Multiple Sclerosis

- Chronic, progressive degenerative disease that affects the myelin sheath and conduction pathways of the central nervous system
- Affects the white matter of the brain and spinal cord by causing scattered demyelinated lesions

Cause of Multiple Sclerosis

- It is an autoimmune disease. Scientists do not know what triggers the onset of the disease but several factors may be involved
  - Gender: affects women more than men
  - Genetics: affects people of Northern European, Northern United States, Australia and New Zealand
  - Environmental triggers
    - Viruses
    - Trauma
    - Heavy Metal exposure: Mercury, Lead, Manganese (common metals that can lead to damage of the nervous system)
Pathophysiology of MS

- Mononuclear and Lymphocytes penetrate CNS Parenchyma
- Damage to Oligodendrocyte
- Proliferation of Astrocytes
- Edema
- Formation of axonal Plaques prevent remyelination

Multiple Sclerosis

- Incidence: onset between the ages of 20 and 40 years old. Only 20% of patients experience the first symptoms after age of 40.
- Appears to have familial tendency
  - Risk of MS in Average Person is 1 in 750
  - Risk of MS in person with a parent with MS is 1 in 40

Diagnosis of Multiple Sclerosis

- Clinical History
  - Signs of Disease in different parts of the nervous system
  - At least 2 separate flare ups of the disease
- MRI of Brain and Spinal Cord to evaluate for Plaques
- Evoked potentials: prolongation of stimuli response occurs in more than 75% of MS patients
- CSF
  - Oligoclonal Bands IgG increased in 2/3 of patient
  - Elevated Protein
**Four Clinical Patterns of MS**

- Benign – 20%
- Relapsing/Remitting – 25%
- Secondary Chronic progressive – 40%
- Primary Progressive – 15%

**Benign MS**

- Least severe type of MS
- Characterized by few, mild early attacks with complete clearing of symptoms
- Minimal or no disability with this type

**Relapsing/Remitting MS**

- This type of multiple sclerosis is characterized by clearly defined flare-ups, followed by periods of remission.
- The flare-ups typically appear suddenly, last a few weeks or months, and then gradually disappear.
- Some degree of disability is usually present

**Secondary Chronic Progressive MS**

- This type of MS is characterized by increasing attacks with fewer and less compete remissions after each attack.
- MS can continue to worse for many years and then level off with moderate to severe disability
Primary Progressive

- This is the most disabling form of MS
- Onset severe and the course is slow progressive without any clearing of symptoms

Signs and Symptoms of MS

- Classic Waxing and Waning of symptoms
- Motor: lower extremity weakness in early stages with progression over time to spastic paralysis
- Sensory: numbness, pain, decreased temperature and vibratory sensation.
- Visual: Optic Neuritis, diplopia, ocular palsy

Treatment of Multiple Sclerosis

- First line of treatment for MS exacerbation is Solumedrol / Prednisone high dose to shut the immune system down to stop cells from causing inflammation.
- Muscle Relaxants for symptom management

Interferon: beta-1a, beta-1b

- Interferons have a broad range of effects in the body and are thought to work by suppressing the activation of the immune cells and limit their passage across the Blood:Brain:Barrier (BBB)
- Given by injections (IM or SC)
Glatiramer Acetate
- Antigen-based therapy thought to have 2 benefits for MS patients – SC injection
  1. Reduce damage within the CNS by suppressing inflammation
  2. Possibly contributing to restoration of normal immune regulation

Mitoxantrone
- Chemotherapy agent delivered IV every 3 months
- Thought to treat MS by suppressing the activity of T cells, B cells, and macrophages
- Due to the toxic effects of the drug it is being used less often (cardiomyopathy and AML)

Tysabri®
- Infusible agent administered monthly
- Inhibits migration of T or B cells to the CNS
- In clinical trials, AFFIRM and SENTINEL, Tysabri reduced the risk of disability progression by 42% and relapse rate by 68%

Tysabri®
- Despite the obvious benefits from this drug, it comes with a significant risk. The most significant is immunosuppression and consequent serious infection, most notably Progressive Multifocal Leukoencephalopathy (PML) a potentially fatal brain infection caused by the JC Virus
Tysabri was voluntarily removed from the market by the drug manufacturer in 2005 after the risk of PML was identified and was re-released in June 2006 with significant safety precautions in the form of the TOUCH Prescribing Program.

