Multiple Sclerosis Update

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Objectives

- Describe epidemiology, etiology, pathogenesis, clinical features of multiple sclerosis.
- Discuss the management of multiple sclerosis in regard to acute relapse, disease modifying therapy, and symptomatic care.
- Describe the clinical presentation, diagnostic workup, and management options for each of the following conditions:
  - Neuromyelitis Optica
  - Acute Disseminated Encephalomyelitis
  - Transverse Myelitis
  - Optic Neuritis

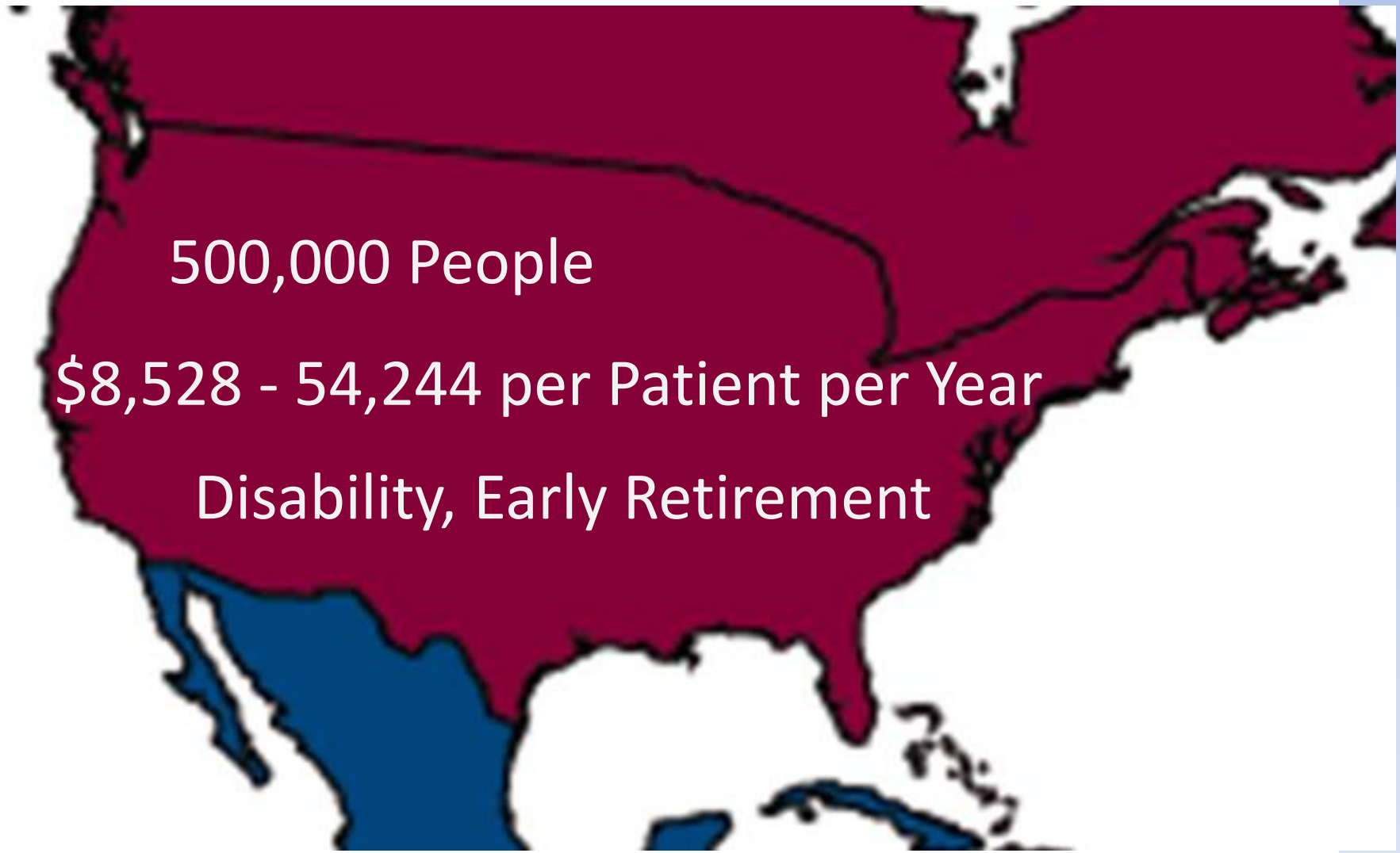
Case

- **Hx**: A 22yo female presents to your outpatient clinic with complaints left vision loss associated with mild eye pain that start about 4 hours ago. Prior neurologic symptoms include 12 days of right vision impairment 2 years ago and 14 days of right arm incoordination 5 years ago.
- **PE**: Left visual acuity 20/70 with correction. Right visual acuity 20/25 with correction. No field cut. Fundoscopic exam reveals swelling of the right optic disk, blurring of disk margins. Otherwise non-focal screening neurologic exam.

Outline

- Epidemiology
- Etiology and Pathogenesis
- Clinical Features
- Approach to Evaluation
- Management
- Prognosis

Epidemiology

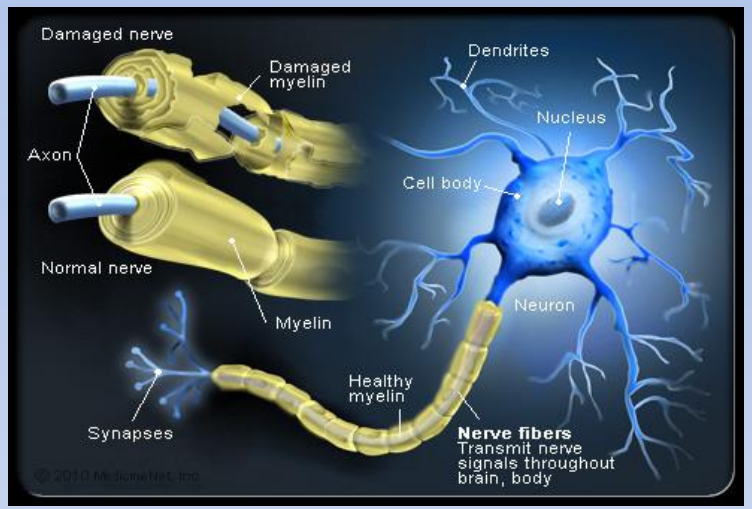


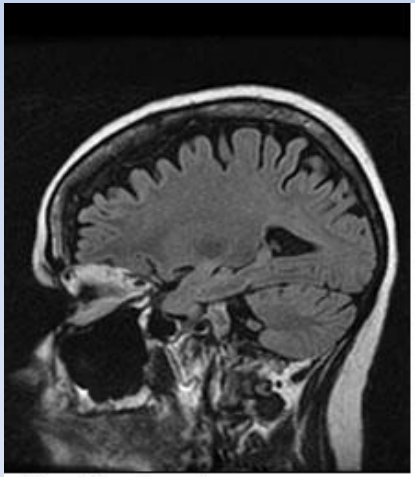
Multiple Sclerosis International Federation. *Atlas of MS 2013*

Neurology, February 2019

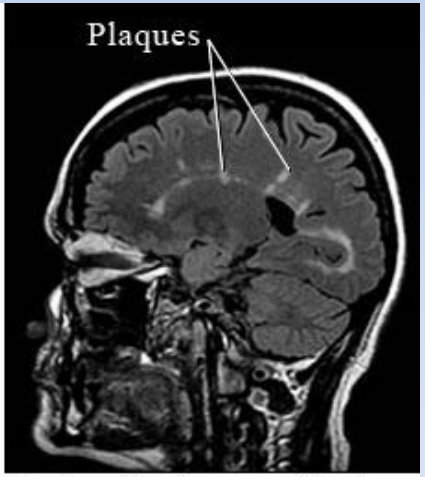
- A study by leading experts estimates that in 2017, nearly 1 million adults (up to **913,925**) were living with MS in the United States. This is more than twice the previously reported number from a national study in 1975 and subsequent updates.

