Multiple Sclerosis (MS)

ANGELO ANTONINI

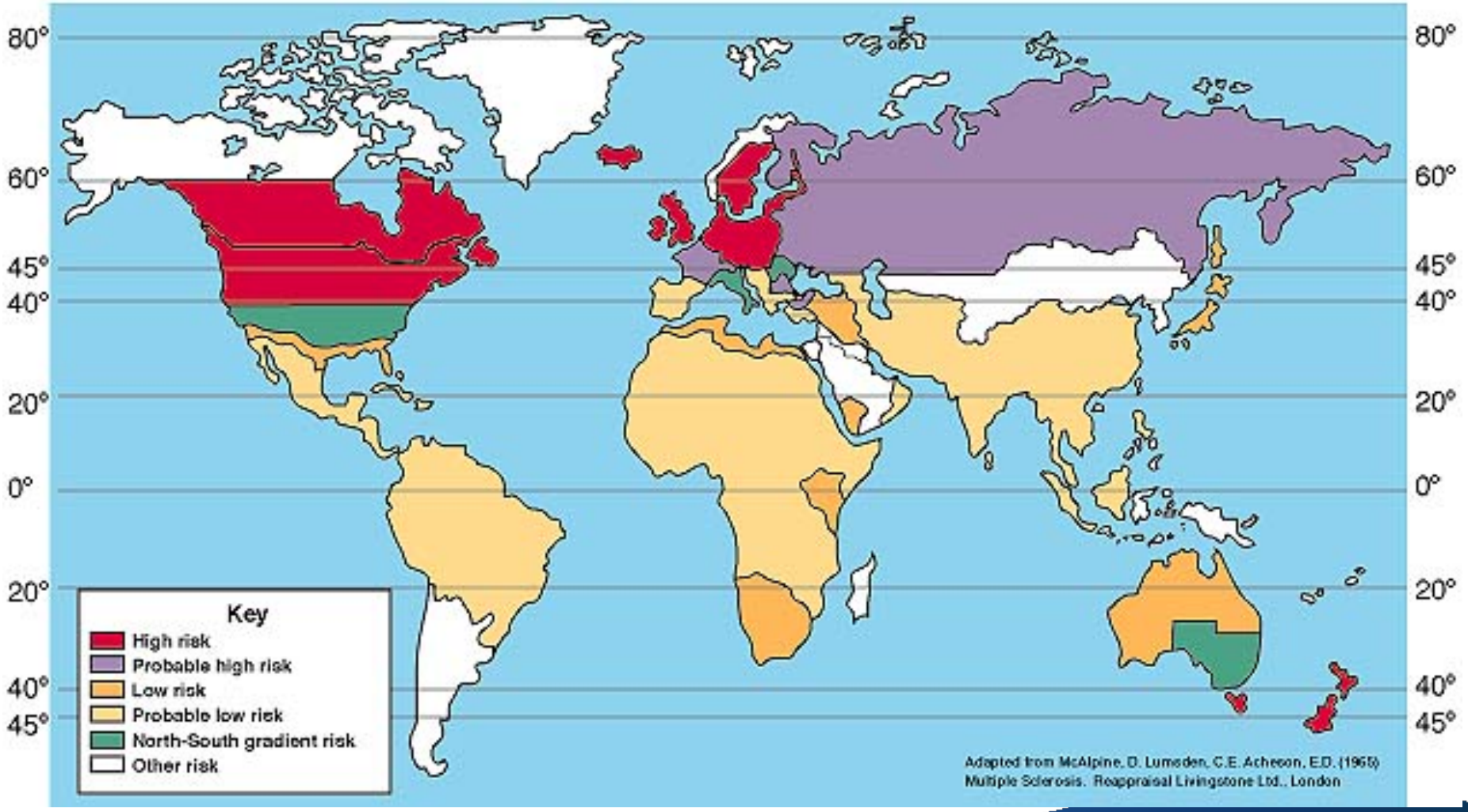
Introduction to Multiple Sclerosis (MS)

