I'm weak!

Myasthenia Gravis, Multiple Sclerosis

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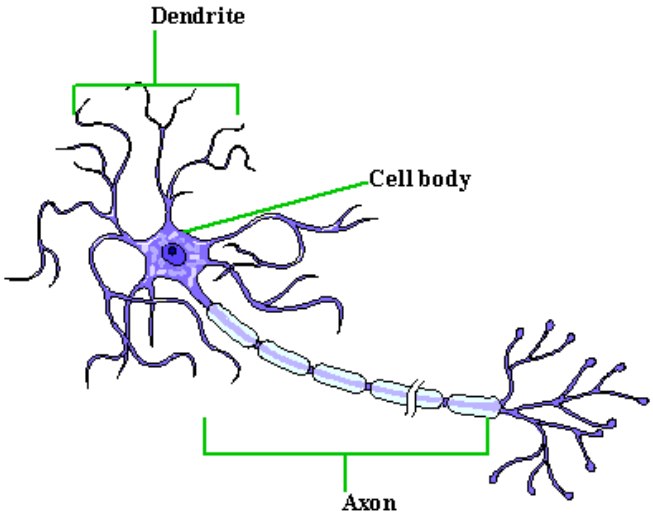
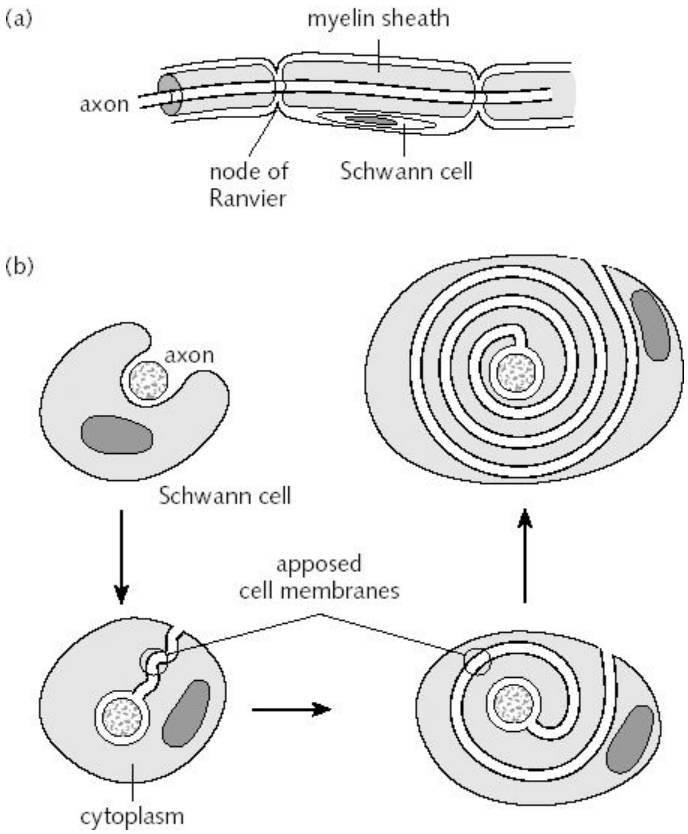
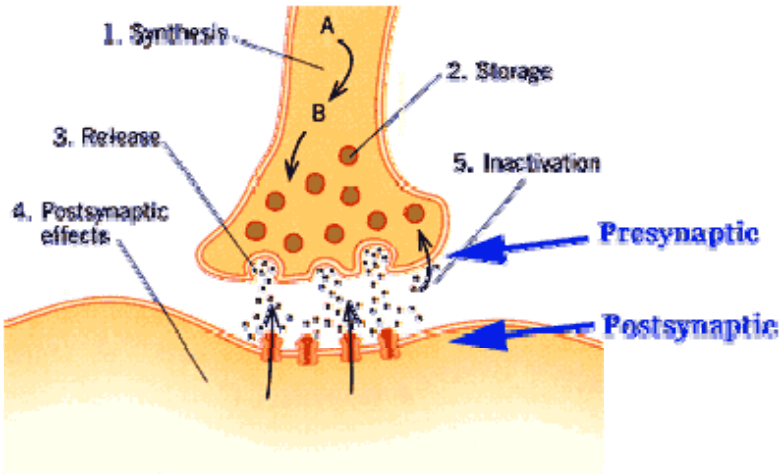
Anatomy & Physiology: Review of Neuromuscular Activation







