**NEUROLOGICAL DISORDERS:**
**MULTIPLE SCLEROSIS, GUILLAIN BARRE, PARKINSON’S DISEASE**

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**MULTIPLE SCLEROSIS (MS)**

- Chronic, progressive, demyelinating disease of the CNS
- Characterized by periods of remission and exacerbation
- Most Common neurological disease affecting young adults

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**MS: ETIOLOGY**

- Idiopathic, etiology unknown
- Theories
  - Abnormality of Immune Regulation
  - Chronic Infection of CNS
  - Environmental factors in childhood
  - Genetic predisposition

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**MS: PATHOPHYSIOLOGY**

- Plaques in the brain and spinal cord
  - Plaques range in size from 1-4 cm
  - More prevalent in white matter (myelin covered) and periventricular regions of brain stem (90%), optic nerves and chiasm, cerebellum, and cervical spinal cord region
  - Plaques slow speed and conduction of nerve impulses
  - Exacerbations and remissions believed to be controlled by some degree of stress (exacerbations) and immune response (remissions)
  - Newer research posits that stress does not CAUSE MS

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**MS: CLASSIFICATIONS**

- Relapsing-Remitting
  - Clearly defined relapses
  - 85%-90% individuals with MS
- Primary Progressive
  - Slow, continuous worsening
  - 10% individuals with MS
- Secondary Progressive
  - Relapsing-remitting on onset, followed by minor remissions
  - 80% of individuals with relapsing-remitting MS
- Progressive-Relapsing
  - Progressive disease from onset
  - Least common
**Cognitive Changes in MS**
- As many as 40%-70% of MS patients experience symptoms of cognitive impairment, such as memory dysfunction and verbal fluency deficits.
- These conditions are often underdiagnosed, in part because it can be difficult to measure cognitive function in the clinical setting.
- New studies have determined that MS patients may find it harder to think clearly and remember things on warmer days of the year.
- Pain is often prevalent in MS and impact cognition
  - It is treated with meds and acceptance-type psychotherapies

**MS: History**
- **Family History of MS - ??**
- **Symptoms**
  - Visual disturbances (diplopia, nystagmus)
  - Emotional lability
  - Bowel, bladder, sexual dysfunction
  - Impaired coordination
  - Extremity weakness, numbness, aching
  - Speech changes (slurring, staccato)
  - Dizziness, vertigo
- **Aggravation of symptoms**
  - Heat
  - Exercise
  - Stress

**MS: 2005, 2011 Revised McDonald MS Diagnostic Criteria**
- The Poser and MacDonald/Polman criteria
- Base the diagnosis of MS on MRI dissemination in time and place
- Heavily base diagnosis on MRI findings
- The 2X2
  - 2 or more attacks and 2 or more lesions
- Now allowed to diagnose MS on first attack with MRI findings and symptoms
- No longer have to wait for new criteria to emerge

**Multiple Sclerosis: Diagnostic Findings**

**Evoked Potential**
- Measure time required to transmit electrical impulses in central regions of CNS
- Slowing of impulses is evidence of plaques
- Visual (85%), auditory (67%), and somatosensory (77%) evoked responses

**MS: Interventions**
- There is no cure for MS
- Medications are used to treat relapses and to modify the course of the disease
- Pharmacological interventions include, but are not limited to:
  - Relapse Management
  - Disease-Modifying Agents
  - Symptom Management
- Early treatment works best!
  - Interferon beta-1b is prolonging survival rate, especially when started early
**MS: Disease-Modifying Agents**

- **Immunomodulating disease-modifying agents:**
  - Interferon-beta-1a (brand ‘Avonex’)
  - Interferon-beta-1a (brand ‘Rebif’)
  - Interferon-beta-1b (brand ‘Betaserone’)
  - Non-interferon therapy (glatiramer/’Capaxone’)
  - Synthetic antineoplastic (mitoxantrone)
  - α4-integrin humanized antibody (Natalizumab “Tysabri”) is back on market primarily for treatment of Crohn’s disease. Caution: May cause brain infection progressive multifocal leukoencephalopathy (PML)

**New Oral Drugs: Bad & Good**

- The US Food and Drug Administration (FDA) says it won’t approve oral cladribine (Movectro, Merck Serono) for multiple sclerosis (MS) without more safety information due to cancer-like effects.
- Fingolimod (brand ‘Gilenya’) is a sphingosine-1-phosphate-receptor modulator that readily crosses the blood-brain barrier. Its proposed mechanism of action is preventing the egress of B- and T-cell lymphocytes from lymph nodes, thereby reducing the potential for autoimmune damage to the central nervous system.

