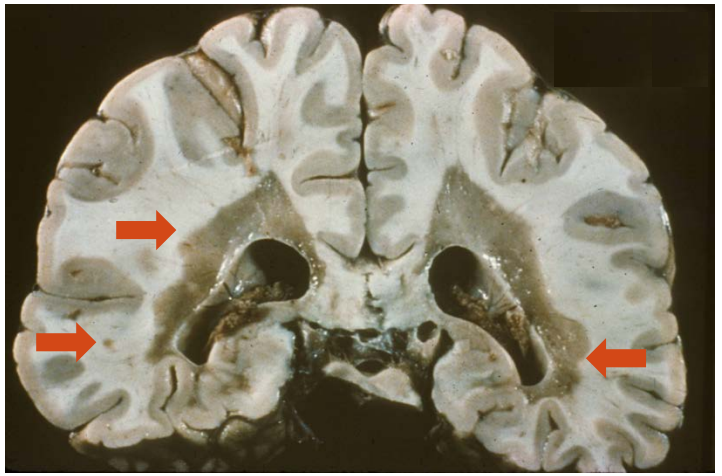


Pathologic Features: Macro

- 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



Normal



MS

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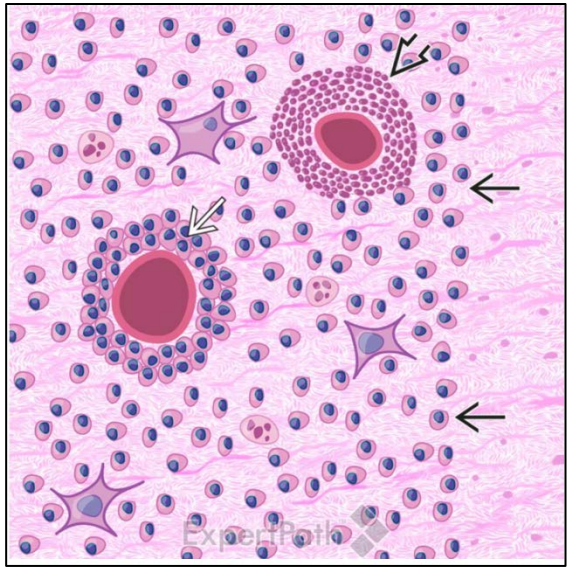
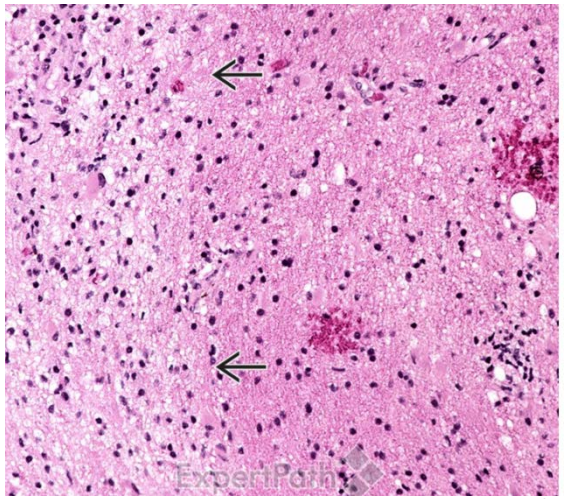
urmc.rochester.edu

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





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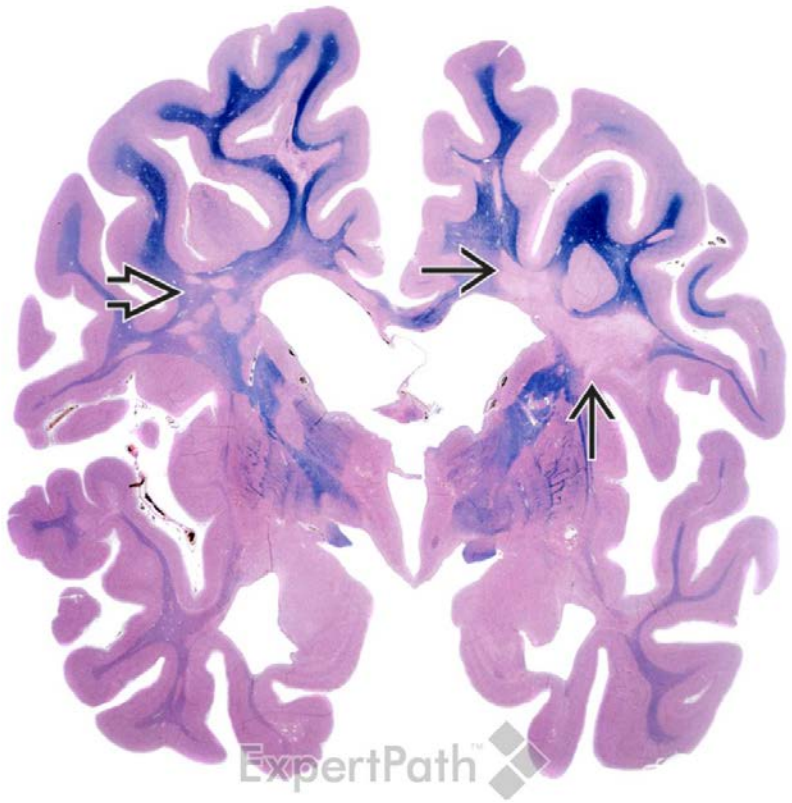
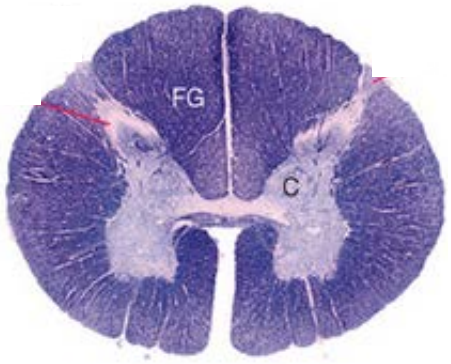
Pathologic Features: Micro