Pathophysiology





Healthy brain



Brain with damage (lesions or plaques) caused by MS

Etiology: Unknown

Pathogenesis: Immune-mediated inflammation, demyelination, *and* axon degeneration in the central nervous system

Risk Factors

- Genetic
  - Family History; Specific Genes (HLA-DRB1); Caucasian; Female
- Environmental
  - Northern Altitudes (N. America, Europe); Dietary(Vitamin D); Infectious (EBV)

Image Reference: http://2.bp.blogspot.com/-6TzdBTmpp2E/TpPUqH-DGBI/AAAAAAAAAEY/YV01_P7DFSA/s1600/myelin+attack.jpg
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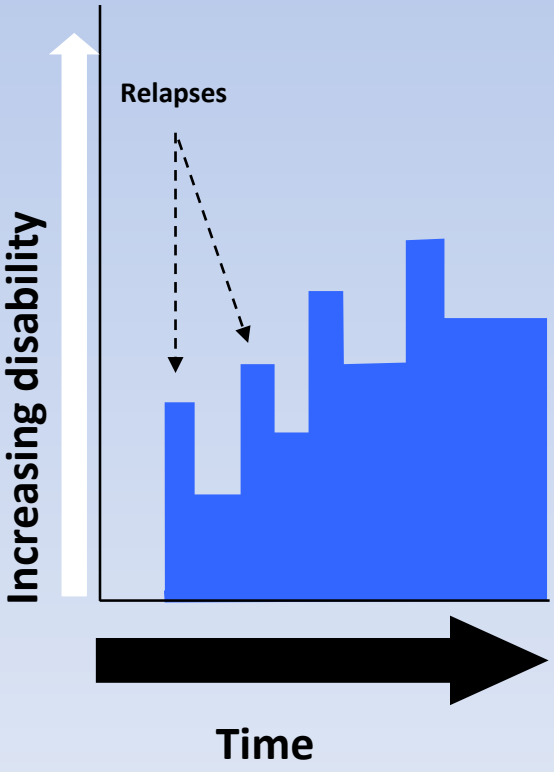
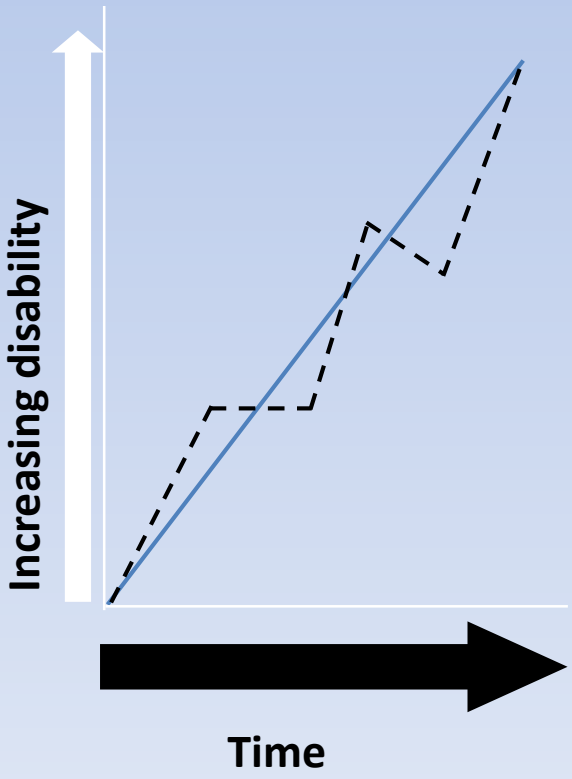
Types of MS

Relapsing Remitting



Primary Progressive



Secondary Progressive

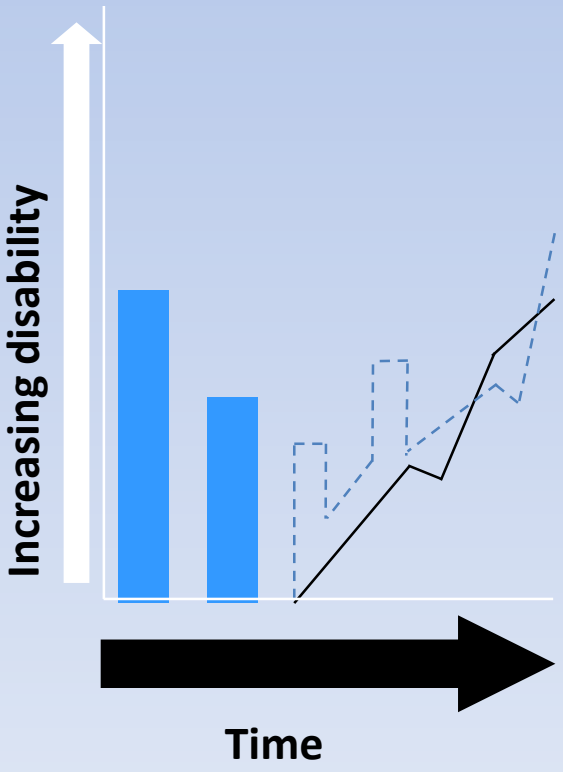
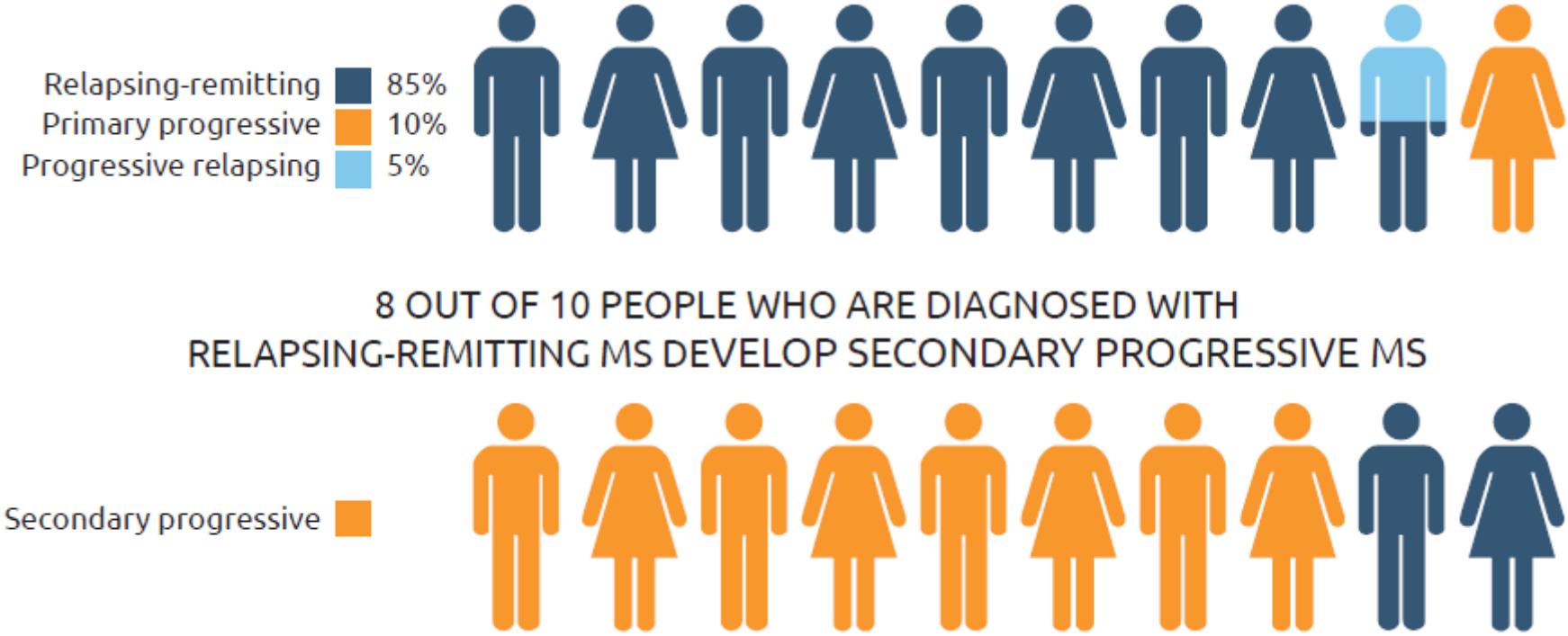