**MS: Disease-Modifying Agents**

- **Immunosuppressive therapy**
  - Cyclophosphamide
  - Azathioprine
  - Methotrexate
  - Cladribine
  - Cyclosporin A

**MS: Treatment**

- **Exacerbation**
  - Methylprednisolone—initially IV to speed recovery
  - Adrenocorticotropic hormone (ACTH) as an alternative to steroids
- **Relapsing-Remitting**
  - Interferon results in fewer relapses and MRI lesions
- **Progressive (gradual deterioration)**
  - Monthly boluses of chemo agent and steroids stabilizes disease progression
  - IV boluses of cyclophosphamide and methylprednisolone
  - Low dose azathioprine and methotrexate

**MS Symptom Management**

- Fatigue (worse in afternoon)
  - Amantadine (side effect = depression)
- Depression (50%)
  - Amtriptyline
  - Screen for suicide
- Spasticity
  - Baclofen (GABA\textsubscript{b} agonist)

**MS Symptom Management**

- Bladder spasms: Anticholinergics
- Bowel dysfunction: Hydration, high fiber diet
- Neuralgia: carbamazepine usually combined with a tricyclic antidepressant
- Sexual dysfunction (90%): lubrication, sex therapy, vibrators, erectile dysfunction
**MS: Treatment**
- Other therapies
  - Physical Therapy – for restoration of strength and maintenance of function
  - Intermittent exercise found to be ideal treatment
  - Occupational Therapy – for energy conservation while performing ADLs, adaptive devices as needed
- Follow up: dependent on disease course – at least every 3-6 months
- Encourage attendance at support groups and wear a medical bracelet indicating MS

**Guillain-Barré Syndrome (GBS)**
- Acute form of polyneuritis
- Due to autoimmune process within peripheral nervous system
- Characterized by rapidly progressive, ascending, symmetrical motor weakness

**Guillain-Barré Syndrome (GBS)**
- Acute inflammatory demyelinating polyneuropathy (AIDP)
- Inflammation and destruction of myelin sheath
- Can be fatal if the diaphragm becomes involved or complications of immobility
- Most often caused by viral infection

**GBS: Classifications**
- Ascending GBS
  - Weakness and paraesthesia/dysaesthesia begins in the legs, ascends to trunk, arms, cranial nerves
- Pure-motor GBS
  - Mild form of ascending type
    - Retains sensory function without muscle pain

**GBS: Classifications Continued**
- Descending GBS
  - Weakness and paraesthesia/dysaesthesia begins in the innervated by the cranial nerves and descends to the trunk and extremities
  - Mild respiratory involvement in most patients
- Miller-Fisher Syndrome (rare)
  - Ataxia, ophthalmoplegia, areflexia, no sensory symptoms
  - Respiratory difficulty uncommon

**GBS: Etiology**
- Exact cause unknown
- Inflammatory autoimmune disease
- Precipitating factors
  - **Infection** 60-70% patients report a recent respiratory or GI infection, which could be viral (15% CMV) or bacterial 10-14 days prior to symptom onset
  - **Surgery** – 5-10% patients report recent surgery or epidural analgesia use
  - **Vaccination** – small percentage of patients report having had vaccination within 8 weeks of symptom onset (antirabies, swine influenza, oral polio)
GBS: PATHOPHYSIOLOGY
- Inflammation due to an autoimmune reaction; results in myelin destruction
  - Areas of focal infiltration by T-cell lymphocytes and macrophages in a segmental pattern throughout cranial nn, autonomic, motor and sensory pathways
  - Macrophages attack and progressively destroy myelin
    - Between nodes of Ranvier
    - Eventually blocks conduction of nerve impulses

GBS: MECHANISM
- Acute polyneuropathy
- Myelin sheath of motor and sensory nerves ingested and destroyed by macrophages
- Recovery possible if no destruction of CB, axon, and Schwann cells
  - CB & Schwann cells reproduce myelin
  - 85% full recovery

GBS: SYMPTOMS
- Reflexes will be severely diminished or absent
- Pins and needles extremity neuropathy
  - Early stages, less common
- Cranial nn involvement includes inability to swallow, chew, talk, or close eyes

GBS: PHYSICAL FINDINGS
- Cardiovascular
  - Autonomic dysfunction
  - Hypertension, hypotension, dysrhythmias
- Respiratory
  - Tachypnea, adventitious sounds due to aspiration, decreased vital capacity
- Gastrointestinal
  - Decreased bowel sounds, abdominal distention, constipation
- Genitourinary
  - Bladder distention, urinary retension
- Skin
  - diaphoresis

