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Multiple Sclerosis: Current concepts in pathophysiology, evaluation, and intervention for rehabilitation

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As a result of this course, participants will be able to:

- Describe the pathophysiology and epidemiology of MS and how it relates to specific mobility related impairments
- Describe the process of how a medical diagnosis of Multiple sclerosis is made
- Recognize how MS pathology leads to specific impairments and functional limitations
- Identify the different functions of the various MS medications
- Distinguish between the various impairments that may be seen in a patient with MS
Part 1

- Epidemiology
- Pathology
- Medical management
- Clinical Presentation

Introduction: The problems of MS and rehabilitation

- MS is a disease of mobility
- Etiology different than other Neuro diseases
- Different PT skills needed
I’d rather stick my tongue in an electric socket than work with a patient with MS

*** *******PT, Name withheld on request

Therapeutic Nihilism

“A disbelief in the efficacy or value of therapy, as of drugs, psychotherapy, etc.”

Stedman’s Online Medical Dictionary, 27th Edition

The doctrine that given the patients condition, it makes no difference whether something is done for the patient or not
Therapeutic Nihilism may occur in MS because:

- Progressive course
- Unpredictability: symptoms can occur at any time
- Symptoms can occur with unknown severity
- Symptoms can occur at any region of the CNS
- PT management is poorly defined

Multiple Sclerosis defined:

- Chronic
- CNS
- Demyelinating
- Autoimmune
- Inflammatory
Multiple Sclerosis Defined

- Variable intensity
- Variable location
- Variable presentation
- Variable prognosis

Disease of Heterogeneity

- Any area on the CNS, any intensity, any time frame
- No stereotypical presentation
- “If you’ve met one person with MS, you’ve met one person with MS”
Multiple Sclerosis Epidemiology

- Worldwide: approximately 400,000 people in the United States and 2.5 million worldwide.
- 200 people dxed each week in the US
- Leading cause of non traumatic disability in young adults

Epidemiology

- Prevalence and incidence increasing over time
- Better diagnostic techniques
- Greater long term survival
- Time to severe disability is increasing
Multiple Sclerosis Epidemiology: Age and Gender

- Most commonly diagnosed in 20-40 yo age group
- Rarely diagnosed before the age of 10 or after 60, but often misdiagnosed at these ages
- More commonly in women than men 2:1

Geographical Pattern of Prevalence

High risk areas
- Northern US, Northern Europe, Southern Canada,
  New Zealand, Southern Australia

Medium risk areas
- Southern US and Europe, Northern Australia

Low risk
- Africa, Asia
Geographical Pattern of Prevalence

Where a person spends the 1st 15 years of life determines the likelihood of developing MS
  
- If you were born in the north and move to the south at 17, higher risk
- If you were born in the south and move north at 17, lower risk
- If you were born in the north and move south at 10, lower risk
- If you were born in the south and move north at 10, higher risk

Indicates an environmental trigger

Genetics

Risk of developing MS is greater if you have a sibling with MS, greater risk for ♀ sibling vs. ♂ sibling
Pathophysiology

- Demyelination
- Axonal Loss
- Inflammation
- Oligodendrocytes
- Maladaptive Neuroplasticity
- Clinical Implication

Demyelination

- Loss of covering over CNS axons
- Slowing and stopping of saltatory conduction through an axon
- Location of demyelination determines symptoms
- Extent of demyelination determines severity
- Remyelination occurs following demyelination, but with less efficiency, resulting in slowing and diminishing of saltatory conduction
Demyelination

- With disease progression, there is increasing loss of myelin
- Eventually the underlying axon is destroyed
- Myelin is replaced by fibrous scarring called gliosis, which inhibits transmission of impulses
- Disease is named for the multiple area’s of scarring (sclerosis)
Oligodendrocytes

- Myelin Producing cells in the CNS
- Responsible for remyelination
- Also attacked by autoimmune process

Oligodendrocyte destruction in MS
Blood Brain Barrier (BBB)

- Semi permeable layer of cells within the capillaries of the central nervous system.
- Allows oxygen and essential nutrients to enter the central nervous system.
- When functioning normally, prevents foreign invaders (immune cells) from passing out of the bloodstream and into the central nervous system.

Blood Brain Barrier in MS

- Immune cells pass through, implying BBB compromise or damage.
- Immune cells, (T-lymphocytes), attack the myelin in the brain and spinal cord, causing the lesions which lead to MS symptoms.
Inflammation

- T-cells cross the BBB and attack myelin incorrectly recognizing it as an invading virus.
- Triggers inflammatory processes, stimulating other immune cells (cytokines, antibodies, macrophages)
- Much of the damage in MS occurs due to inflammation, and therefore can be limited by controlling it
Primary Damage vs Secondary Damage

- Demyelination and Inflammation are the primary substrate for disability
- Deconditioning and maladaptive movement patterns are the secondary substrate for disability
- Much of MS disability is learned.
- Can it be unlearned?