- Markowitz, C.E. (2011). Current Injectable and Infusible Disease-modifying Therapies, Supplement to the International Journal of MS Care, 13, 5-10

Myasthenia Gravis “Grave Muscle Weakness”

- Chronic progressive disease of muscular weakness caused by a defect at the myoneural junction. Estimated 70,000 cases in US.
- Decreased Acetylcholine in the post-synaptic membrane thereby decreasing the transmission of impulse down nerve.
- Loss of normal muscle contraction.
- Incidence: peak between age 20 – 30 years. Up to the age of 40 women to men ratio 3:1; after age 40 women to men 1:1.
- Antibodies block, alter or destroy the receptors for Acetylcholine at the neuro- muscular junction which prevents muscle contraction.
- Significant number of patients with MG will have thymic hyperplasia or thymoma. Thymus gland plays an important role in development of the immune system.
Myasthenia Gravis

Signs and Symptoms

- Muscles of eyes affected first with bilateral ptosis, ocular palsy and diplopia. To compensate for ptosis the frontalis muscles in the forehead may be chronically contracted producing a worried or surprised on the patient.

- Facial, masticatory, speech and neck muscles affected next.
- Progression of weakness downward to eventually affect diaphragm and intercostal muscles.
- Muscle weakness fluctuates throughout the day. It is usually less severe in the morning and worse as the day wears on and the muscles are fatigued.

Diagnosis of MG

- Clinical History: often diagnosis is delayed by 1 to 2 years due to the work up of generalized weakness.
- Ach receptor antibodies are positive in up to 90% of patients with MG.
- EMG testing: detects impairment of nerve to muscle transmission.
- MRI / CT scan to evaluate Thymus.
**Diagnosis of MG**

- **Tensilon Test:** IV Tensilon (edrophonium Cl) blocks Ach breakdown and temporarily increased levels of Ach at neuromuscular junction with temporary resolution of eye muscle symptoms. Tensilon test is + in more than 90% of patients with MG.

**Treatment of MG**

- **Steroids:** suppress the immune system
- **Anticholinesterase:** slows down breakdown of Ach and promotes accumulation of neurotransmitter at the neuromuscular junction
  - Mestinon: Preferred treatment 30 -60 mg q 4 – 6 hours ATC as needed
  - Neostigmine: 7.5 – 15 mg q 4 – 6 hours ATC as needed
- **Thymectomy:** reduces symptoms in more than 70% of patients with Thymoma

**Treatment of Myasthenia Gravis**

- **Immunosuppressant Medication:** Produces marked sustained improvement in patients who have not responded to Steroids or Surgery
- **Plasmapheresis:** short term intervention in patient’s with rapidly progressing symptoms
- **Immunoglobulin:** last option used for short term intervention

**Amyotrophic Lateral Sclerosis**

- **“Lou Gehrig’s Disease”**
  - Rapidly progressive fatal neurological disease that attacks the motor neurons responsible for voluntary muscles.
  - Cognition is mostly preserved during the disease progression
  - Incidence 1 : 50,000
ALS

- Amyotrophic: Muscle Atrophy
  - lower motor neuron symptoms: muscle weakness, atrophy, muscle cramping
- Lateral Sclerosis: scarring of the corticospinal tracts:
  - upper motor neuron symptoms: spasticity, hyper-tonicity, hyperflexion

Etiology Theories of ALS

- In familial cases genetic mutation Super oxide Dimutase 1 (SOD1) on Chromosome 21 decreases free radical breakdown, theorized that with increased free radicals > motor neuron death
- Increased Glutamate levels in ALS patients thought to contribute to neuronal death
- Auto immune response

Symptom Onset of ALS

- Onset of symptoms of ALS is usually insidious over months. Two primary presentations:
  - Limb onset occurs in 56–75% of patients
  - Speech/swallowing (Bulbar onset) occurs in 25–44% of patients

Signs and Symptoms of ALS

- Muscle weakness, wasting and atrophy distal to proximal
- Muscle spasticity and hyperreflexia
- Dysphagia and dysarthria
- Fatigue
- Dyspnea
Diagnosis of ALS

1. Clinical signs and symptoms of both upper motor neuron and lower motor neuron disease which presents as a combined picture of muscle atrophy and fasciculation
2. EMG / Nerve Conduction studies
3. Exclusion of other diagnosis have been ruled out

Due to the variability of initial presentation and broad differential diagnosis it is estimated that between 26 – 42% of patients with ALS are misdiagnosed. For those patients, the true diagnosis is delayed by 13 – 18 months.


Case Presentation of ALS

54 year old male in general good health
5/03: Right knee repeated buckling. Initially symptoms thought to be related to an old running injury.
7/03: Work up for right knee complaint discovers herniated disc, and the patient undergoes the 1st of 3 back surgeries. No improvement in right knee complaints.
5/04: Right arm spasms while lifting weights
6/04: Diagnosed with ALS at the age of 55
Progression of ALS

- Progressive Paralysis of voluntary muscles > muscles of chest wall > muscles of diaphragm
- Preservation of extraocular and sphincter muscles
- Cognition remains intact
- Progression of disease from onset to death averages 3 years
- 10% of ALS patients survive 10 years or more

Drug therapy treatment for ALS

- Currently there is not cure or proven therapy that will prevent or reverse the course of the disease
- The only FDA approved drug is Riluzole, a neuroprotective agent which decreases glutamine release in the CNS, but has little effect on other physiologic systems.