Plaques, atrophy



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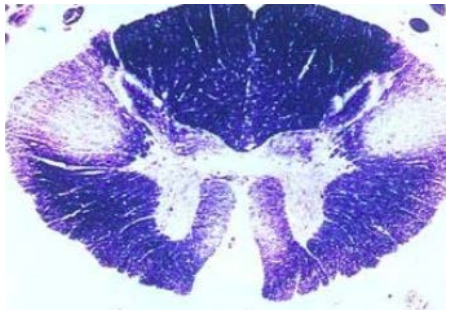

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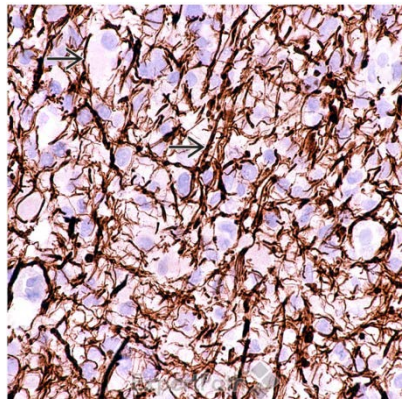
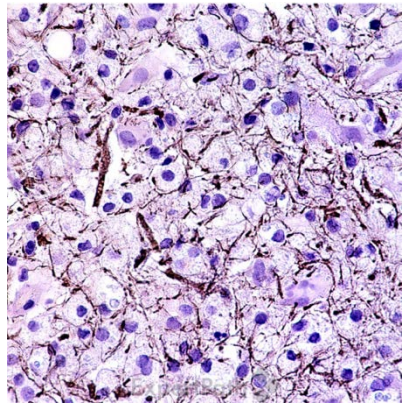


Axonal Preservation



Axonal Damage

Nolte:The Human Brain 2009
patalogia.gabeents.com
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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

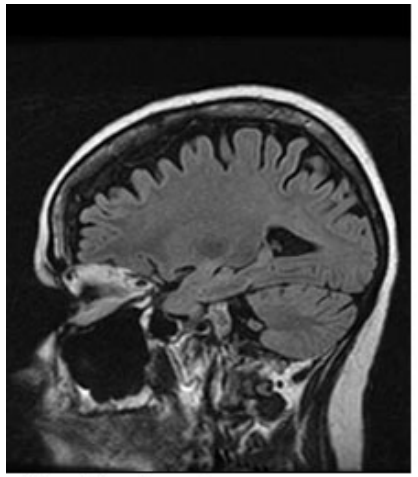
- Primarily a clinical diagnosis supported by imaging and laboratory findings

- 2010 McDonald Diagnostic Criteria
  - ≥ 2 attacks AND clinical evidence of ≥ 2 lesions
  - ≥ 2 attacks AND MRI evidence of ≥ 2 lesions
  - Combination

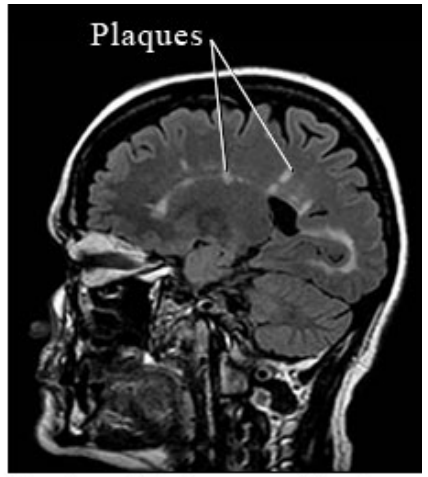
  - 1 year of progressive disability AND two of the following:
    - ≥ 1 brain lesion
    - ≥ 2 spinal cord lesions
    - CSF oligoclonal bands

Clinical Evaluation: Imaging

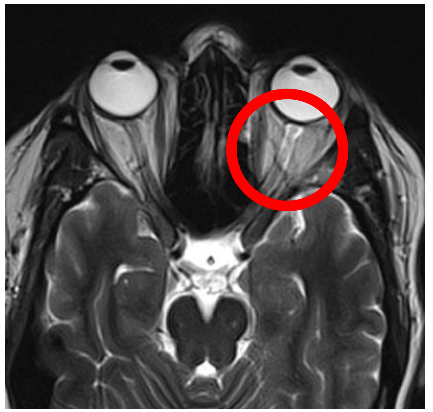
- Active lesions
  - Gadolinium enhanced MRI
  - Ill-defined, irregular large lesions
  - Blood brain barrier damage
    - Enhancement diminishes 30-40 days following steroid treatment
- Chronic lesions
  - Smaller, ovoid lesions with sharp borders
- Absence of lesions does not exclude diagnosis