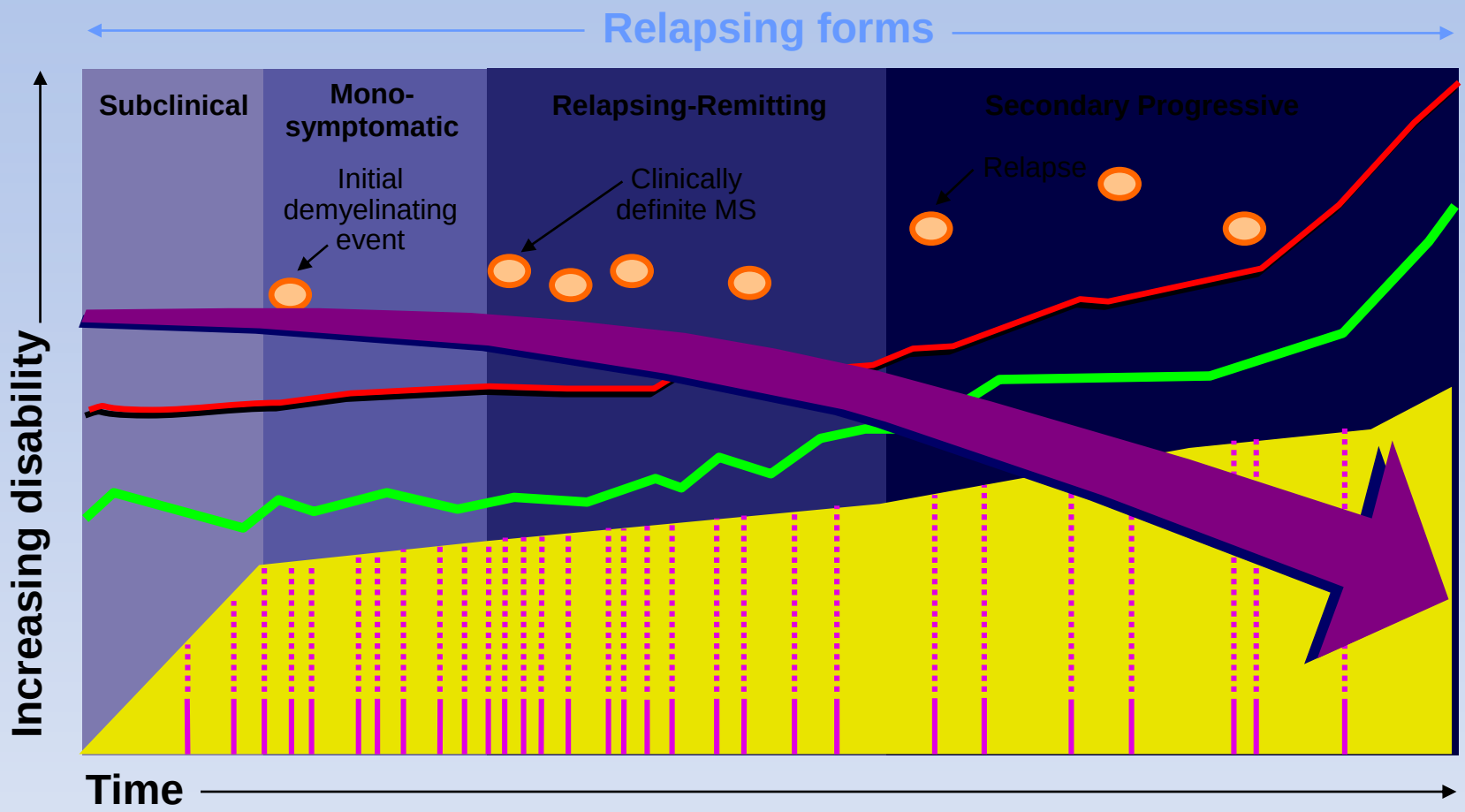
Image Courtesy of Mark B. Skeen, MD, Duke University Medical Center

Types of MS at Time of Diagnosis



Multiple Sclerosis International Federation. *Atlas of MS 2013*

Natural Progression of MS



Gd = gadolinium.