Medical management

- Disease modifying therapy
- Exacerbation management
- Symptom management
- PT implications of medical management
Medical Management in MS: Implications for Rehab

Earlier diagnosis
Earlier treatment
Decreased lesion load
More effective rehab

Medical Management

- Disease Modifying Therapy (DMT)- CRAB drugs (Copaxone, Rebif, Avonex, Betaseron), Tysabri,
- Newer/Second order drugs-Rituxan, Ocrevus, Mitoxantron, methotrexate, IVIG
- Exacerbation treatment- Steroids
- Symptomatic treatment
Disease Modifying Therapy

- Beta Interferons - Avonex, Betaseron, Rebif
  - Heals the BBB by preventing immune cells from entering CNS
  - Efficacy – reduced relapse frequency and intensity in RRMS by 1/3
  - Side effects - Flu like sx 1-2 days after injection
  - Limitation - not effective in progressive disease
    - by lowering immune response, increases likelihood of infections

Disease Modifying Therapy

- Copaxone - (Glatiramer Acetate)
  - Limits inflammatory properties of immune cells that cross the BBB
  - Efficacy - equally effective to beta-interferons
  - Side effects - no flu like sx, but daily vs weekly injections
  - Limitations - not effective in progressive disease
Disease Modifying Therapy

- Tysabri (Natalizumab)
- Blocks passage of inflammatory cells across the blood brain barrier
- Efficacy- twice as effective as CRAB drugs in RRMS
- Administration-monthly infusion
- Limitations- Progressive Multifocal Leukoencephalopathy (PML)

Progressive Multifocal Leukoencephalopathy (PML)

- Rare but fatal inflammation of white matter in the brain
- JC Virus, normally suppressed, becomes activated during immunosuppression
- JC Virus can be tested for via LP or brain bx
Disease Modifying Therapy - Second order drugs

- **Mitoxantrone (Novantrone)**
  - Suppresses Immune function, injection every 3 Months, some effectiveness in SPMS, cardiac side effects

- **IT Methotrexate** - may be effective in PPMS and SPMS

- **IVIG** - mixed success in progressive MS

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Rituxan (rituximab)

- Suppresses the immune system
- Targets & depletes B-cells from the blood
- Given by infusion every 6-12 months
- Well tolerated and effective
Omecrelezumab (Ocrevus)

- Treatment of RR and progressive disease
- Given by infusion

Side effects
- upper respiratory tract infections,
- infusion reactions (itching, rash, hives, redness, bronchospasm, swollen and sore throat, mouth pain, shortness of breath, flushing, hypotension, fever, fatigue, headache, dizziness, nausea, and fast heart rate),
- skin infections

Oral DMT’s

- Dimethyl fumarate (Tecfidera)
- Fingolimod (Gilenya)
- Teriflunomide (Aubagio)
- No complications associated with injections/infusions
- Possible contraindications for patients with dysphagia
Steroids

- Methylprednisolone (Solumedrol)
- Limits the inflammatory process of an acute attack
- Stabilizes the BBB
- Limits immune response
- Occasionally used as a monthly pulse for progressive disease
- Energizing effect

Steroids- Limitations

- LT use leads to osteoporosis, wound healing difficulties
- Steroid psychosis
- Less effective in progressive disease
- Decreased effectiveness over time
- Immediate effect which does not persist
Symptomatic Treatment - Spasticity

- Baclofen (Lioresal) oral and intrathecal
- Zanaflex (Tizanidine)
- Dantrium
- Sedation/specificity

Spasticity

- Intrathecal Baclofen for spasticity refractory to oral medication
- Requires neurosurgical procedure
- Excessive spasticity control can limit movement - requires dialogue with MD
Symptomatic Treatment - Fatigue

- **Ampyra (Dalframpridine)**
  - Potassium channel blocker improves CNS transmission
  - Motor fatigue
  - Seizure risk
- **Provigil (Modafinal)**
  - Antinarcoleptic
  - Global/mental fatigue

Abnormal Flow of Potassium Ions in Demyelinated Axons Interferes With Nerve Impulses

\[ K^+ = \text{potassium} \]

Improved Nerve Impulse Conduction by Blocking Potassium Channels

K⁺ = potassium

Sx. Management: pain

Neurogenic pain vs secondary
Neurontin (Gabapentin) frequently used for neurogenic
PT/OT- for musculoskeletal/mechanical pain syndromes
Diagnosis

Dx is difficult.
Often requires a very accurate history that may reveal vague complaints that have gone on for years without being diagnosed.