- Chronic autoimmune disease
- Progressive disease
- Involves Immune System & Neurological System
- Multifocal areas of demyelination
- Disrupts ability of the nerve to conduct electrical impulses
- Leads to symptoms

Epidemiology of MS

- Age onset 20 – 50 years old
- Women are 2 times more likely to develop MS
- 500,000 cases in US
- Over 2.5 million people around the world
- More prevalent whites of northern European ancestry
- 110/100.000 occurrence
- Vitamin D3
- Genetic Influences

World Distribution of Multiple Sclerosis

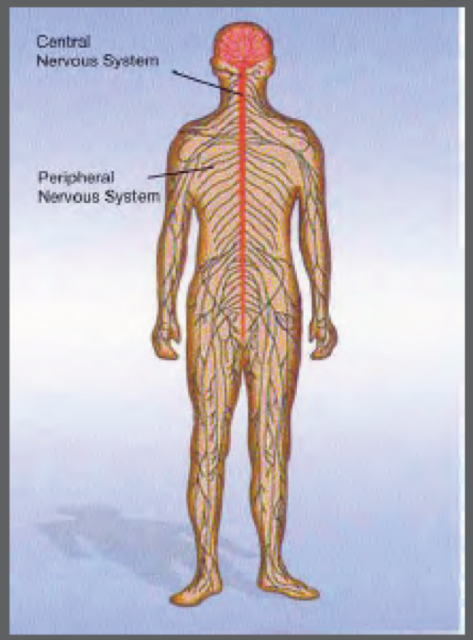


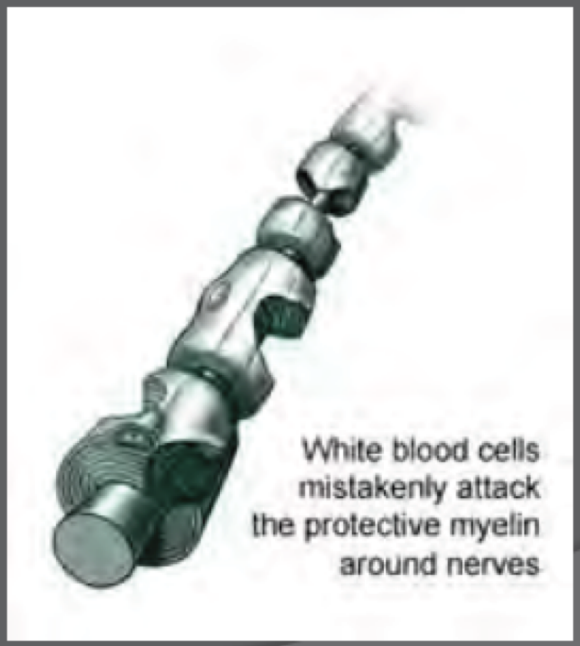
Topics

- What is MS
- Who gets MS
- Symptoms
- Types of MS
- Common Questions

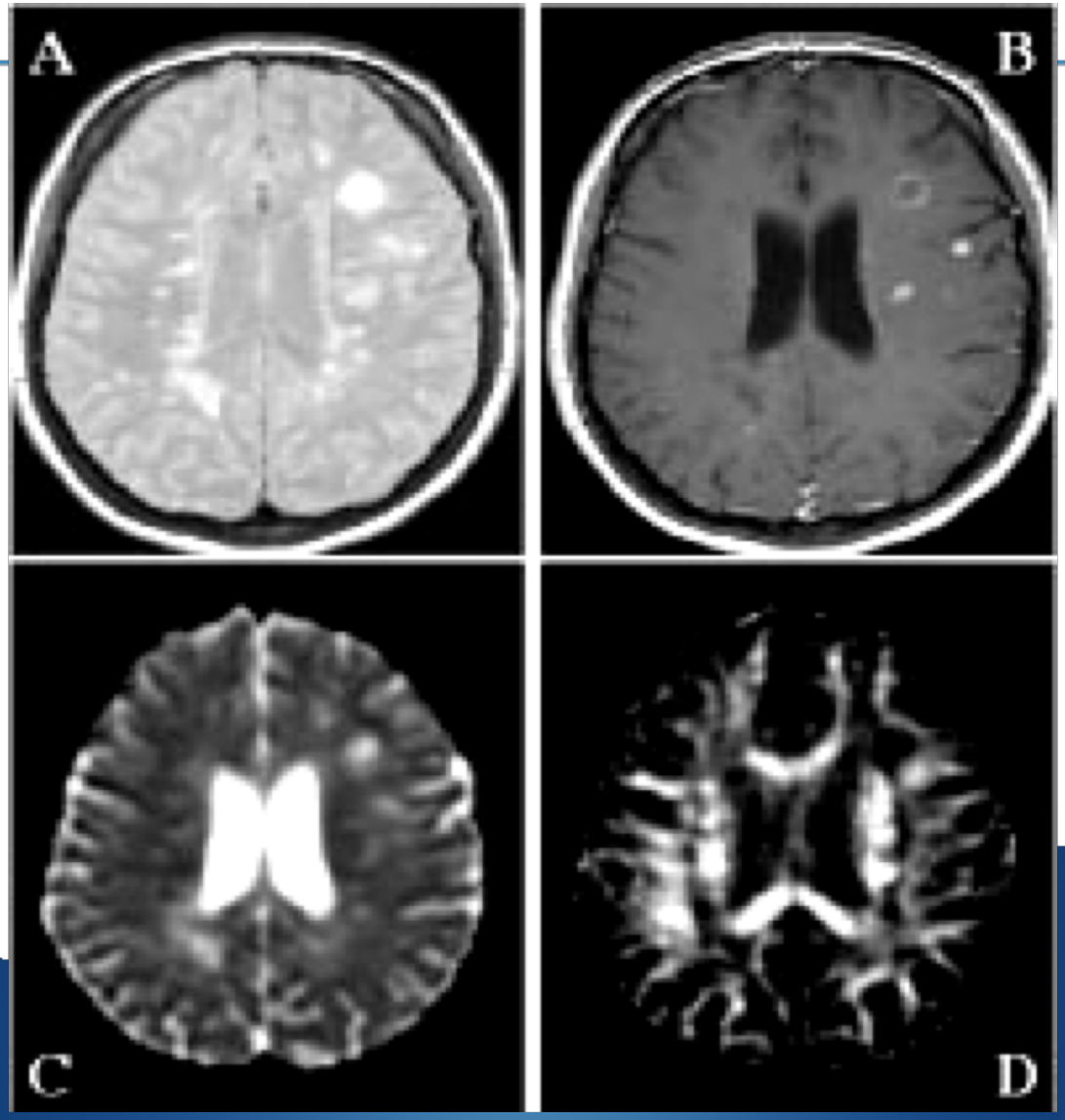
What is MS?