Clinical Features

History

- A single episode or multiple episodes of neurological impairment separated by a period of time with less or no symptoms

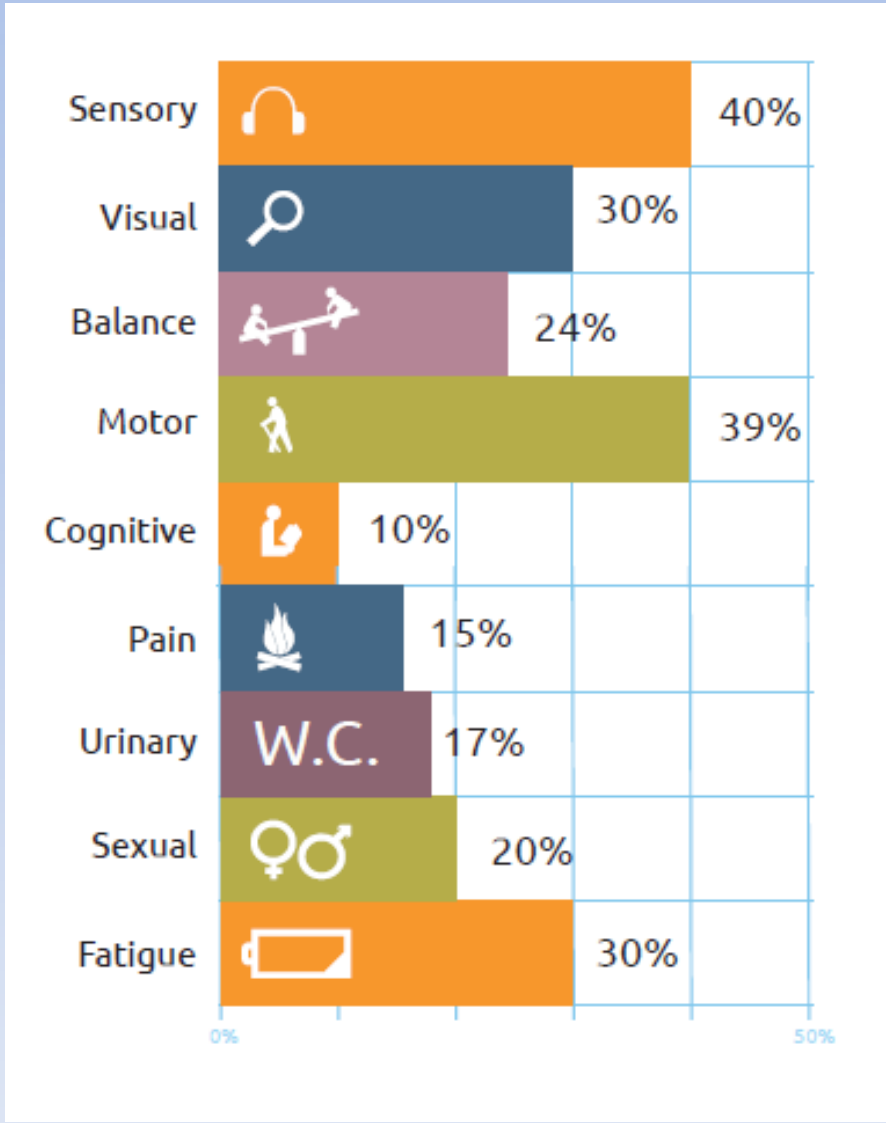
or

- A progressive decline in function

Clinical Features

- **Neurocognitive**
  - **Cognitive impairment**
  - **Depression**
- **Motor - Somatic**
  - **Spasticity**
  - **Weakness**
  - **Incoordination**
  - **Gait Impairment**
  - **Tremor**
- **Motor - Autonomic**
  - **Sexual Dysfunction**
  - **Overactive Bladder**
  - **Underactive Bladder**
- **Sensory**
  - **Visual Impairment**
  - **Trigeminal Neuralgia**
  - **Sensory Disturbance**
  - **Pain**
- **Other**
  - **Fatigue**
  - **Seizure**
  - **Dysphagia**
  - **Lhermitte's Sign**
  - **Uhthoff Phenomenom**

Most Common Presenting Symptoms



Multiple Sclerosis International Federation. *Atlas of MS 2013*

Relapse, Remission, & Pseudo-Relapse

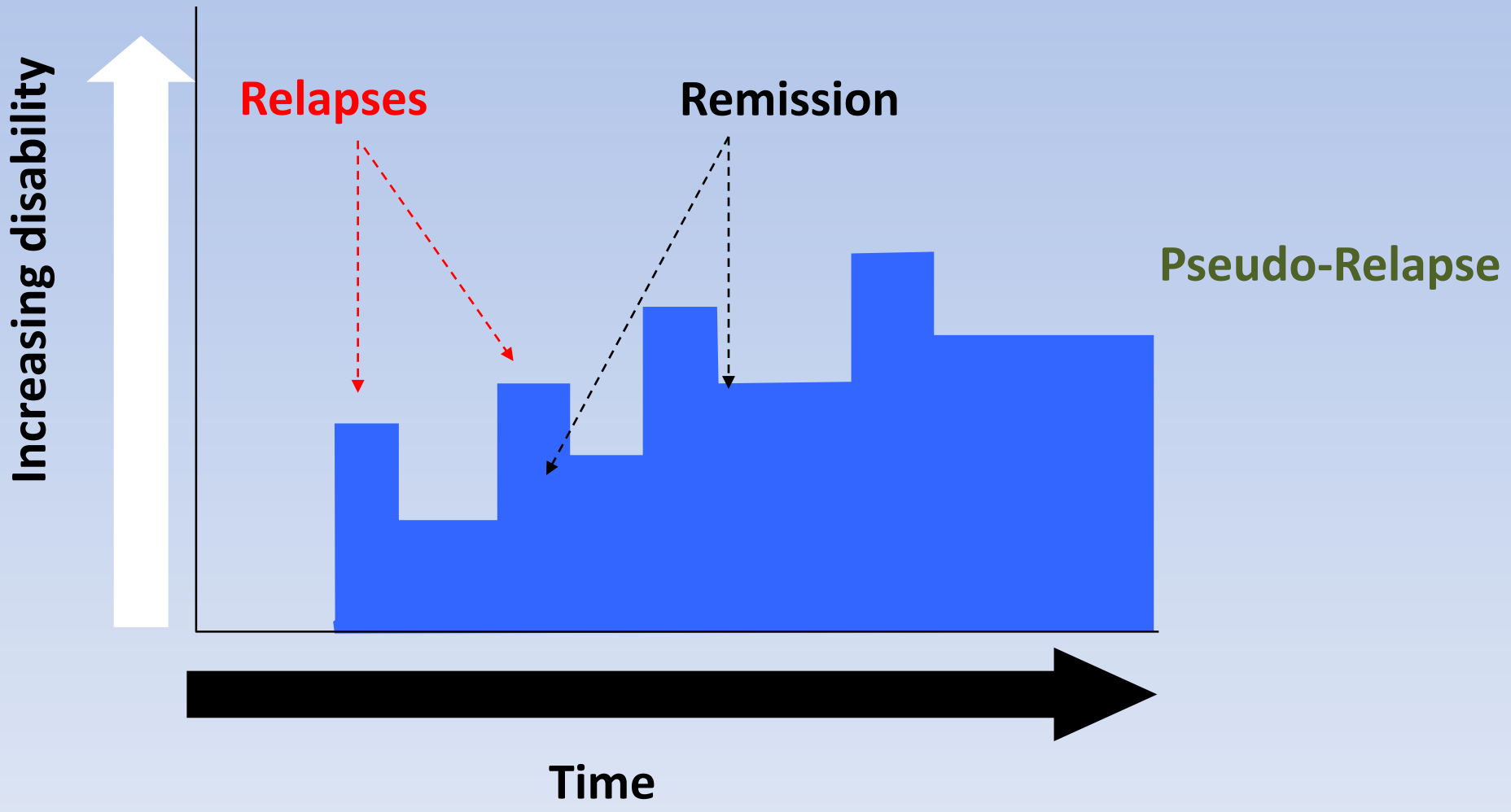


Image Courtesy of Mark B. Skeen, MD, Duke University Medical Center

Differential Diagnosis

- Cerebrovascular Disease
- Deficiences in vitamin B_{12}, vitamin E, or copper
- Systemic Lupus Erythematosus
- Syphilis
- Lyme Disease
- Sjogren Disease
- Isolated CNS Angiitis
- Human Immunodeficiency Virus
- Sarcoidosis
- Spinal Cord Compression
- Clinical Isolated Syndrome (CIS): Transverse Myelitis, Optic Neuritis
- Polyphasic/Multifocal Demyelinating Disease: Neuromyelitis Optica