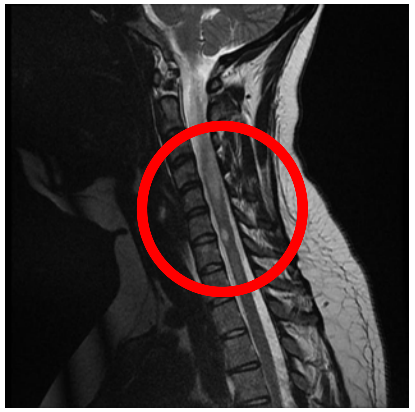


Healthy brain



Brain with damage (lesions or plaques) caused by MS





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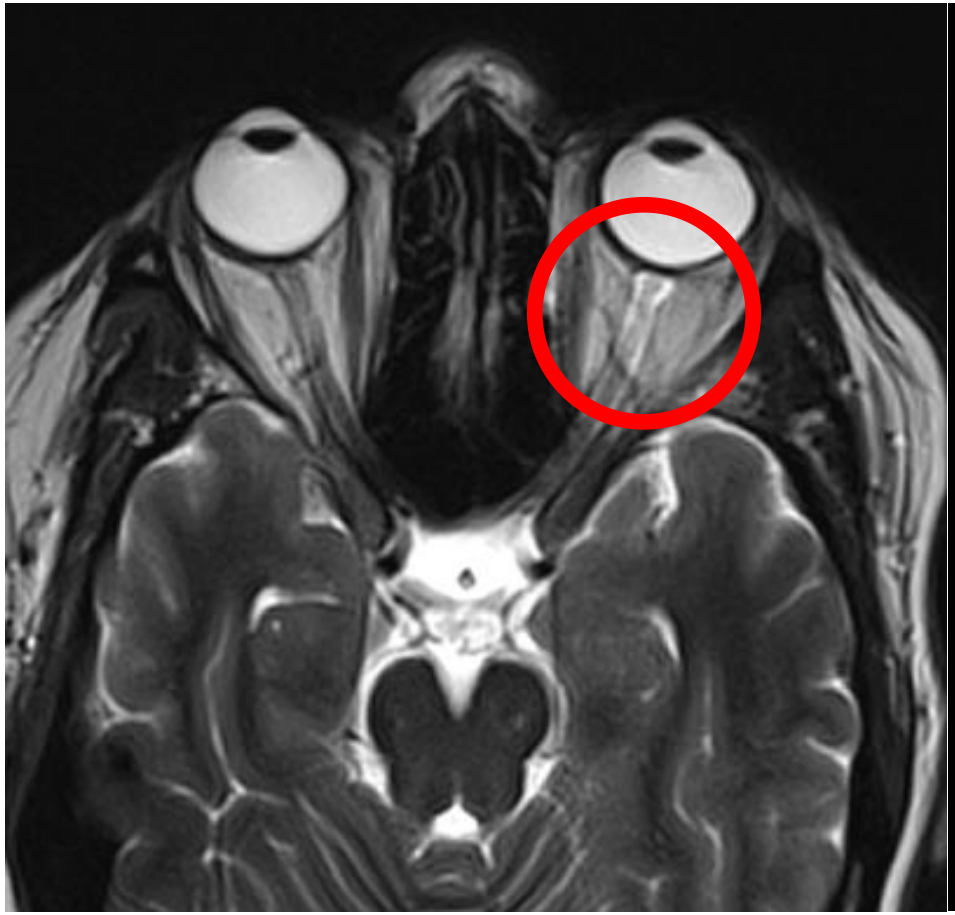
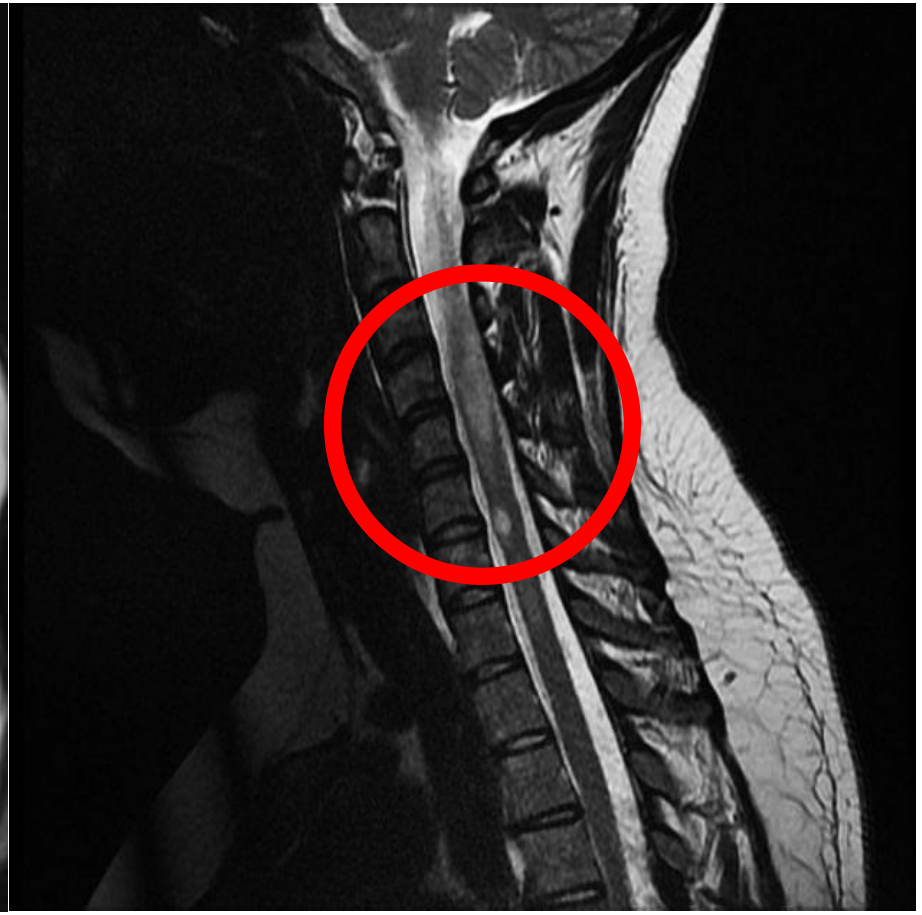
Clinical Evaluation: Imaging