- Action potential travels down axon to terminal bulb
- Vesicles filled with Acetylcholine (Ach) are released into the synaptic cleft via a Ca++ mediated mechanism
- Ach diffuses across synapse and bind to Acetylcholine receptors (AchR).
- Upon binding to the AchR, Ach activates ligand-gated Na+ channels that allow entry of Na+ ions into the post-synaptic membrane.
- When enough positive ions enter the post-synaptic membrane, this generates an excitatory action potential that results Ca++ to be released from sarcoplasmic reticulum, ultimately producing muscle contraction.
- Ach molecules are quickly hydrolyzed (inactivated) by "the perfect enzyme," Acetylcholinesteras (AchE).

Myasthenia Gravis

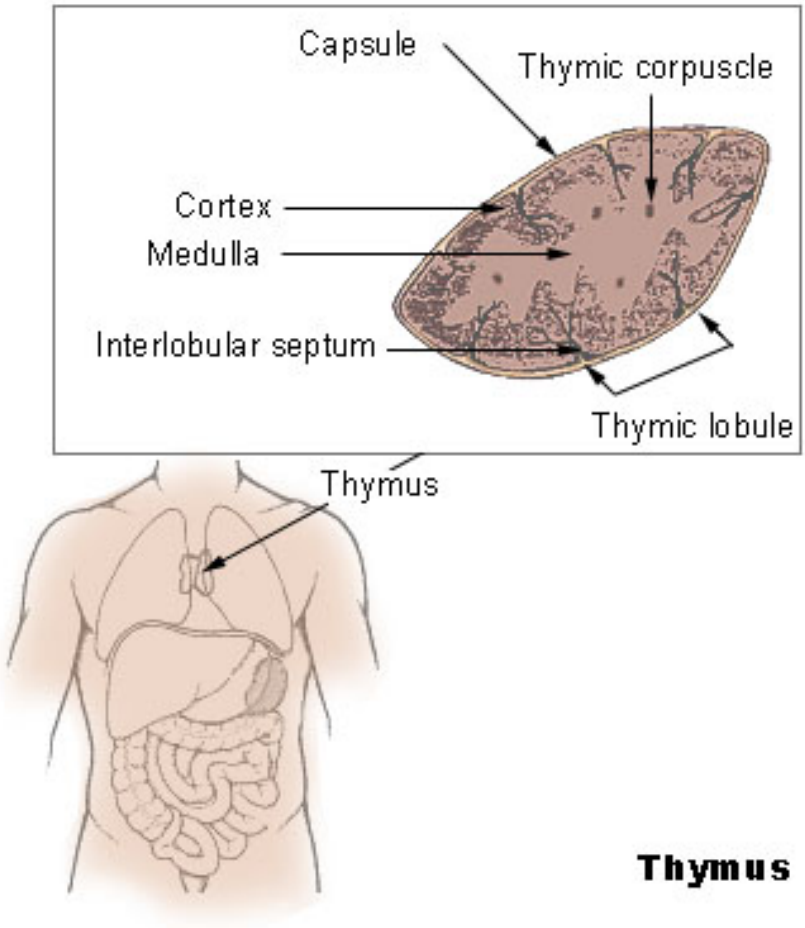
- Auto-immune disease—UNCOMMON! 10-20:1,000,000 new cases in U.S. (prevalence ~200:1,000,000)
  - But most common disease of neuromuscular transmission (so says UpToDate)
- Ab against nicotinic AchR at NMJ (Ab vs nAchR @ NMJ)
- Some Ab impair ability of Ach to bind to AchR, other Ab destroy AchR
- Also, Ab against MuSK (muscarinic tyrosine kinase)
  - MuSK proteins mediate clustering of AchR during NMJ formation and associated with AchR maintenance—research ongoing to explain pathogenetic role of MuSK
- Manifestations:
  - Ocular—limited to lids, EOM
  - Generalized
    - About 50% of those with ocular progress to generalized in 2yrs.