Treatment for ALS

- Drug treatment is directed towards minimizing the symptoms and include baclofen and diazepam to treat spasticity.
- Speech and Physical therapy and Nutritionists
- BIPAP > Mechanical Ventilation

Possible Therapies Coming for ALS...

- Stem-cell based therapies in rat and mouse models show improve strength and survival time
- Gene therapy- to improve motor neuron survival
- RNA therapy – to silence mutant SOD1 expression

Guillain-Barre Syndrome

- Immune-mediated response creating destruction of the myelin sheath surrounding the peripheral nervous system including cranial and spinal nerves.
- Nerves surrounded by inflammation, edema resulting in axonal injury
- Incidence 1.7 : 100,000

Etiology unknown but thought to be an autoimmune response to viral infection
- 2/3 of patients with GBS have been affected by recent infection or illness within 4 weeks*
- Onset of GBS was connected to the Swine Flu Vaccine 1976.**

* National Institutions of Health  ** Center for Disease Control

40% of GB patient have positive Campylobacter Jejuni serum antibodies. This bacterium is one of the most common causes of diarrheal illness.
- Exposure comes from handling or eating raw or undercooked poultry or meat

Signs and Symptoms of GBS
- Weakness and numbness beginning in the legs and progress upward to the trunk, arms and cranial nerves
- Motor deficits are symmetrical
- Diminished reflexes
- 50 % of patients affected will experience respiratory insufficiency
- Cardiovascular symptoms include decreased heart rate and blood pressure
Diagnosis of GBS

- Clinical History and Physical Exam
- EMG: absent or profound delayed conduction
- Pulmonary Function Test
- ESR, Antiganglioside antibodies, Anti-Gq1b antibodies
- MRI brain and spine for nerve root enhancement
- CSF sampling: in acute phase
  - Elevated Protein (up to 400mg/L)
  - Normal WBC

Stages of GBS

- Stage I: Acute onset begins with onset of symptoms and ends when no further symptoms are noted (lasts 1 – 3 weeks)
- Stage II: Plateau period lasts several days to 2 weeks
- Stage III: Recovery phase; characterized by remyelination and axonal regeneration process. Recovery process can take up to 2 years and fixed deficits may result. 30% of patients have residual weakness after 3 years

Treatment of GBS

- Supportive treatments for symptoms
  - Up to 1/3 of patients require mechanical ventilation
- Plasmapheresis
- Intravenous IgG
- There is no data to support the use of Steroids in GB

Parkinson’s Disease
Parkinson’s Disease

- Pigmented cells in the substantia nigra are depleted of dopamine.
- Dopamine is an inhibitory neurotransmitter.
- Affects the cells of the extra pyramidal tract – results in impairment of automatic and coordinated movements.

Incidence: Commonly begins after the age of 40 years with peak age of onset between 58 and 62 years.
- 2nd most common neurological disorder behind Alzheimer’s Disease.
- 40,000 new cases diagnosed in United States each year.
- Etiology: unknown.

Pathophysiology of PD

- Imbalance of Inhibitory (Dopamine) and Excitatory (Ach) neurotransmitters.
- Extrapyramidal System is impaired including:
  - Voluntary Motor Movement
  - Motor Tone
  - Coordination and Postural Tone

Signs and Symptoms of PD

- Muscle rigidity
- Tremors
- Bradykinesia
- Postural instability
- Masked facies
- Monotone voice
- Generalized weakness
- Autonomic dysfunction
MPTP

- Neurotoxin which is a by-product of Meperidine synthesis.
- Creates selective destruction of cells of the Substantia Nigra
- Discovery of MPTP has promoted research into the field of Parkinson’s Disease since a true animal model could be replicated

Treatment

- Medications:
  - Dopamine: supplement Dopamine
    - Sinemet (Caridopa/Levodopa)
  - Dopamine agonists: maximize Dopamine availability by activating Dopamine Receptors
    - Permax, Mirapex, Requip, Parlodel * these drugs are associated with obsessive behaviors
  - Anticholinergic drugs: block central and peripheral Muscarinic Ach receptors
    - Artane, Cogentin
  - COMT inhibitor: maximize time for Dopamine to remain available
    - Comtan


Surgical Treatment of Parkinson’s Disease Symptoms

- Many undesirable side effects with medications

- Implantation of deep brain stimulators in subthalamic nucleus and globus pallidus
- Ablative surgery in globus pallidus or thalamus
"Everything that gets born dies," Morrie wrote. "The best way to deal with that is to live in a fully conscious, compassionate, loving way.... Don't wait until you're on your deathbed to recognize that this is the only way to live."