Differential Diagnosis

Clinically Isolated Syndrome

- Single first clinical episode reflecting a focal or multifocal demyelinating event in the CNS
- MS Likelihood
  - Baseline MRI w/ demyelinating lesion: 60%
  - Baseline MRI w/o demyelinating lesion: 20%
- Monitor for MS or Consider DMT

Radiographically Isolated Syndrome

- Incidental brain or spinal cord MRI findings that are highly suggestive of MS, based upon location and morphology within the CNS
- Can be seen with cerebro-microvascular disease, aging, history of head trauma, history of headaches
- Monitor for MS

Diagnosis

Two or more neurologic events separated in time or a progressive course over 1 year, with objective demonstration of two or more affected areas of the CNS by physical examination, MRI, or evoked potentials. Other causes must be excluded.

Clinical

- History & Physical Examination

Paraclinical

- Magnetic Resonance Imaging (MRI)
- Evoked Potential Studies (EPS)
- Cerebrospinal Fluid (CSF) Analysis – Support Diagnosis
  - Elevated Immunoglobulin G (IgG) Index
  - Two or more oligoclonal bands

Diagnostic Criteria

Revised MacDonald Criteria [2010]

Relapsing Course

- Diagnosis based on objective demonstration of dissemination of lesions in space (DIS) and time (DIT)
- DIS = MRI with 1 or more T2 lesions in at least 2 of 4 CNS areas
- DIT = New lesion on MRI with reference to baseline MRI reference **or** presence of enhancing and non-enhancing lesions (no comparison MRI needed)

Progressive Course

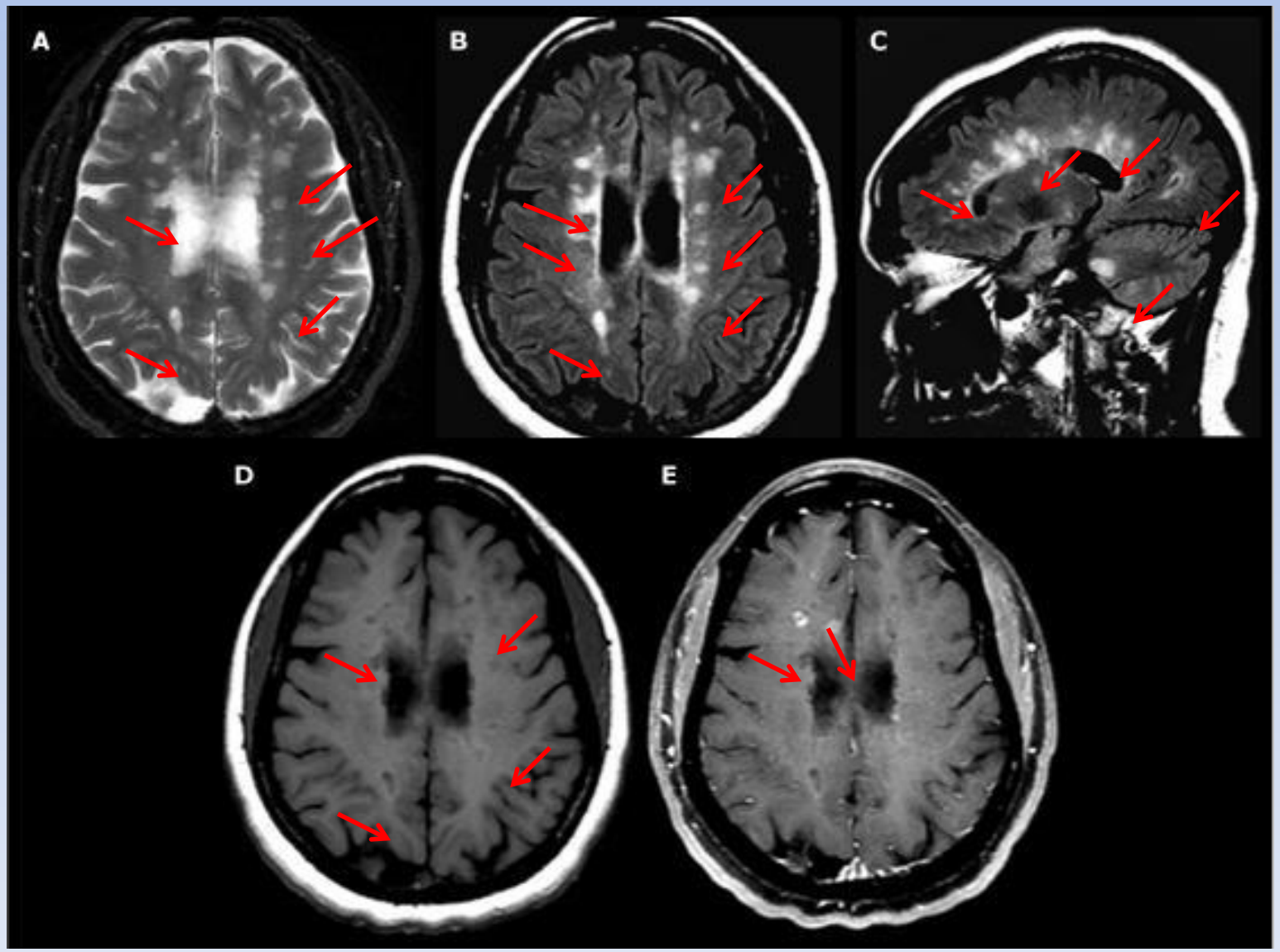
- One year of disease progression plus 2 of the 3 following criteria
  - DIS 1 or more T2 in at least 1 characteristic area; DIS 2 or more T2 in spinal cord; Positive CSF

- Other Criteria: Schumacher; Poser

Diagnostic Studies

- **Magnetic Resonance Imaging (MRI)**
  - Brain and Spinal Cord
  - MS most commonly involves cerebral hemispheres, peri-ventricular regions
  - Gadolinium enhancement is indicative of active inflammation
  - Other causes of “white spots” include aging, cerebrovascular disease, migraine, monophasic demyelinating disorders, immune-mediated diseases affecting the CNS