Epidemiology:

- Common in men and women (slight predisposition for women).
- Occurs at all ages (infancy to elders)
  - Women more likely to develop onset during child bearing age, men more likely to present later in life (6^{th}-7^{th} decade).
  - In women, sx/s may be exacerbated by pregnancy or menstrual period
- May be transient in neonates—placental transmission of maternal Ab
- Congenital myasthenia—different—will not be discussed here—babies terrify me.
- Genetic predisposition (HLA DR3), also, commonly found in patients with other auto-immune disorders

Pathogenesis:

- Where do these Ab come from?
- Cross reaction with infective pathogen???
- Up to 75% of patients have thymic abnormalities



Thymus

- Organ located in the upper anterior portion of the chest cavity just behind the sternum.
- The main function of the thymus is to provide an area for T lymphocyte maturation
- Is vital in protecting against autoimmunity
- Enlarges through childhood, largest in puberty, atrophies through the remainder of life, but still remains active

Thymus / Immune Response Review

- Lymphocytes—formed in marrow
- Mature in two different sites
    - Bone marrow—B cells
    - Thymus—T cells
        - Killer T cells
        - Helper T cells
- Antigen presenting cells with epitope (antigen fragment) interact with Helper T cell which secretes Interleukins which activate B cells, inducing antibody formation. Antibodies bind to antigen allowing for more efficient immune response (when antigen is really an antigen and not self!)

Certain medications may unmask MG:

Anesthetic agents
Chloroprocaine
Diazepam
Ether
Halothane
Ketamine
Lidocaine

Neuromuscular blocking agents
Propanidid
Procaine

Antibiotics
Aminoglycosides
- Amikacin
- Gentamicin
- Kanamycin
- Neomycin
- Netilmicin
- Paromomycin
- Spectinomycin
- Streptomycin
- Tobramycin

Fluoroquinolones
- Ciprofloxacin
- Levofloxacin
- Norfloxacin

Others
- Ampicillin
- Clarithromycin
- Clindamycin
- Colistin
- Erythromycin
- Lincomycin
- Quinine
- Telithromycin
- Tetracyclines

Anticonvulsants
Gabapentin
Phenytoin
Trimethadione

Antipsychotics
Chlorpromazine
Lithium
Phenothiazines

Antirheumatic drugs
Chloroquine
→Penicillamine←

Cardiovascular drugs
Beta blockers
Bretylium
Procainamide
Propafenone
Quinidine
Verapamil and calcium channel blockers

Glucocorticoids
Corticotropin
Methylprednisolone
Prednisone

Neuromuscular blockers and muscle relaxants
Botulinum toxin
Magnesium sulfate and magnesium salts
Methocarbamol

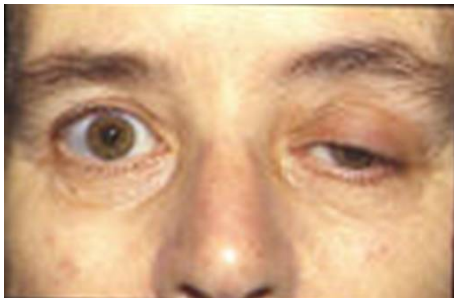
Ophthalmologic drugs
Betaxolol
Echothiophate
Timolol
Tropicamide
Proparacaine

Other drugs
Anticholinergics
Carnitine
Cholinesterase inhibitors
Deferoxamine
Diuretics
Emetine (Ipecac syrup)
Interferon alpha
Iodinated contrast agents
Narcotics
Oral contraceptives
Oxytocin
Ritonavir and antiretroviral protease inhibitors
Statins
Thyroxine

* Drugs listed here should be used with caution in patients with myasthenia gravis. Aminoglycosides should be used only if absolutely necessary with close monitoring.