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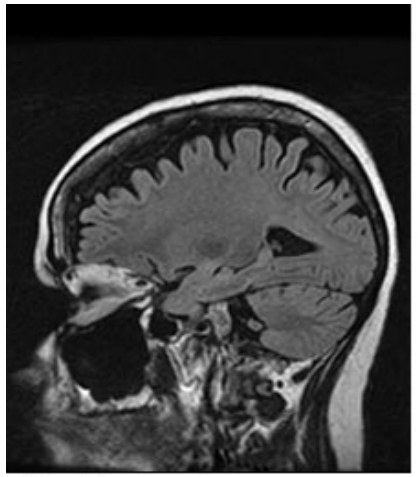
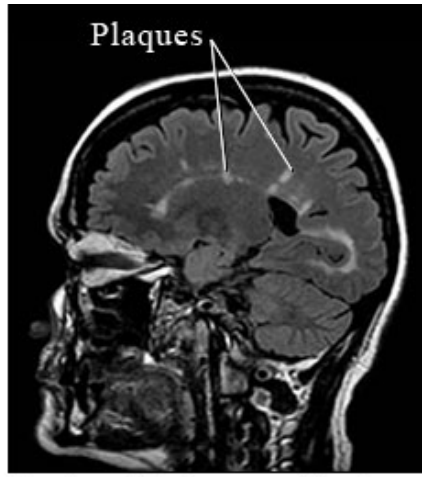


Healthy brain



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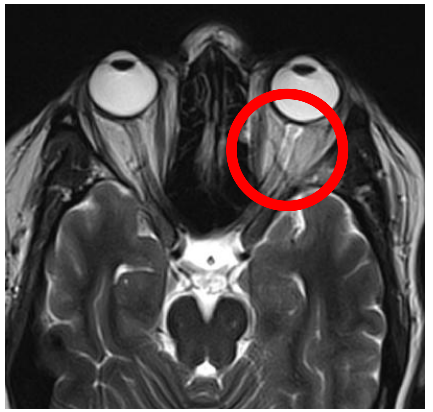

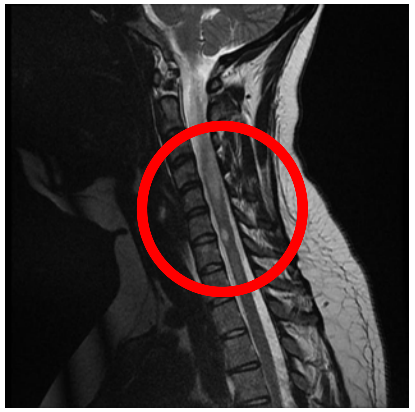

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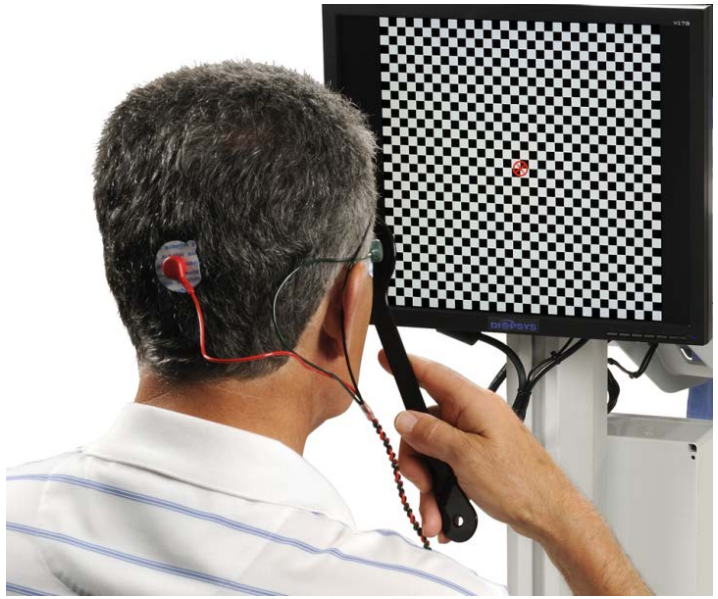
Clinical Evaluation: Evoked Potentials