Diagnosis

- Early diagnosis is critical to start early treatment and prevent further CNS damage
- Early diagnosis and better treatments primary reason for decreasing disability
Diagnosis: McDonald Criteria: Definite MS

- Clinical evidence of 2 spatially and temporally distinct attacks
  and
- Laboratory evidence of 2 or more distinct lesions on MRI, CSF, or EP
  and
- Exclusion of other, better explanations for the clinical features

Spatial and temporal Distinction

- Spatial distinction - Symptoms must be in 2 different regions of the body (i.e. LE spasticity and ON)
- Temporal distinction - Symptoms must be at least 6 months apart
MRI

- Multiple foci in brain and/or cord
- Gadolinium-enhanced T1-weighted scans - shows inflammation, indicative of new lesions
- T2-weighted scans - shows older, inactive lesions, number and size of lesions
- 5% false negatives on MRI

MRI - Diffuse cortical lesion

Healthy brain

Plaques

Brain with damage (lesions or plaques) caused by MS
Relapsing Remitting MS

Relapse 3 months later

Cerebrospinal Fluid Analysis (CSF)

- Elevated IgG Antibodies
- Oligoclonal Bands
- R/O other non-MS causes
- Differentiate between RR and other types?
Clinically Isolated Syndrome (CIS)

- First neurologic episode that lasts at least 24 hours, and is caused by inflammation/demyelination in one or more sites in the central nervous system (CNS).
- The episode can be monofocal or multifocal
- To treat or not to treat?

McDonald Criteria

- **Definitions:** Attack (exacerbation, relapse)
- An episode of neurological disturbance of the kind seen in MS
- Should last for at least 24 hours
- Event should not be a pseudoattack, such as might be caused by a change in core body temperature or infection
Karpatkin Criteria
Exacerbations vs pseudoexacerbations

- Exacerbation - acute demyelinating event
- Pseudoexacerbation - acute but transient worsening of symptoms brought on by fatigue, temperature rise, stress etc
- Not demyelinating
- Pseudoexacerbations can be caused by excessive exercise - BUT EXERCISE DOES NOT CAUSE EXACERBATIONS

Types of MS

Describes behavior over time, not disease severity
- Relapsing-remitting
- Relapsing-progressive
- Chronic progressive (primary progressive)
- Secondary progressive
- Less common
- Benign
- Fulminant
Relapsing-Remitting

- Episodes of rapid, abrupt deterioration with variable degrees of recovery over time
- Also known as exacerbating - remitting

![Relapsing-Remitting Diagram](source: Lublin et al., 2014)

Relapsing-Progressive

- Also known as exacerbating - progressive
- Steadily worsening neurologic function from the beginning with occasional relapses

![Relapsing-Progressive Diagram]
Primary Progressive/Chronic Progressive

- Pace of deterioration can vary
- Relapses with a large degree of residual impairment
- Plateaus rather than remissions

Secondary Progressive

- Begins as relapsing-remitting, then becomes progressive
Benign

- Occasional symptoms without significant functional impairment

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Fulminant (Marburg Syndrome)

Rapidly progressive
Leading to early, severe disability and death
Due to mass affect and displacement
Marburg syndrome

Early vs. Later treatment

The progression of HS will increase significantly if left untreated or treatment is delayed. Starting treatment early shows lower amounts of progression, which supports beginning treatment at the time of diagnosis.
Primary Signs and Symptoms

MS can present in any number of ways, depending on where the lesions are located
Cortex, subcortical, brainstem cerebellum, cord
Temporal, spatial, qualitative, and quantitative differences
“If you’ve seen one patient with MS, you’ve seen one patient with MS”

Variability of findings

- No stereotypical presentation
- Few “rules of treatment”
- Primary and secondary findings
Clinical Presentation-Impairments

- Fatigue
- Thermosensitivity
- Motor control
- Strength
- Spasticity
- Range of motion
- Sensation
- Vision
- Respiratory
- Vestibular

Fatigue

- Most common MS symptom
- Tremendous impact on function
- Can worsen impact of impairments
- Objective and Subjective Components
- Primary and Secondary components
Objective vs Subjective

- Objective: “fatigability” - worsening of motor performance over time
- Related to decrease in action potential traveling through a demyelinated nerve
- Subjective: "Fatigue" Feeling “tired”, lethargy, lassitude, depression, overwhelmed, sleepiness
- Not correlated

Primary vs secondary fatigue

- Primary due to a specific pathology of the disease
- Secondary - due to an adaptation, compensation, or lifestyle choice that occurs as a result of the disease.
- Deconditioning
Interaction of Primary and Secondary Fatigue/fatigability

Deconditioning → Fatigue → ↓ Activity

Less movement is performed, deconditioning results, tasks become “unlearned”

Where can clinicians intervene in this cycle?