Signs & Symptoms (Sx/S):

- MG—"mind to ground"
- Commonly associated with facial symptoms: ptosis (unilateral/bilateral), diplopia, bulbar muscle weakness (chewing, swallowing speech, expressionless face, neck muscles (head drop)
- May progress DOWN to respiratory muscles, limb weakness
- Weakness may be focal or generalized
- Weakness may fluctuate throughout the day (may be worse at night or after exercise)
- Weakness may remit and relapse—a pattern that can last for weeks
- THE SYMPTOMS USUALLY PROGRESS TO BECOME MORE FREQUENT—sx/s may peak years after disease onset
- Fluctuation of symptoms is helpful to distinguish from myopathy and motor neuron diseases



Exam:

- FATIGABILITY of muscles—normal sensation, normal reflexes
- May have frank ptosis on exam, slack jaw
- The Simpson test
- Cogan lid twitch sign
- MG crisis—respiratory failure (more on this later)

Differential Diagnosis (DDX):

Other conditions that can produce similar symptoms should be considered.

- Brainstem or motor cranial nerve pathology
- Kearns-Sayre Syndrome
- Generalized fatigue
- Motor neuron disease (ALS)
- Lambert-Eaton Myasthenic Syndrome (LEMS)
- Botulism

Diagnosis (DX):

- Tensilon test (edrophonium)—no longer commercially produced.
  - Short-acting AchE inhibitor
  - Has limitations and dangers—especially in elderly
  - Contraindicated in patients with cardiac disease or asthma
  - May produce increased salivation or abdominal cramping
  - May produce symptomatic bradycardia or bronchospasm—need Atropine at bedside as well
  - Administered incrementally (2mg q 1min up to total of 10mg)
  - May see response at lower dose before onset of side effects
  - May not see a response at all, may see a response with other diseases

Note the degree of ptosis before and after Tensilon administration.

Ice pack test

- Neuromuscular transmission improved at cooler temperatures
- Ice pack test not helpful for testing weak muscles that can't be cooled (EOM)
- Eyelid muscles easily cooled (ice pack for two minutes)
- Ptosis may immediately improve after removal of ice pack
- About 80% sensitive but may have many false positives

Blood Tests:

- 80-90% of pts with generalized MG have circulating Ab against nAchR
    - Three types: binding, blocking, modulating—most go with binding
    - Highly specific with virtually no false-positives
- 3-7% have circulating Ab against MuSK (muscarinic tyrosine kinase)
- **Seropositive** (about 50% of those with ocular MG, about 90% with generalized)
- Levels of circulating Ab do NOT correlate with severity of disease
- **Seronegative**—no Ab against AchR or MuSK, but similar response to treatment (discussed below), similar findings on electropysiologic testing

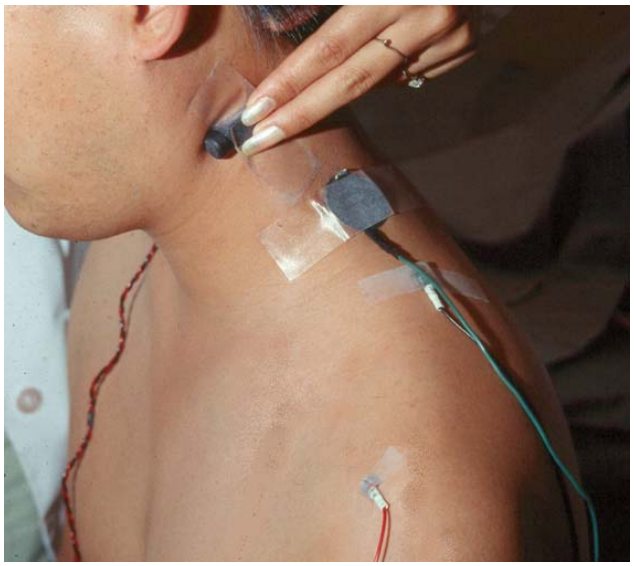
- Because of association with other auto-immune diseases, consider checking for RA, SLE, Grave's, etc…