- 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



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Laboratory Evaluation

- CSF Oligoclonal bands
- CSF IgG Index

ESSENTIAL

- CSF IgG synthesis rate
- CSF Cell count

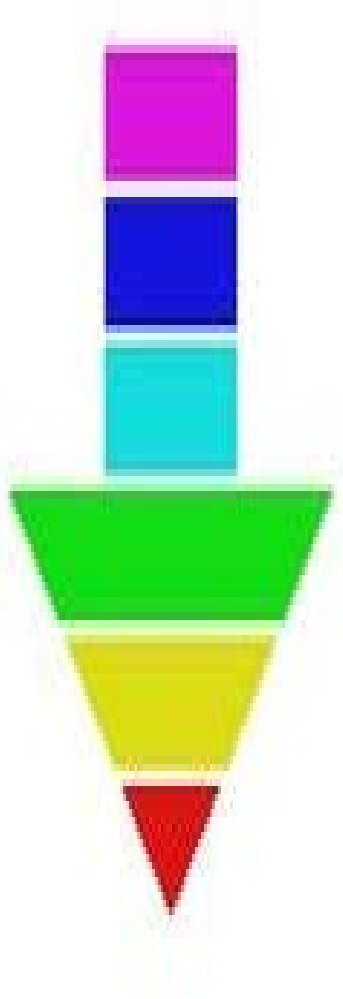
SUPPORTIVE

- CSF Myelin basic protein
- CSF Anti-MBP antibodies

LESSER ROLE

- CSF Kappa free light chains

FUTURE

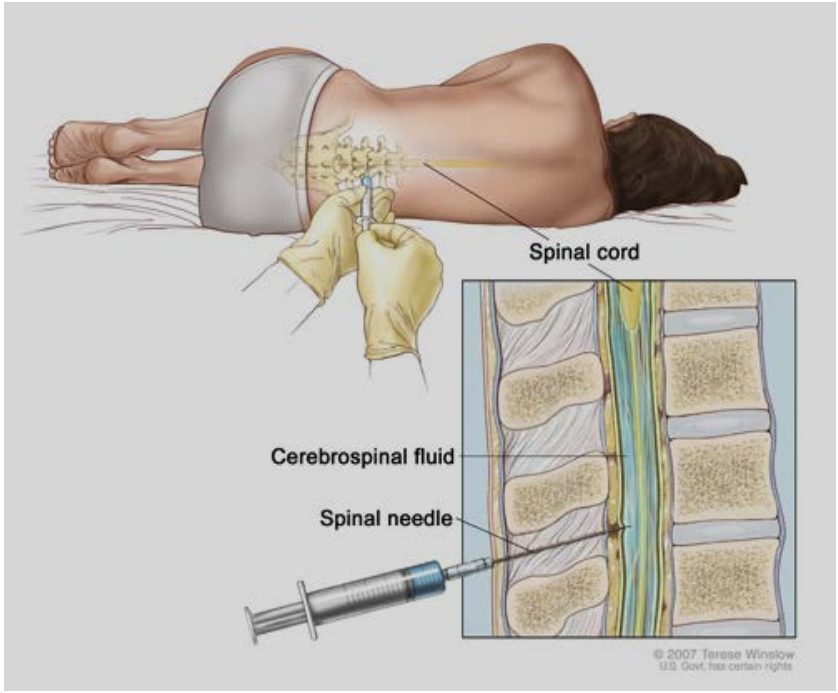


Lumbar Puncture

- 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



cdc.gov

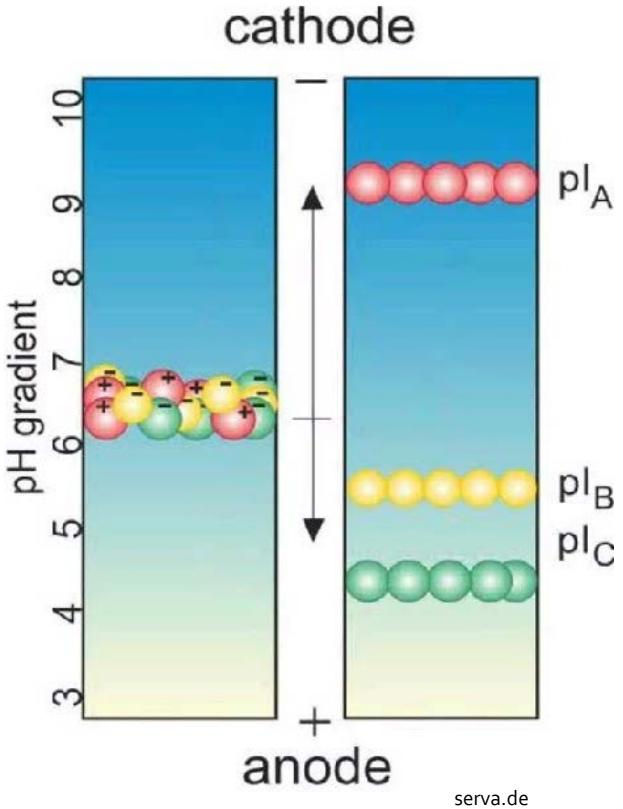
Oligoclonal Band Detection

- **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

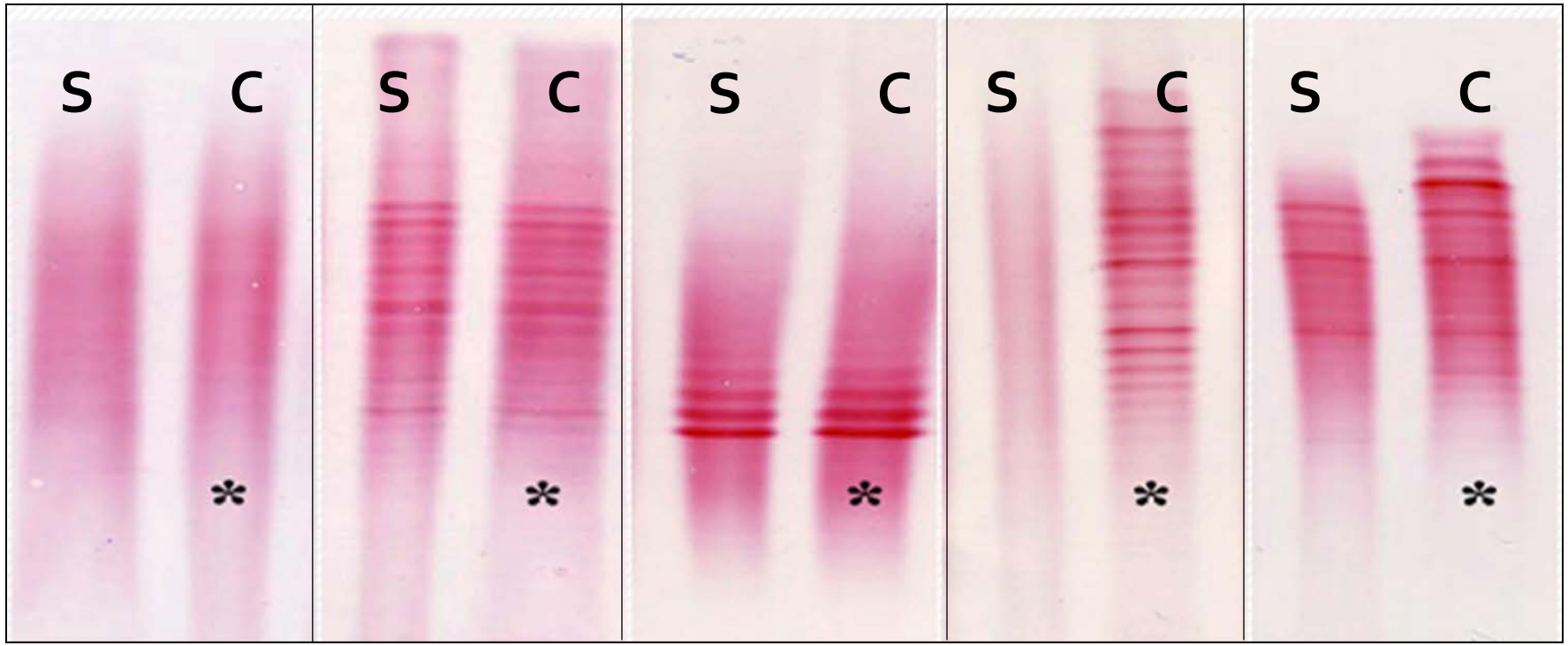
- **Isoelectric focusing on agarose gel**
  - Sample proteins travel through a continuous pH gradient under an electric field
  - Stop at (separated by) isoelectric point
- **Immunofixation with IgG antiserum**
  - Sample IgG binds to anti-IgG antibodies
  - Precipitate out, visualized as bands
- **Serum and CSF analyzed in parallel**
  - Distinguish between IgG produced in CSF vs serum IgG
  - ≥ 2 bands in CSF not in serum