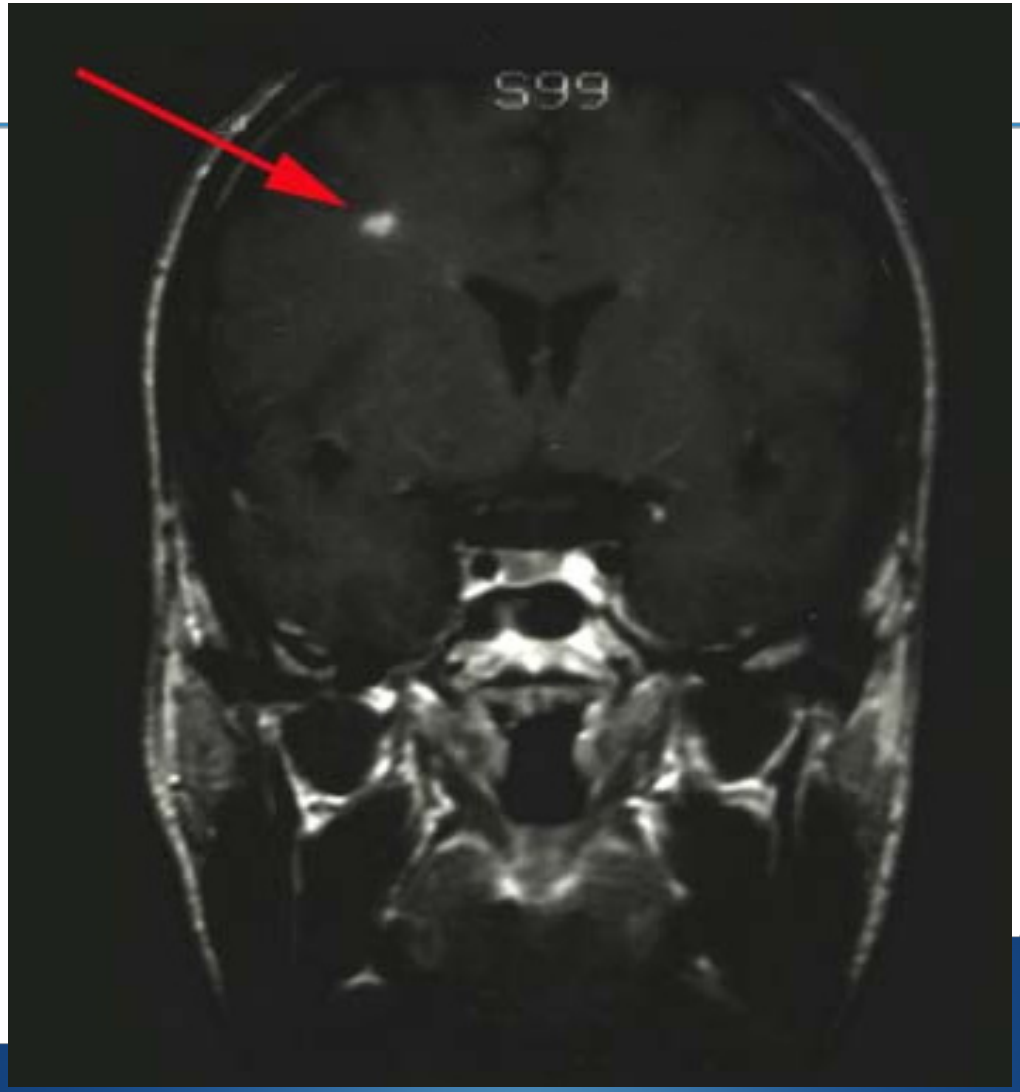
- Demylination of the Central Nervous System





MRI patterns

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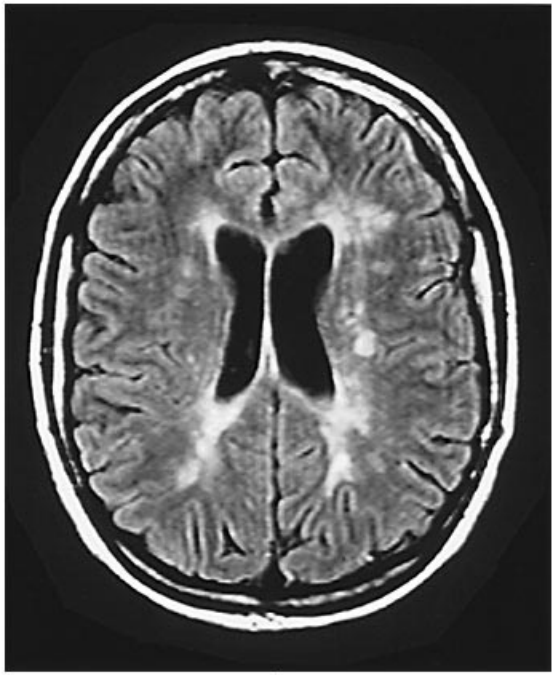