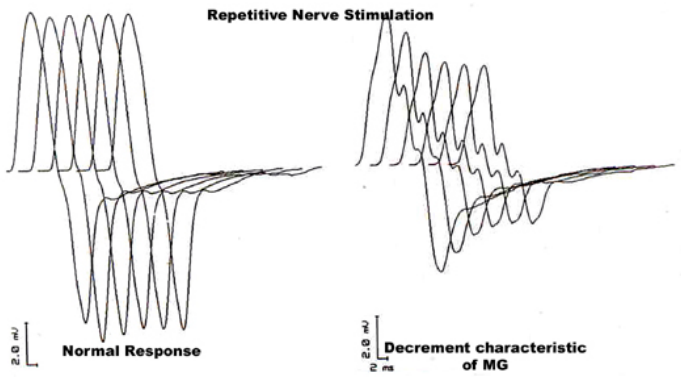
Back to the Thymus for a moment:

- Most patients with Seropositive MG have thymic abnormalities, especially AchR-Ab
- Mostly hyperplasia, also some with thymoma
- Anti-striated muscle antibodies are present in 30% of patients with MG and in 80% of patients with thymoma. May be helpful, but majority of patients are going to go on to have imaging of thymus (CT or MRI).

Electropysiologic testing

- Repetitive nerve stimulation studies
    - More commonly performed, easier to do, fairly good sensitivity and specificity





- Single fiber EMG
    - More complex specialized procedure, usually reserved for patients with suspected MG that have not been adequately Dx'ed through other tests.

Treatment (TX):

Anticholinesterase inhibitors (slightly less effective for Musk-Ab+)

Inhibits the enzymes that breakdown Ach=more Ach=more muscle stimulation

Neostigmine (7.5-30mg PO QID)

Pyridostigmine (30-180mg PO QID)

Thymectomy—often leads to symptomatic relief and remission

Immunosuppression

Corticosteroids—start high (prednisone 60-100mg PO QD, QOD?), taper to low dose maintenance therapy

Individualized protocols for different patients

Other forms of immunomodulation: azathioprine, mycophenolate, cyclosporine

IVIg—up to $10,000 per infusion!!

- Useful for acute decline or myasthenic crisis
- > 2/3 of patients will improve with treatment
- onset of improvement 7-10 days after starting IVIg therapy, lasts weeks (range days to months)
- 2 g/kg IV given over 2-5 days, as per protocol
- Half-life ~ 21 (12-45) days
- Monitor for side effects: volume overload, rash, fever and flu-like symptoms, headaches, chest and abdominal pain, anaphylaxis, renal failure, transaminitis, aseptic meningitis

Plasma Exchange (PLEX)—expensive, but thousands less than IVIg, preferred over IVIg

- Useful for acute decline or myasthenic crisis
- > 2/3 of patients will improve with treatment, may see improvement in 2-3 days
- Equally efficacious as IVIg but may have more adverse effects
- Reduces AChR titers by 50-70%
- 3-5 exchanges of 5% of body weight (50ml/kg) each over 3-10 days
- Duration of benefit 2-8 weeks
- Also effective in seronegative MG

MG Crisis

- Respiratory weakness may lead to respiratory failure
- Can occur spontaneously during active phase of disease or be precipitated by surgery, infection, medications (memorize list) or tapering of immunosuppresion.
- Worsening generalized weakness may precede MG Crisis, but variable time course
- Must monitor FVC, up to q2hrs
- Accessory muscle weakness may mask underlying respiratory distress