GBS: DIAGNOSTIC TESTS
- No specific tests
- LP w/ CSF studies
  - Increased protein (>45mg/dl) (IgG)
  - Absence of increased WBCs
  - Normal opening pressure
- Electromyelogram (EMG)
  - Lack of nerve stimulation
- Nerve Conduction Velocity (NCV)
  - Slow, demyelination

GBS: COURSE
- Acute Stage
  - Onset of symptoms, rapidly progresses
- Plateau Stage
  - Symptoms remain for few days – few weeks
- Recovery Stage
  - Slowly over weeks to months to 2 years
  - Remyelination and axonal regeneration
  - Varying degrees of muscle weakness, paresthesia, hyperreflexia, distal muscle atrophy, facial paralysis
GBS: Treatment

- Plasmapheresis
  - Removes damaging antibodies
  - 3-4 treatments, 1-2 days apart
  - Monitor calcium level, replace
  - May receive second set of treatments

- High-dose Immunoglobulin therapy (IVIg)
  - Blocks damaging antibodies
  - 1.2 mg/kg in divided doses over 2-5 days

- Corticosteroids
  - Weak evidence, ineffective
  - Increase muscle usage
  - 1 mg/kg daily, taper

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GBS: Treatment continued

- Immunosuppressive Agents
  - Azathioprine: monitor bone marrow suppression, elevated liver function

- Anticoagulants
  - Heparin, low molecular weight heparin
  - Prevent DVT

- Antibiotic agents
  - Early treatment, erythromycin, campylobacter
  - Adrenocorticotropic hormone (ACTH)

GBS: Management

- Respiratory support
  - Hourly vital capacity check
  - > 1000 cc, otherwise intubation and vent
  - Check tidal volume, RR, pulse oximeter
  - Months of ventilatory support
  - Bacterial pneumonia
  - Pulmonary embolus

- CV support (autonomic dysfunction)
  - Tachycardia, dysrhythmias
  - Impaired hemodynamics

- Pain management
  - Acetaminophen, NSAIDs, antidepressants, opioids

- Bowel and bladder function
  - Fluids, high fiber diet

- Mobility
  - DVT prophylaxis
  - Impaired mobility
  - Joint contractures, pressure ulcers
  - Positioning, ROM
  - PT, OT, early rehab

GBS: Management continued

- Psychosocial support and counseling
  - Sudden onset of symptoms in relatively good health
    - Anxiety
    - Fear
    - Depression
  - Accurate information regarding prognosis and treatment, calm environment
  - Communication issues
  - Sleeping patterns
  - Financial issues
  - Empathy, compassion, sensitivity, keen listening, positive reinforcement
  - Educate family and include in patient care

- Physical Therapy
  - Maintains strength and flexibility
  - Reduce chance of contractures
  - Transfers
  - Gait and balance training
  - Assistive devices, braces, wheelchairs

- Occupational Therapy
  - Retraining ADLs
  - Manage and pace ADLs

GBS: PT & OT in Rehab
**GBS: OUTCOMES**
- 5% mortality
- 90% recover completely
- Some continue with weakness or abnormal sensation
- 20% permanent disability
- 60% ongoing fatigue
- 3% relapse

**PARKINSON’S DISEASE (PD)**
- Chronic and slowly progressive, degenerative condition resulting in impaired voluntary movement and loss of control of the autonomic nervous system
- Course may span >10 years
- Death usually results due to complications such as aspiration or other infections

**PD: ETIOLOGY & INCIDENCE**
- May be some etiologic correlations between parkinsonism and encephalitis, head trauma, cerebral ischemia, exposure to toxins, and long-term use of phenothiazines and amphetamines
- 1 million Americans have PD
- 1 in 100 people over 60
  - 5-10% people < 40
- Men slightly > women
- Mean age at onset 58-62
- 20-60% eventually develop cognitive decline

**PD: PATHOPHYSIOLOGY**
- Idiopathic condition resulting from a degeneration and depigmentation of the substantia nigra (basal ganglia)
  - Leads to deficiencies of dopamine (inhibitory transmitter)
  - Loss of dopamine thought to account for many of the hypotonic motor symptoms experienced
  - Presence of Lewy bodies in remaining nigral tissue
    - Found within neurons that produce dopamine
    - 50% nigral neurons degenerate to produce symptoms