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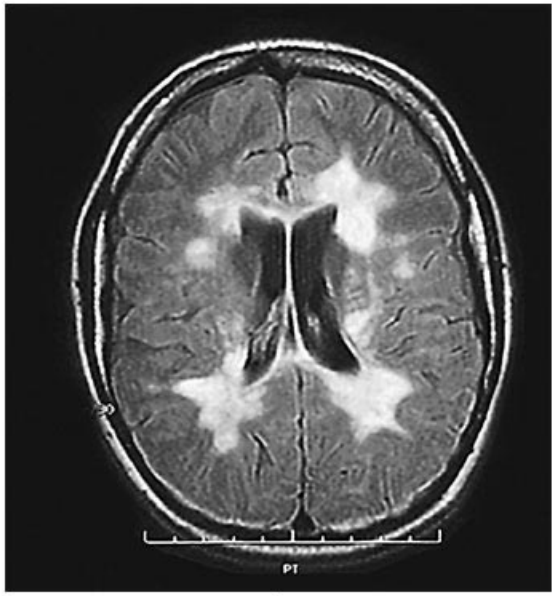

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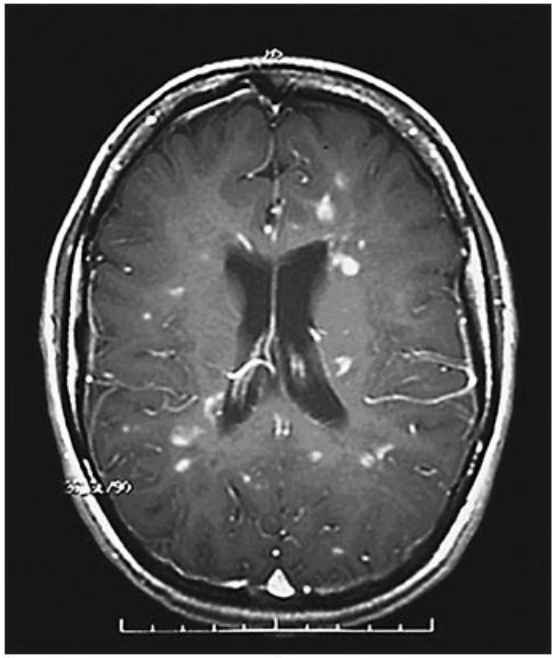

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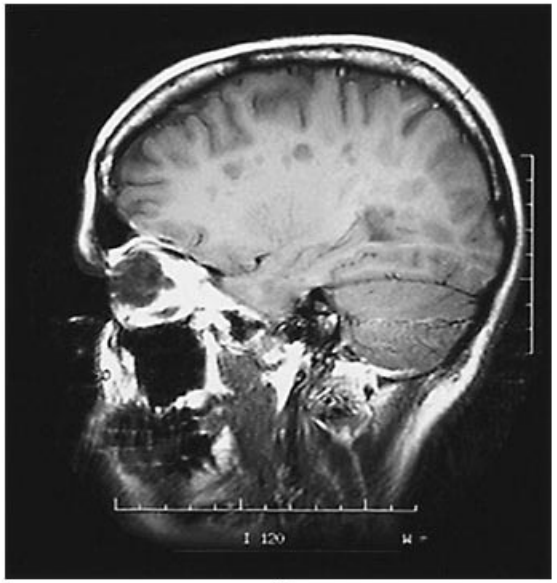