  - Admit to ICU
  - monitor FVC q2-4hrs
  - electively intubate if FVC <15mL/kg or serial decline approaching 15mL/kg or clinical signs of respiratory distress
  - withdraw acetylcholinesterase inhibitors
  - begin IVIg or plasmapheresis
  - Begin high dose immunomodulating therapy
  - Wean off mechanical ventilation as FVC improves

Classification of Myasthenia Gravis

- *Class I*
  - Any ocular muscle weakness
  - May have weakness of eye closure
  - All other muscle strength is normal
- *Class II*
  - Mild weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
  - IIa - Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
  - IIb - Predominantly affecting oropharyngeal respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both
- *Class III*
  - Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
  - IIIa - Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
  - IIIb - Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- *Class IV*
  - Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
  - IVa - Predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles.
  - IVb - Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
- *Class V*
  - Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Multiple Sclerosis

Autoimmune disease (or not?) which causes inflammatory demylination of CNS
- No specific autoantibody found
- Demylination of axons reduces neurons ability to function

Many theories, no cure
Found primarily in young adults, usually under age of 55 at onset
Different forms:
- CIS, RRMS, primary progressive, secondary progressive, progressive relapsing

Epidemiology
- Age of onset typically mid-20's to 30
  - If older onset, *may* be more severe
- Women>men
  - Disease *may* be more severe in men
- *Likely* autoimmune in etiology—higher risk in patients with other autoimmune diseases
- High risk populations: Northern Europe, Southern Canada, Northern US (100:100,000)
- Low risk populations: Asian, African, American-Indian

Risk factors?
- Patients of Western European lineage (genetics) who live in temperate zones (environmental)
- If patients move from one "zone" to another before age 15, he/she appears to adopt that zone's risk
- Less risk closer to equator—is sunlight or Vitamin D protective?
- HLA-DR2 association
- Exposure to viral infections—EBV? Varicella?
- Genetic predisposition? Increased risk if (+) FHX
- Exposure to vaccines?
- Smoking?
- Month of birth? May>November

Pathogenesis
- Still an area of research
- Inflammation→demyelination→axonal degeneration
- Autoimmune=MS shows response to TX w/ immunomodulating RX
- Disruption of BBB=RX that block T cell movement into CSF improve MS sx/s

Signs & Symptoms
- Weakness
- Fatigue
- Numbess
- Tingling
- Unsteadiness in a limb
- Spastic paraparesis
- Retrobulbar neuritis /optic neuritis
  - blurred or dimmed vision
  - blind spots, particularly with central vision
  - pain with eye movement
  - headache
  - sudden color blindness
  - impaired night vision
  - impaired contrast sensitivity
- Diplopia
- Disequilibrium/vertigo
- Pain
- Sphincter disturbance (urinary urgency or hesitancy)

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50
Optic neuritis
Lhermitte's sign
Internuclear ophthalmoplegia
Fatigue
Uhthoff's phenomenon
Features not suggestive of multiple sclerosis
Steady progression
Onset before age 10 or after age 50
Cortical deficits such as aphasia, apraxia, alexia, neglect
Rigidity, sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

- Symptoms may be present for a few days or weeks, then disappear—a diagnostic challenge!

Because of the variability and non-specificity of symptoms, a person may not be diagnosed with MS until later in the course of the disease.

Other associated symptoms include depression, cognitive impairment, seizures

Presenting symptoms in multiple sclerosis

Symptom	Females, percent	Males, percent	Total, percent
Sensory in limbs	33.2	25.1	30.7
Visual loss	16.3	15.1	15.9
Motor (subacute)	8.3	10.4	8.9
Diplopia	6.0	8.5	6.8
Gait disturbance	3.2	8.3	4.8
Motor (acute)	4.4	4.2	4.3
Balance problems	2.5	4.0	2.9
Sensory in face	2.9	2.5	2.8
Lhermitte's sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	1.6	2.3	1.8
Vertigo	1.8	1.5	1.7
Bladder problems	0.9	1.1	1.0
Limb ataxia	0.9	1.3	1.0
Acute transverse myelopathy	0.8	0.6	0.7
Pain	0.3	0.8	0.5
Other	2.6	2.5	2.5
Polysymptomatic onset	14.5	11.9	13.7

Data from Paty, D, Studney, D, Redekop, K, Lublin, F, Ann Neurol 1994; 36:S134 and Studyney, D, Lublin, F, Marcucci, L, et al, J Neurol Rehab 1993; 7:145.