MRI Brain



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MRI Cervical Spine

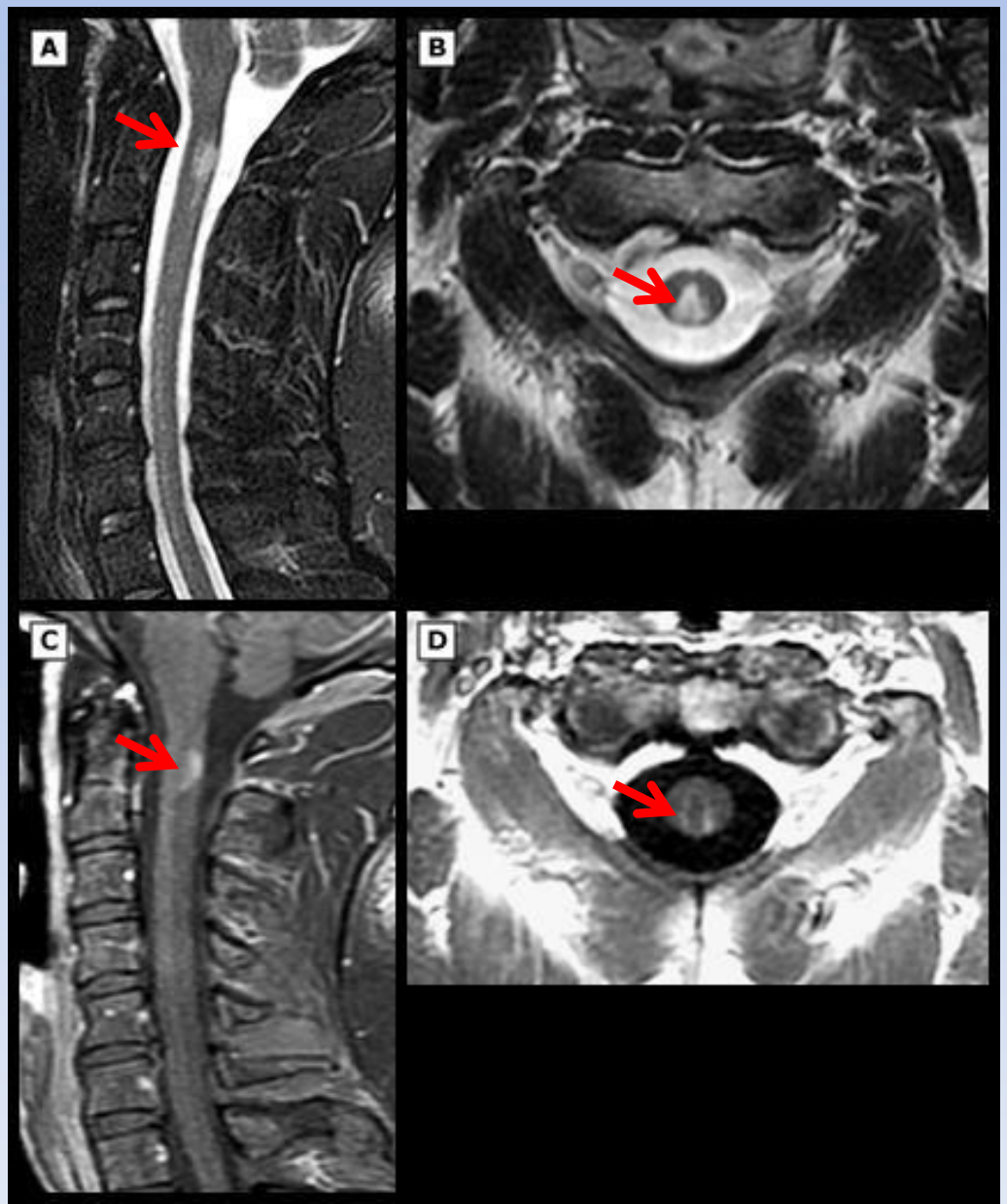

Image Reference: UpToDate

Diagnostic Studies

- **Evoked Potential Studies**
  1. Visual: evaluation of optic pathway
  2. Brainstem-Auditory: evaluation of brainstem
  3. Somatosensory: evaluation of the spinal cord

- **Cerebrospinal Fluid Analysis**
  - Description: Clear, Colorless
  - Cell Count: Usually < 5/mm^3, Rarely > 50/mm^3
  - Protein: normal or slightly elevated (rarely > 100/dL)
  - Glucose: normal
  - **IgG Index: elevated**
  - **Oligoclonal IgG Bands >4**

Management

Relapsing

1. Treat acute inflammation
2. Treat with Disease-Modifying Therapies
3. **Treat Co-Morbid Neurological Symptoms**

Progressive

1. Treat acute inflammation, though uncommon
2. In select cases, Treat with Disease-Modifying Therapies
3. **Treat Co-Morbid Neurological Symptoms**

While No Cure Exists, this lifelong disease is manageable

Management: Relapsing Course

SUMMARY

1. Acute Inflammation
   - Corticosteroids
2. Disease-Modifying Therapy
   - **IM/SC**
     - Interferon Beta (1a or 1b)
     - glatiramir acetate
     - daclizumab
   - **Oral**: fingolimod (Gilenya); dimethyl fumarate (Tecfidera); teriflunomiade (Aubagio); siponimod (Mayzent)
   - **Infusion**: natalizumab (Tysabri); alemtuzumab (Lemtrada); ocrelizumab (Ocrevus)
3. Neurological Symptom Management

Management: Relapsing Course

Acute Inflammation

- **Goal**: Reduce severity and duration of inflammation
- **Indication**: Objective neurological impairment
- **Medication**: Glucocorticoids
  - methylprednisolone 500-1000mg IV daily for 3-7 days
  - prednisone 1250mg by mouth daily for 3-7 days
  - dexamethasone 80mg compounded capsule by mouth twice daily for 3 days

  Note: prednisone taper is optional

- **Adjuvant Treatment**
  - Indication: neurological symptoms refractory to glucocorticoids
  - Plasma Exchange every other day for seven total treatments

Management: Relapsing Course

<u>Disease Modifying Therapies (DMT)</u>

- **Goal**: Reduce risk of acute inflammation, disability progression, MRI lesion load
- **Mechanisms of Action:** Immunomodulation
- **Principles to Medication Selection**
  - Single Agent
  - Provider Knowledge of DMTs; Refer when indicated
    - Efficacy: Based on Studies of Adult Populations; Few head to head studies; Few placebo-controlled studies
    - Adverse Effects: Common, Serious, Short-Term, Long-Term
  - Patient Factors
    - Knowledge of DMTs, Adherence, Cost, Route of Delivery
    - Autonomy & Decision-Making

<u>Note</u>: DMT agents to be presented in order according to route of administration

interferon beta-1a

Avonex

- IM: 30mcg weekly
    - No Titration Necessary

Plegridy [pegylated]

- SC: Initial: 63 mcg on day 1; 94 mcg on day 15. Maintenance: 125 mcg every 14 days beginning on day 29.