serva.de

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

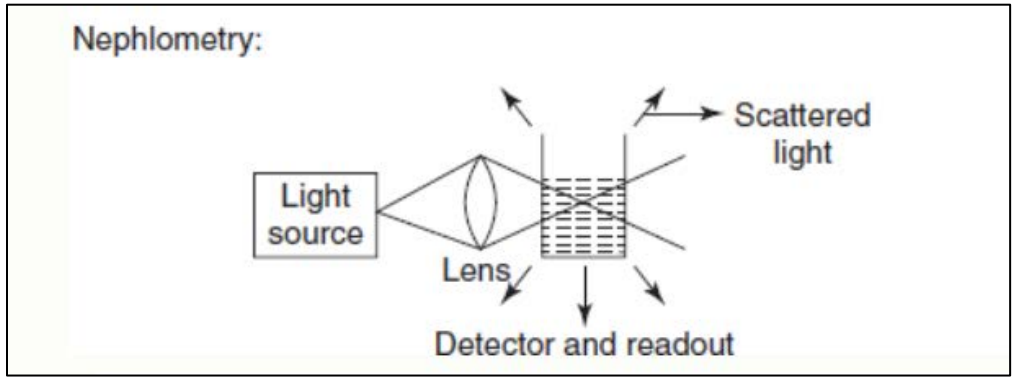
Adapted from multiple-sclerosis-research.blogspot.com

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

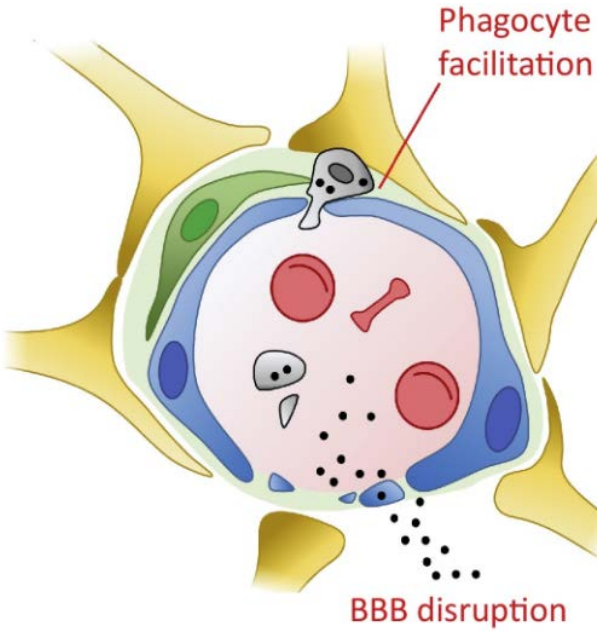


IgG Index: CSF Albumin Quotient

- Serum and CSF analyzed in parallel

$$QAlb = \frac{\text{Albumin CSF (mg/dL)}}{\text{Albumin Serum (g/dL)}}$$

- **QAlb x 1000 = Albumin Index**
  - < 9 – intact BBB
  - 9-14 – slight impairment
  - 14-30 – moderate impairment
  - > 30 – severe impairment
- Caveat:
  - Traumatic LP ("bloody" tap)

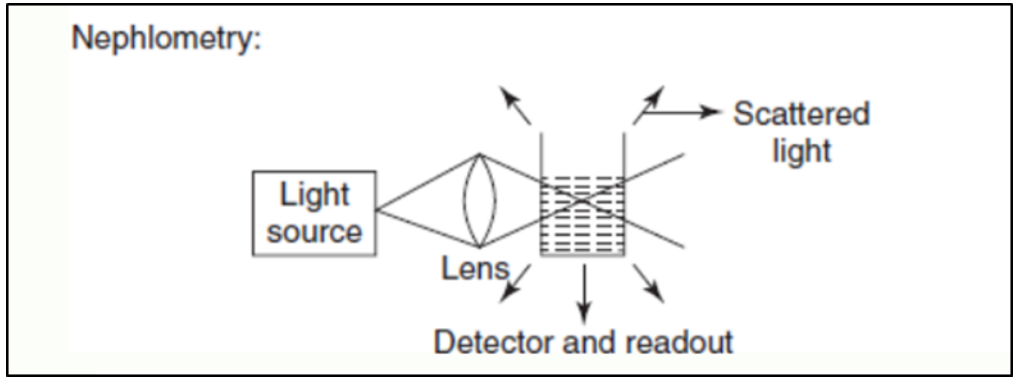


cell.com/trends/microbiology

IgG Index: CSF IgG Quotient

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

$$\text{QIgG} = \frac{\text{IgG CSF (mg/dL)}}{\text{IgG Serum (g/dL)}}$$



IgG Index

$$\text{IgG Index} = \frac{\text{QIgG}}{\text{QAlb}} = \frac{\text{IgG CSF (mg/dL)/IgG Serum (g/dL)}}{\text{Albumin CSF (mg/dL)/Albumin Serum (g/dL)}}$$