DDX:
- B12 deficiency
- HIV
- Lyme Neuroborreliosis
- Neurosyphilis
- Acute Disseminated Encephalomyelitis (ADEM)
- Acute Hemorrhagic Leukoencephalitis
- Acute and Subacute Transverse Myelitis

Several forms of MS are recognized:

Relapsing-remitting (RRMS): an initial episode then months or years before new symptoms emerge or previous symptoms return.
- This cycle can lead to incomplete remissions and progressive disability with weakness, spatsticity, ataxia of limbs, impaired vision and urinary incontinence.
- Physical findings may include optic atrophy, nystagmus, dysarthria, pyramidal/sensory/cerebellar deficits in one or multiple limbs.
- Relapse=defined as an acute exacerbation of symptoms lasting days to weeks, at minimum—24hrs
- Can be previous symptoms (above) or new symptoms
- Relapse triggers? Infection? *Trauma?* Stress? Pregnancy?
- Frequency of relapses is variable but more common early in the disease
- Uhthoff's phenomenon!

In some patients, clinical course changes to **secondary progressive (SPMS).** Some studies indicate that most patients will progress to SPMS

Primary progressive (PPMS)—less common (~10%), Symptoms are steadily progressive from onset.

Progressive relapsing MS (PRMS)—a subset of MS which has some remissions, but steady decline still dominates disease course.

Disease Severity
Benign—fully functional in all neurologic systems 15yrs after disease onset
Malignant—rapidly progressive course leading to significant disability

Progression of disease is highly variable, but can mostly be defined as slow.

Diagnosis:
Must show two or more **different** areas in central areas of white matter affected at **different** times
Only one area may be clinically affected—but a "probable" diagnosis can be made in patients with multi-focal disease on imaging but with only one clinical attack or with a history of at least two clinical attacks but signs of only one lesion

- Imaging with MRI: Test of choice to diagnosis clinically suspected MS
- Lesion is the cerebral or spinal plaque—discrete region of demyelination with initially preserved axon
- Found in the periventricular region, corpus collosum, centrum semiovale, deep white matter structures & basal ganglia
- Increased Gadolinium enhancement may indicate acute lesion

Ancillary testing in multiple sclerosis

Test	**Percent abnormal in patients with definite multiple sclerosis**
Visual evoked response (VER)	85
Brainstem auditory evoked response (BAER)	67
Somatosensory evoked potentials (SEP)	77
Cerebrospinal fluid oligoclonal banding	85 to 95
IgG index of spinal fluid	90
Cerebrospinal fluid albumin	23
Brain MRI	70 to 95

Labs:
- Lumbar puncture should be performed
    - May have mild lypmhocytosis, may have IgG in CSF
    - Probably have normal opening pressure
    - Albumin in CSF indicated disruption of BBB
    - The presence of oligoclonal bands (OCB= A series of distinct bands found in the immunoglobulin of the cerebrospinal fluid) is highly suggestive of MS
- Other labs useful to eliminate other possible cause of symptoms (B12, Lyme, etc…)