Rebif

- SC: Initial: 8.8 mcg (20 % of final dose) 3 times/week for 2 weeks <u>then</u> 22 mcg (50% of final dose) 3 times/week for 2 weeks <u>then</u> 44 mcg 3 times/week

interferon beta-1b

Betaseron

- SC: Start 0.0625 mg every other day; gradually increase dose by 0.0625 every 2 weeks to target of 0.25 mg

Extavia

- SC: Start 0.0625 mg every other day; gradually increase dose by 0.0625 every 2 weeks t o target of 0.25 mg

Interferon Beta
General Notes

- **Adverse Effects**
  - Injection site reactions, flu-like symptoms, elevated aminotransferase level, leukopenia, anemia
  - Some variance among different medications
- **Neutralizing Antibodies**
  - Variable among medications and are generally associated with reduced medication efficacy
- **Extension Studies**
  - Several available for review
- **Pregnancy**
  - Category C; discontinue prior to and during pregnancy

glatiramer acetate (Copaxone)

- **SC:** 20 mg once daily or 40 mg 3 times per week administered at least 48 hours apart
    - No Titration Necessary

- **Adverse Effects**
    - local injection site reactions and transient systemic post-injection reactions such as chest pain, flushing, dyspnea, palpitations, and/or anxiety.
- **Neutralizing Antibodies**
    - Demonstrated in clinical studies; clinical significance unknown
- **Extension Studies**
    - Several available for review
- **Pregnancy**
    - Category B; discontinue prior to and during pregnancy

daclizumab (Zinbryta)

- **Withdrawn from Market – March 2018**

fingolimod (Gilenya)

- **Oral**: 0.5mg daily

- **Adverse Effects**
  - **Common**: headache, influenza, diarrhea, back pain, elevated liver enzymes, mild hypetension, and cough
  - **Serious**: bradycardia and atrioventricular conduction block at the time of fingolimod initiation, macular edema, nonfatal herpesvirus infections, and skin cancer.
- **Pre-Evaluation**
  - CBC, EKG, PFTs, Zoster Antibody, Neuroophthalmological Exam
- **First-Dose Monitoring**
  - baseline pulse and blood pressure should be measured and the patient observed for six hours after the first dose for signs of bradycardia or atrioventricular block
- **Extension Studies** – In Progress
- **Pregnancy**
  - Class C; should be stopped two months prior to conception

teriflunomide (Aubagio)

- **Oral**: 7mg or 14mg daily

- **Adverse Effects**
  - headache, alopecia, diarrhea, nausea, lymphocytopenia, influenza, transient renal failure, decreased platelet count
- **Pre-Evaluation**
  - TB; Pregnancy
- **Monitoring**
  - CBC within 6 months of initiation and periodically thereafter based on signs/symptoms of infection; serum creatinine; serum transaminase and bilirubin within 6 months of initiation of therapy and monthly during the initial 6 months of treatment
- **Pregnancy**
  - teriflunomide may cause major birth defects if used in pregnant women. Teriflunomide is contraindicated in pregnant women or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during therapy or prior to completing the accelerated elimination treatment protocol
  - Note: teriflunomide is also found in semen. Males and their female partners should use reliable contraception during therapy. Males taking teriflunomide who wish to father a child should consider discontinuing therapy and using the accelerated elimination procedure to decrease the potential risk of fetal exposure.

dimethyl fumarate (Tecfidera)

- **Oral**: Initial: 120 mg twice daily for 7 days; then increase to the maintenance dose: 240 mg twice daily

- **Adverse Effects**
  - **Common**: flushing, abdominal pain, diarrhea, nausea, infection
- **Pre-Evaluation**
  - CBC with lymphocyte count
- **Pregnancy**
  - Class C; should be stopped two months prior to conception

natalizumab (Tysabri)

- **IV Infusion**: 300mg Every Four Weeks

- **Adverse Effects**
  - **Common**: fatigue, allergic reactions, anxiety, pharyngitis, sinus congestion, and peripheral edema
  - **Serious**: PML; hepatic dysfunction, melanoma in patients with with atypical moles, ocular nevi, or a family history of melanoma
- **Pre-Evaluation and Follow-Up**
  - MRI before First Dose; Follow-up at 3 and 6 months, then every 6 months
- **Neutralizing Antibody**
  - Associated with reduced medication efficacy
- **Prescriber and Pharmacy Risk Management Program (TOUCH)**
  - Monitor for follow-up with checklist
- **PML Stratification**
  - Serum JC Virus Testing
- **Pregnancy**
  - Category C; discontinue prior to and during pregnancy

alemtuzumab (Lemtrada)

- **IV Infusion**: 12 mg daily for 5 consecutive days (total 60 mg), followed 12 months later by 12 mg daily for 3 consecutive days (total 36 mg); total duration of therapy: 24 months
    - **Note:** Premedicate with prednisone; Administer antiviral
- **Adverse Effects**
    - **Common**: headache, rash, lymphocytopenia, antibody development, infusion reaction, nasopharyngitis, fever
    - **Serious**: immune thrombocytopenia, anti-glomerular basement membrane disease, malignancies (thyroid, melanoma, lymphoproliferative)
- **Monitoring**
    - Monitor complete blood counts with differential, serum creatinine levels, and urinalysis with urine cell counts at periodic intervals for 48 months after the last dose of alemtuzumab; annual skin exams
- **Neutralizing Antibody**
    - Not associated with reduced medication efficacy
- **Prescriber and Pharmacy Risk Management Program (REMS)**
- **Pregnancy**
    - Category C; discontinue prior to and during pregnancy

ocrelizumab (Ocrevus)

- **Subcutaneous Injection**: IV: 300 mg on day 1, followed by 300 mg 2 weeks later; subsequent doses of 600 mg are administered once every 6 months
  - Pre-medicate to prevent infusion reaction (34-40%): methylprednisolone (100 mg IV) 30 minutes prior to each infusion, and an antihistamine (eg, diphenhydramine) 30 to 60 minutes prior each infusion; may also consider premedication with acetaminophen.
- **Adverse Effects**
  - **Common (>10%)**: skin infection; decreased neutrophils; upper respiratory inection
  - **Serious**: breast neoplasm (<1%)
- **Monitoring**
  - Prior to initiation: Hepatitis B; Hepatitis C; HIV; Tuberculosis;
  - Infusion reaction
  - Evaluate immunization status prior to treatment.
- **Pregnancy**
  - None assigned; discontinue prior to and during pregnancy

Management: Progressive Course

- Acute Inflammation as part of Relapsing Progressive Course
  - Corticosteroids: shorten course of demyelination
- Disease-Modifying Therapy
  - ocrelizumab (Ocrevus)
  - mitoxantrone (Novantrone) 12mg/m^2 IV every 3 months
    - approved for progressive relapsing and secondary progressive multiple sclerosis
    - use is limited by potential risks such as cardiotoxicity and leukemia
    - Maximum lifetime cumulative dose: 140mg/m^2
- Neurological Symptom Management

2 New DMTs – April 2019

- siponimod (Mayzent)
  - Relapsing Remitting: reduced relapse rate, new T2 lesions, disability progression
  - Secondary Progressive: reduced disability progression
  - Clinically isolated syndrome
  - Oral tablet
- Cladribine (Mavenclad)
  - Relapsing Remitting: reduced relapse rate, new T2 lesions, disability progression
  - Active Secondary Progressive
  - Oral; two treatment courses