- 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%

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

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

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Normal serum:CSF IgG

CSF IgG Synthesis Rate

- If BBB is damaged, permeability to albumin should be proportional to that of IgG

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Normal serum:CSF albumin

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

IgG:albumin molecular weight ratio

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

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

Daily CSF production (dL)

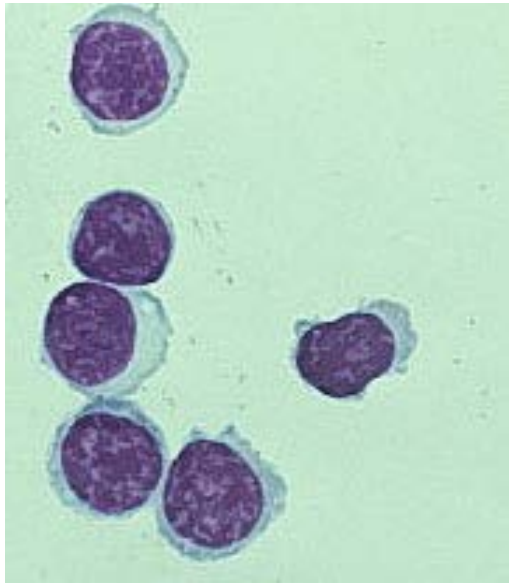
$$\left[\text{IgG CSF} - \frac{\text{IgG serum}}{369} - \left(\text{Alb CSF} - \frac{\text{Alb serum}}{230}\right) \times \frac{\text{IgG serum (0.43)}}{\text{Alb serum}}\right] \times 5$$

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

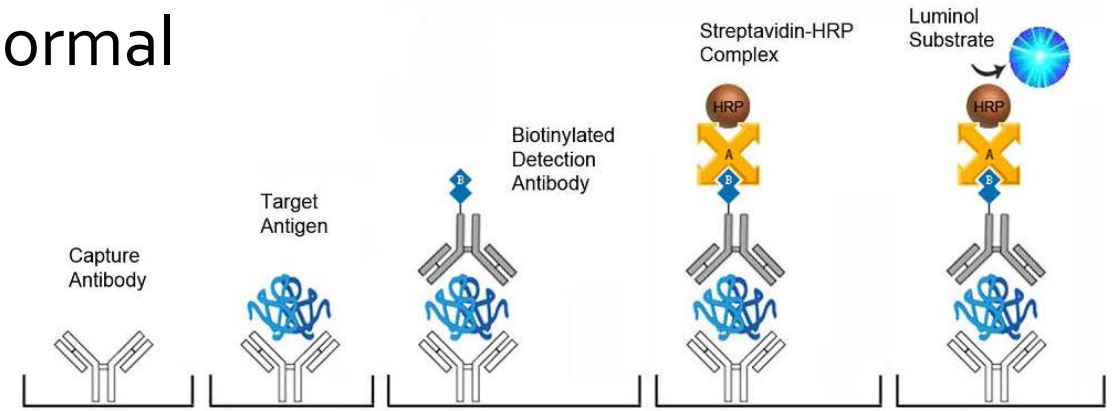


vet.uga.edu

- Differential: primarily lymphocytes
  - T-cells
  - Other cell types, consider another etiology

Myelin Basic Protein

- 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



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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
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- Oligoclonal band detection: Positive (3 bands)
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- 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

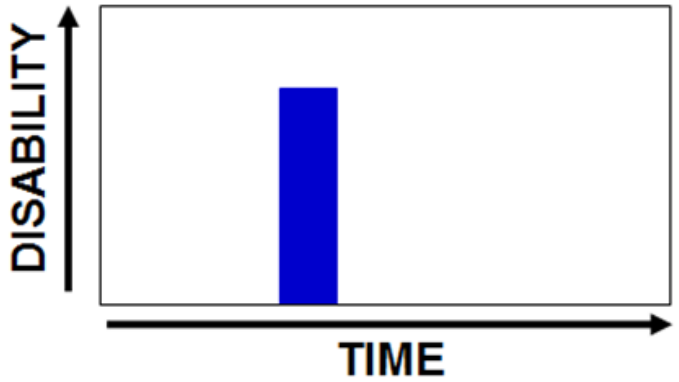
- Discuss the epidemiology, etiology, pathophysiology, and risk factors for Multiple Sclerosis (MS)
- Describe the clinical manifestations, differential diagnosis, and clinical and laboratory evaluation of MS
- Describe the clinical course, management, and monitoring of patients with MS

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

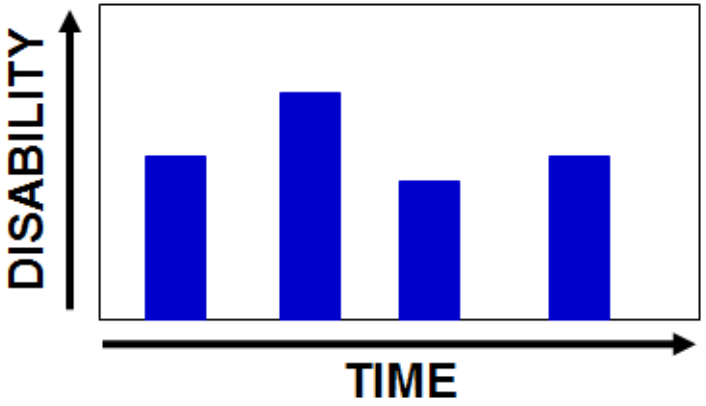


Adapted from Neurology 1996; 46(4):907-911

- 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)