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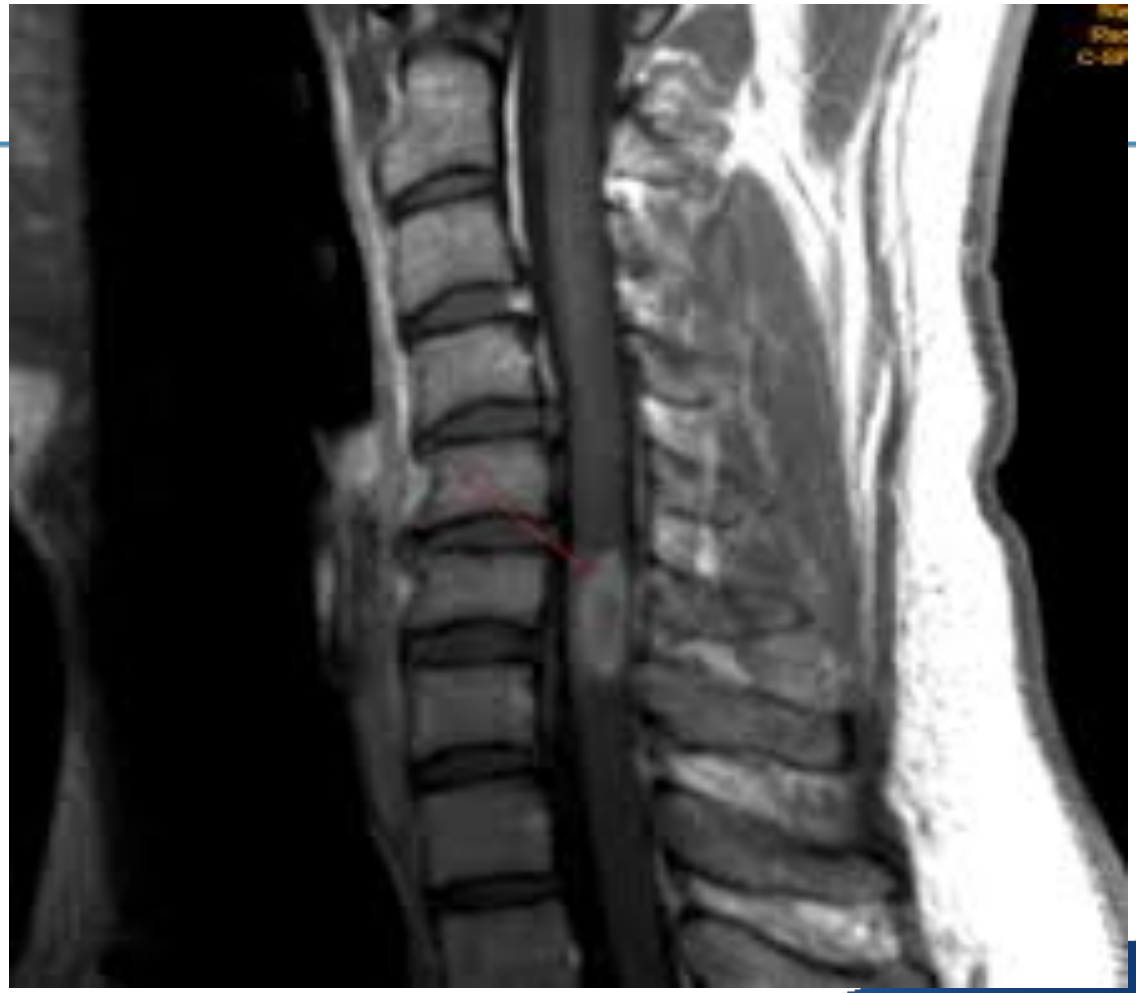