2005 McDonald criteria revisions diagnostic criteria for multiple sclerosis

Clinical presentation	Additional data needed for MS diagnosis
Two or more attacks*; objective clinical evidence of two or more lesions	None●
Two or more attacks*; objective clinical evidence of one lesion	Dissemination in space, demonstrated by: - MRI△ or - Two or more MRI-detected lesions consistent with MS plus positive CSF◊ or - Await further clinical attack* implicating a different site
One attack*; objective clinical evidence of two or more lesions	Dissemination in time, demonstrated by: - MRI§ or - Second clinical attack*
One attack*; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	Dissemination in space, demonstrated by: - MRI△ or - Two or more MRI-detected lesions consistent with MS plus positive CSF◊ **and** Dissemination in time, demonstrated by: - MRI§ or Second clinical attack*
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) **and** Two of the following: - Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP)¥ - Positive spinal cord MRI (two focal T2 lesions) - Positive CSF◊

MS: multiple sclerosis; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; VEP: visual evoked potential. If criteria indicated are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is MS; if suspicious, but the criteria are not completely met, the diagnosis is "possible MS"; if another diagnosis arises during the evaluation that better explains the entire clinical presentation, then the diagnosis is "not MS."

* An attack is defined as an episode of neurological disturbance for which causative lesions are likely to be inflammatory and demyelinating in nature. There should be subjective report (backed up by objective findings) or objective observation that the event lasts for at least 24 hours.

●No additional tests are required; however, if tests (MRI, CSF) are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS. Alternative diagnoses must be considered. There must be no better explanation for the clinical picture and some objective evidence to support a diagnosis of MS.

△MRI demonstration of space dissemination must fulfill the criteria derived from Barkhof et al.# and Tintoré et al.** and presented in a separate table

◊Positive CSF determined by oligoclonal bands detected by established methods (isoelectric focusing) different from any such bands in serum, or by an increased IgG index.

§ MRI demonstration of time dissemination must fulfill specific criteria presented in a separate table.

¥ Abnormal VEP of the type seen in MS.

Barkhof, F, Filippi, M, Miller, DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997; 120 (Pt 11):2059.

** Tintoré, M, Rovira, A, Martinez, MJ, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. AJNR Am J Neuroradiol 2000; 21:702.

Treatment

- No cure, tx aimed at improving quality of life and limiting disability
- Needs strong support network—family, therapists, social services
- Acute attacks—treated with glucocorticoids most commonly (methylprednisoline 1g IV x 3-5 days)
- Disease Modifying Therapy—aimed at reducing relapses and slowing progression
    - Treat aggressively and early (but for how long?)
        - Interferon-β-- cytokine that modulates immune responsiveness
        - Betaseron (Interferon-β1b)—
            - 250mcg SC administered QOD
        - Avonex (Interferon-β1a)
            - 30mcg IM administered weekly
        - Rebif (Interferon-β1b)
            - 44mcg SC administered 3x/week
        - Interferon side effects—injection site reactions, flu-like symptoms, depression, elevated LFT's, leucopenia/anemia
        - Response to INFB tx is variable
        - Neutralizing antibody formation—can develop and limit the effectiveness of IFNB treatment
    - Glatiramer—mixture of amino acids antigenically similar to myelin protein. Works by competing for T cells
        - Daily SC administration
    - Natalizumab—decreases migration of immune cells into CSF, fewer lesions seen on MRI, fewer relapses
        - Given monthly IV
        - Associated with a rare but fatal complication progressive multifocal leukoencephalopathy
        - Voluntarily pulled from the market in 2005, back in in 2006 but with restrictions
    - Statins?
    - Naltrexone?

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- **Multiple Sclerosis**
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Up To Date (online)

- **Epidemiology, Risk Factors, and the Clinical Features of Multiple Sclerosis in Adults**
- **Diagnosis of Multiple Sclerosis in Adults**
- **Treatment of Relapsing-Remitting Multiple Sclerosis in Adults**
- **Comorbid Problems Associated with Multiple Sclerosis**

- **Clinical Manifestations of Myasthenia Gravis**
- **Pathogenesis of Myasthenia Gravis**
- **Diagnosis of Myasthenia Gravis**
- **Treatment of Myasthenia Gravis**
- **Myasthenic Crisis**

2009 CURRENT Medical Diagnosis and Treatment