**PD: PHYSICAL FINDINGS**
- Specific symptoms (TRAP)
  - (T) resting tremor of the hands, exaggerated by anxiety, absent during sleep, decreased during purposeful movement
  - (R) cogwheel rigidity (ratchet-like resistance during passive ROM)
  - (A) akinesia/bradykinesia: slowing of difficulty initiating movement
  - (P) Posture/gait disturbances: stooped position and poor balance leads to falls, shuffling gait
PD: PHYSICAL FINDINGS

- Muscle cramping, aching, stiffness
  - Dystonia (turning in of foot)
  - Mask-like facial expression
- Constipation, Urinary frequency, Stress incontinence
- Speech and swallowing difficulty
  - Voice may become softer in volume, monotonous
- Dementia: Progressive memory difficulty, recent occurs first followed by distant

PD MEDICATIONS

- Dopaminergics & dopa decarboxylase inhibitors – reduce rigidity, bradykinesia
  - Levodopa-carbidopa
    - Combo increases amount of levodopa that reaches brain
    - Regular, controlled-release, liquid
    - Give with meals
    - Side effects
      - Nausea, vomiting
      - Orthostatic hypotension
      - Dyskinesia (involuntary movements)
- Anticholinergics – reduce acetylcholine to balance lowered dopamine activity
  - Controls tremor; used for disabling tremor
    - Trihexyphenidyl (Artane)
    - Benztropine mesylate (Cogentin)
    - Diphenhydramine (Benadryl)
    - Biperiden (Akineton)
  - Contraindicated in elderly cognitively impaired
  - Side effects
    - Dry mouth
    - Constipation
    - Confusion
    - Impaired memory
    - Blurred vision
    - Tachycardia

PD MEDICATIONS

- Dopamine agonists – control motor fluctuations, balance
  - Mimic effects of dopamine, causes neurons to react
  - Bromocriptine (Parlodel)
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)
  - Rotigotine (Neupro)
    - Transdermal patch Q daily: provides 24 hr medication
    - Pergolide mesylate (Pergolide) – no longer used due to heart valve disease
  - Side effects:
    - Compulsive behavior, drowsiness, confusion
    - Hallucinations, tremors
    - Severe allergic inflammatory reactions, difficulty breathing

PD MEDICATIONS

- MAO-B inhibitor – for motor fluctuations and to reduce the levodopa-carbidopa dose if possible
  - Monoamine oxidase B
  - Prevent breakdown of dopamine
  - Inhibits activity of enzyme MAO-B
  - Selegiline hydrochloride (Zelapar);
    - Psychomotor enhancement r/t methamphetamine metabolites of drug – headache, insomnia, nausea, sweating
    - Never give to patient taking MAOIs
    - Do not give with amitriptyline or sumatriptan
  - Rasagiline (Azilect) – irreversible MAO-B inhibitor
  - Phenylzine (Nardil)- MAOI; rapid onset
COMT inhibitors
- Help increase energy, ADL function and sleep, decrease muscle cramps
- Catechol-O-methyltransferase
  - Increase bioavailability of levodopa
  - Block enzyme that breaks down dopamine
  - Take in conjunction with dopaminergic
  - Tolcapone (Tasmar) – used less due to severe liver damage
  - Entacapone (Comptan) – plain or in combination drug with levodopa-carbidopa

Botox injections
- Helpful for dystonia, blepharospasm, torticollis, dysphonia relief

Antiviral
- Amantidine 100 mg BID or TID
  - Treats dyskinesia due to dopaminergic drugs
  - Side effects:
    - Edema
    - Lower extremity mottling

Thalamotomy
- Reduces tremor
- Destruction of tissue in thalamus
- One side of brain

Pallidotomy
- Reduces tremor, rigidity, bradykinesia
- Electric current destroys tissue in globus pallidus
- Both are irreversible

Deep Brain Stimulator (DBS)
- Control symptoms – rigidity, bradykinesia, tremor
- Decrease medications
- Transmit electrical impulses through wire in tiny electrodes in globus pallidus (Gpi), subthalamic nucleus (STN), ventral intermediate nucleus of thalamus (Vim)
- Poor patient selection
  - Poor response to levodopa, atypical PD, age > 75, presence of psychiatric disorders, DM, CAD, abnormal MRI, poor patient motivation
- Restart PD medications post op
- DBS not turned on until follow-up visit
- Turned on and off with magnet

Transplant surgery
- Experimental implantation of dopamine-producing cells into striatum
- Moderate effectiveness
- Patients < 60
- Stem cells to create dopamine-producing cells
Thanks for attending today’s seminar.
Please make certain to have your CE credit sheet checked by the Advance coordinator.