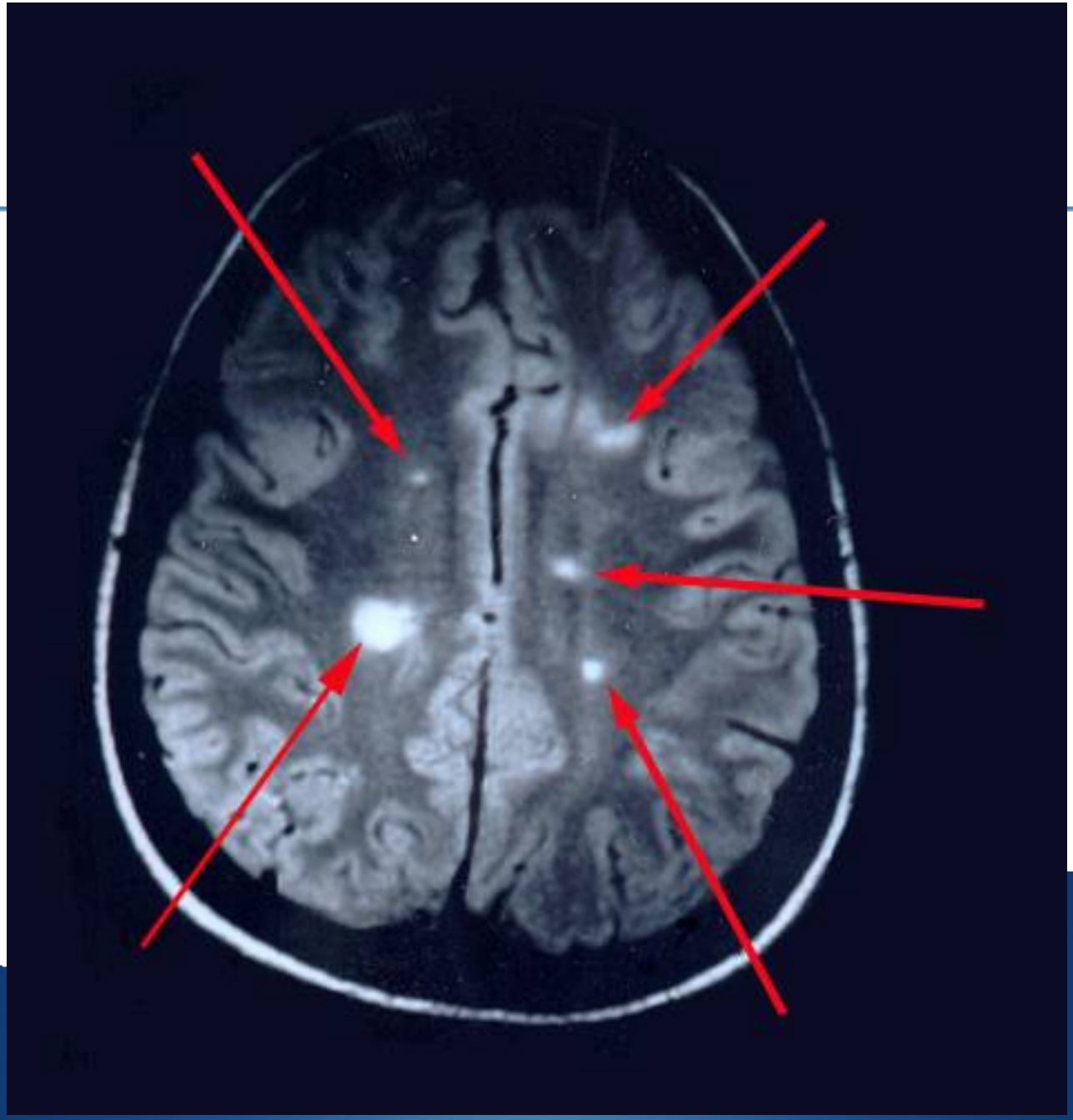
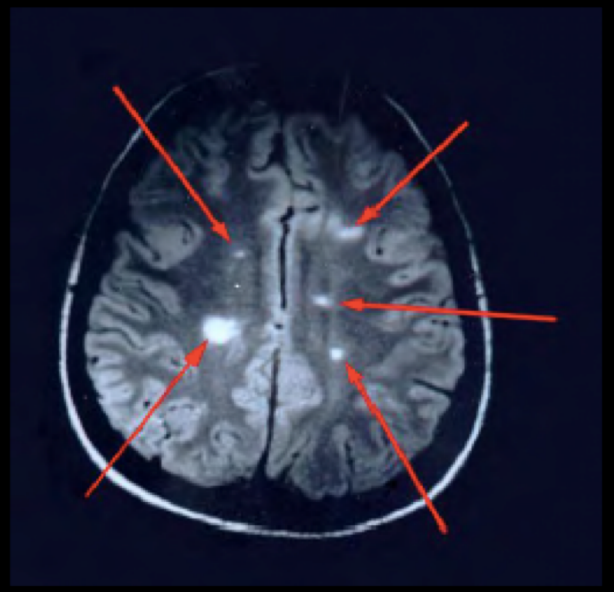
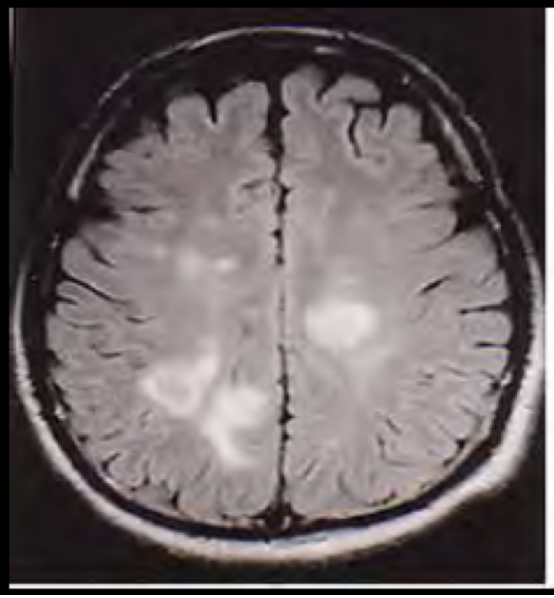