Fatigability with repeated task repetition
Fatigability: Continuous vs intermittent 6 minute walk (Karpatkin et al, 2014)

- Distance decreases when walks are continuous
- Increases, then stabilized when intermittent

Subjective fatigue: Continuous vs intermittent walking: Less fatiguing (Karpatkin et al IJMSC 2016)

- 29 patients with MS
- Randomized crossover design
- 6MW continuous vs intermittent (2 minutes walk/2 min seated)
- VASF increased less in the intermittent condition (from 37.93 mm to 44.83 mm; difference = 6.90 mm) compared to the continuous condition (from 34.33 mm to 54.43 mm; difference = 20.10 mm; \( P < .001 \))
Fundamental problem of Physical therapy and MS

- For change to occur, a sufficient volume of exercise must be performed
- Neurogenic fatigue prevent this from occurring in MS
- The primary symptom of the disease prevents remediation of the disease
- How should evaluation and intervention be structures to address this?

Thermosensitivity

Worsening of symptoms with increase in heat
The increase in sx from heat is transitory, and will not cause any primary permanent damage
Heat rise can be environmental or internal
Exercise raises internal temp
Activity Dependent Conduction Block (ADCB)- decreased ability of demyelinated axons to conduct action potentials when temperature increases
Thermosensitivity

- Some patients worsen in cold
- Humidity often worsens sx as well
- Precooling can be an effective intervention
- MS Thermosensitivity does not preclude use of local heat.

Effect of temperature on gait in MS
(Hunter College 2014)

- Randomized crossover trial
- Subjects with or without cooling vest for 6MW

![Bar chart showing mean 6MWT distance for cooled and uncooled conditions.]
Gait and temperature

- Suggest that increasing body heat may be a causal factor in slowdown
- Exercise increased core temperature
- If we can mitigate body heat perhaps mitigate slowdown?

Strength

- Primary loss- due to involvement of Motor tracts
- Secondary loss- due to deconditioning
- Interaction of strength and fatigue- first repetition can be strong following ones are week
Fatigability with repeated task repetition

Motor Control

- Loss of ability to perform a task due to loss of skilled movement
- Due to CNS involvement or lack of practice?
- Lack of ability to perform a task may suggest the issue is not related to range or strength, but “unlearning”.
- Suggests that relearning could be possible
Range of Motion

- Common finding due to spasticity, lack of antagonist strength, prolonged positioning
- Common areas: plantiflexors, hip flexors, hamstrings, trunk flexors (prolonged sitting postures)
- Vicious circle of inactivity and decreased range

Spasticity

- Velocity dependent reaction to stretch
- Part of the UMN syndrome
- Common in plantiflexors, hamstrings
- PT can address the tissue shortening, but medications are needed to treat spasticity (baclofen, tizanidine)
- Intrathecal baclofen often needed due to progressive nature of disease
Sensation

- Loss of proprioception > sharp dull
- Worsens with fatigue
- Can worsen due to non-use; increased use of visual strategies for balance
- Suggests improvements are possible

Effects of fatigue on sensation in pwMS
(Hunter College 2015)

- 17 pwMS
- Randomized crossover study
- Sensation tested using biothesiometer
- 6 minute walk or 6 minute rest
- Repeat Sensation test
Changes in sensation after gait in pwMS

Clinical Implications

- Changes in gait mechanics when fatigued may be due to worsening sensory loss
- Can interventions to improve sensation mitigate this?
Vision

- Visual deficits common first sign due to demyelination affinity for brainstem optic tracts
- Vision worsens with fatigue, heat
- Optic neuritis a common first symptom

Respiration

Changes in respiration can occur due to:
- Demyelination of central respiratory tracts
- Deconditioning due to sedentary lifestyle
- Contractures of respiratory muscles
- Decreased space for gas exchange in thoracic category
- Weak ineffective cough
- Mortality in MS frequently due to respiratory compromise
Ataxia

Usually due to cerebellar involvement, occasionally can be from posterior column involvement
Dysmetria, dysdiadochokinesia, tremor and vestibulopathy are also possible
If vertigo is present, it must be differentiated from peripheral vestibular complaints

Vestibular

- Commonly due to involvement of cerebellum and brainstem structures
- Higher than normal incidence of BPPV
- Differentiate Central from peripheral vestibulopathy with Hallpike Dix test and type of nystagmus
Central vs Peripheral Vestibulopathy

**Central**
- Direction changing Nystagmus
- Rotatory OR linear components
- Can be separate from vertigo
- Unable to suppresses with fixation

**Peripheral**
- Unidirectional nystagmus
- Rotatory AND linear components
- Matches with vertigo
- Suppresses with fixation

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**Part I - summary and conclusion**
- MS is a chronic progressive disease of tremendous variability
- No stereotypic presentation
- Medical intervention has a large impact
- Loss of mobility and fatigue are major and interacting components.
Citations