Clinical Course: Relapsing-Remitting

- 80-90% of patients, initially
- Discrete attacks separated by periods of return to near-normal function

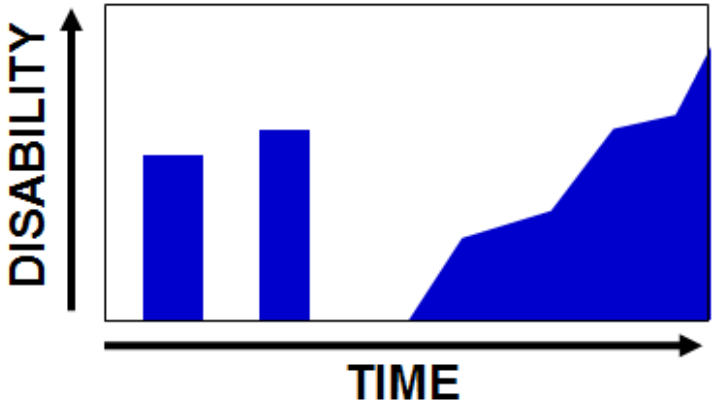


Adapted from Neurology 1996; 46(4):907-911

- 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

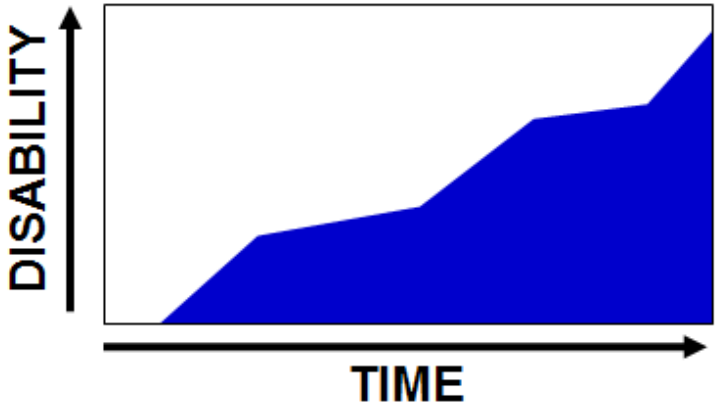
- 60-70% of initial relapsing-remitting MS cases
- Progressive neurologic decline without definite periods of remission
- Transition usually 10-20 years after disease onset
- Distinction is usually made retrospectively



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

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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

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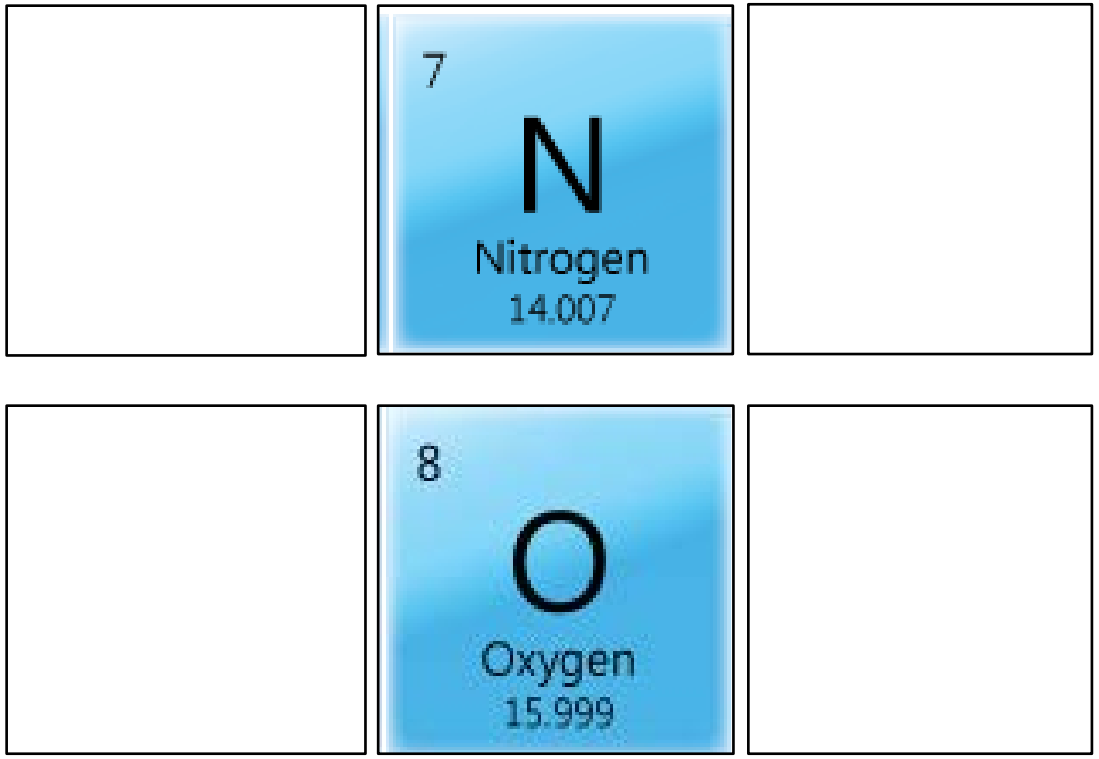
Summary

- 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

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