Management

Neurological Symptom Management

- **Spasticity**: baclofen, tizanidine, cyclobenaprine; botulinum toxin; intrathecal baclofen; physical therapy
- **Urinary Urgency, Incontinence**: oxybutynin, tolterodine, hyoscyamine; physical therapy for pelvic floor exercises
- **Urinary Retention**: intermittent catheterization
- **Fatigue**: modafinil, amantadine, stimulants; energy conservation
- **Trigeminal Neuralgia**: carbamazepine, gabapentin
- **Depression**: SSRIs, SSNRIs; psychotherapy
- **Sexual Dysfunction**: sildenafil, vardenafil, tadalafil; psychotherapy
- **Gait**: physical therapy; assistive devices; dalfampridine
- **Cognitive Impairment**: neuropsychological evaluation, guidance
- **Seizure**: consider anti-epileptic therapy

Management

Other Considerations

- Mental Health
- Physical Disability
- Medication Cost
- Medication Adherence
- Substance Use
- Complementary and Alternative Therapies
- Social Support System
- Cultural Sensitivity

Team-Based Approach to Care

- Primary Care Providers
- Medical Specialists
- Nursing
- Physical Therapy
- Occupational Therapy
- Speech Therapy
- Mental Health
- Pharmacists
- MS Educators
- Vocational Rehabilitation
- Financial Care Counselor

Prognosis

- The relapsing course is generally associated with a better prognosis than a progressive course
- Some data suggests that all patients with relapsing courses will eventually have a progressive course
- African Americans are more likely to develop MS at a later age and have ambulatory disability
- High lesion load on MRI early in the disease is associated with greater long-term disability
- Psychosocial stress has been associated with an increased risk of relapse

Natural History of Untreated MS

- 30%–50% of patients worsen by 1.0 EDSS unit within 2–3 years
- Up to 44% of patients need an assistive device for walking within 5 years
- Relapsing MS leads to progressive MS after 10 years in 50% of cases
- 43%–65% of patients with MS experience cognitive impairment, affecting employment, social life, and daily functioning

EDSS = Extended Disability Status Scale.

Weinshenker et al. *Brain.* 1989;112:133; Munschauer and Stuart. *Clin Ther.* 1997;19:868; Rao et al. *Neurology*. 1991;41:685.

Optic Neuritis

- General
  - DDx: SLE, sarcoidosis, Sjögren's, neoplasm, infectious, ischemic, compressive, toxic, trauma
- Pathogenesis
  - Inflammatory demyelination of the optic nerve
- Clinical Features
  - painful, monocular visual loss evolves over several hours to a few days
  - Papillitis in 1/3 of cases
  - Long-term: relative afferent pupillary defect, color desaturation, optic atrophy
- Diagnostic Studies
  - Ophthalmologic examination
  - MRI brain w/wo contrast to evaluate for MS
- Management
  - High dose steroids
- Prognosis
  - MS presenting symptom 15-20%; Occurs in up to 50% of cases
  - Visual improvement begins within weeks, often complete

Transverse Myelitis

- General
  - Idiopathic; often post-infectious
  - Secondary to multiple sclerosis, neuromyelitis optica, and acute disseminated encephalomyelitis
- Pathogenesis
  - Inflammatory demyelination of the spinal cord
- Clinical Features
  - Rapid onset
  - Weakness, sensory alterations, and bowel/bladder dysfunction
- Diagnostic Studies
  - MRI brain and spine to rule out compressive myelopathy, secondary causes
  - CSF for markers of secondary causes
- Management
  - High dose steroids
- Prognosis
  - MS presenting symptom 5-10%
  - Usually partial recovery, idiopathic not usually recurrent

Neuromyelitis Optica

- General
  - AKA Devic Disease
  - Distinct from MS
  - Female 10x risk
  - More common than MS in Africa, East Asia, Latin American
- Pathogenesis
  - Immune-mediated demyelination of the CNS
  - Humoral > Cellular
- Clinical Features
  - Transverse Myelitis
  - Optic neuritis (bilateral > unilateral OR rapidly sequential)
- Diagnostic Studies
  - International diagnostic criteria
  - MRI Brain usually normal
  - MRI Spine demonstrates evidence of demyelination (3_ segmens)
  - CSF without Oligoclonal Bands, and a positive serum aquaporin-4-antibody test (NMO-Ab).
- Management
  - Disease-Modifying Therapy: azathioprine, rituximab, or mycophenolate
  - Acute Relapse: high dose steroids
- Prognosis: more severe disability; higher mortality rate

Acute Disseminated Encephalomyelitis (ADEM)

- General
  - Distinct from MS
  - Typically follows immunization or infection
  - May be more frequent in children
- Pathogenesis
  - Immune-mediated demyelination of the CNS
  - Usually monophasic
- Clinical Features
  - Multi-focal neurologic symptoms plus nonspecific symptoms such as headache, malaise, and altered mental status
  - Variant: Acute hemorrhagic encephalomyelitis
- Diagnostic Studies
  - MRI Brain demonstrates multiple, asymmetric, poorly marginated lesions with variable enhancement
  - CSF: elevated protein, lymphocytes +/- OCBs, elevated IgG
  - No biomarker
- Management
  - High dose steroids
  - Refractory: IVIG, Plasmapheresis
- Prognosis
  - Relapses rare; may progress to MS
  - more severe disability; higher mortality rate

Conclusions

- Have a high index of suspicion for MS
- Be confident in the diagnosis of multiple sclerosis
- Comprehensive management encompasses
  - Acute Inflammation
  - Disease Modifying Therapy
  - Management of Co-Morbid Neurological Symptoms
- Disease Modifying Therapy should be managed by providers familiar with the evidence-based efficacy and safety
- Management of multiple sclerosis and its related symptoms may involve many health care providers
- While no cure exists, this lifelong disease is manageable
- Stay tuned for new research and treatment options!

Case

- **Hx**: A 22yo female presents to your outpatient clinic with complaints left vision loss associated with mild eye pain that start about 4 hours ago. Prior neurologic symptoms include 12 days of right vision impairment 2 years ago and 14 days of right arm incoordination 5 years ago.
- **PE**: Left visual acuity 20/70 with correction. Right visual acuity 20/25 with correction. No field cut. Fundoscopic exam reveals swelling of the right optic disk, blurring of disk margins. Otherwise non-focal screening neurologic exam.

What is the most likely diagnosis?

A. Multiple sclerosis, primary progressive type

B. Multiple sclerosis, relapsing Type

C. Acute ischemic stroke

D. Acute Disseminated Encephalomyelitis

What therapeutic intervention is indicated to shorten the duration of these symptoms?

A. Disease-modifying therapy

B. High dose corticosteroids

C. Intravenous immunoglobulin

D. Low dose corticosteroids

What is the next most appropriate step in evaluation of this patient?

A. CT head non-contrast

B. CT head with contrast

C. MRI Brain non-contrast

D. MRI Brain with contrast

In clinical research studies, primary and secondary outcomes for the disease-modifying therapies include all of the following EXCEPT:

a) Reduction in risk of clinical relapse
b) Reduction in risk of new lesions on MRI
c) Reduction in the number of established lesions on MRI
d) Reduction in disability progression over time

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- Text: CMDT
  - Required Reading: Chapter 24
- Text: Cecil's
  - Recommended Reading: Chapter 29
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Discussion