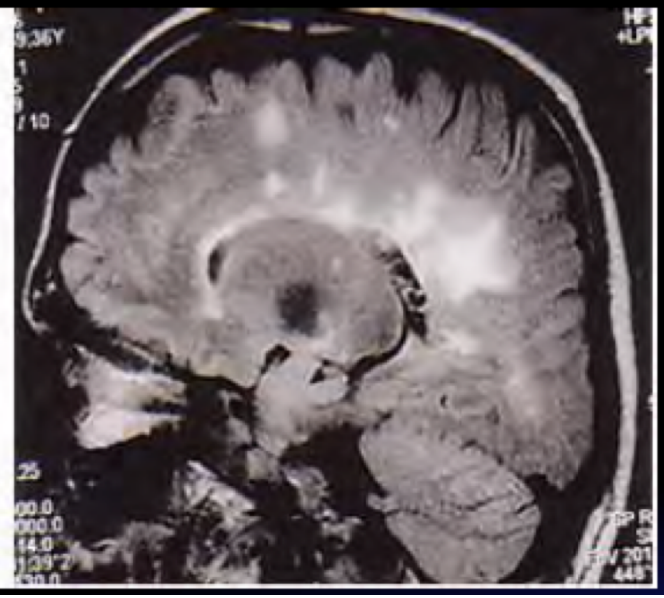
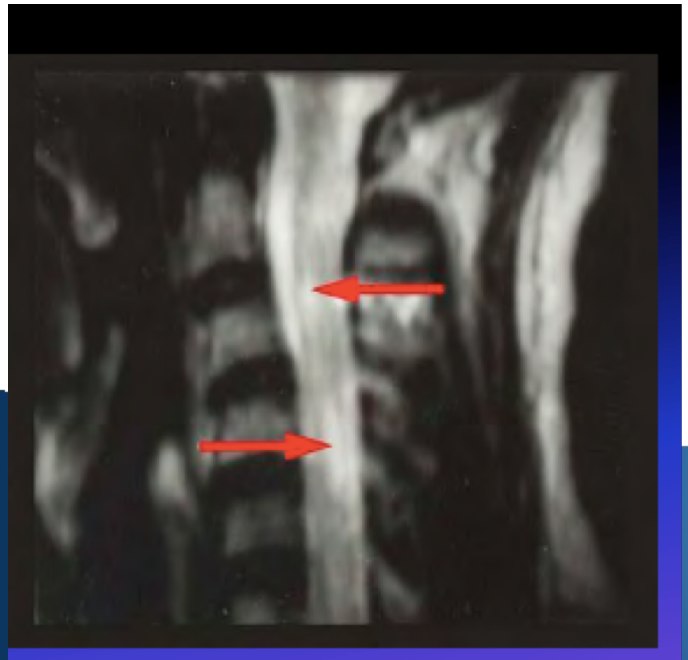




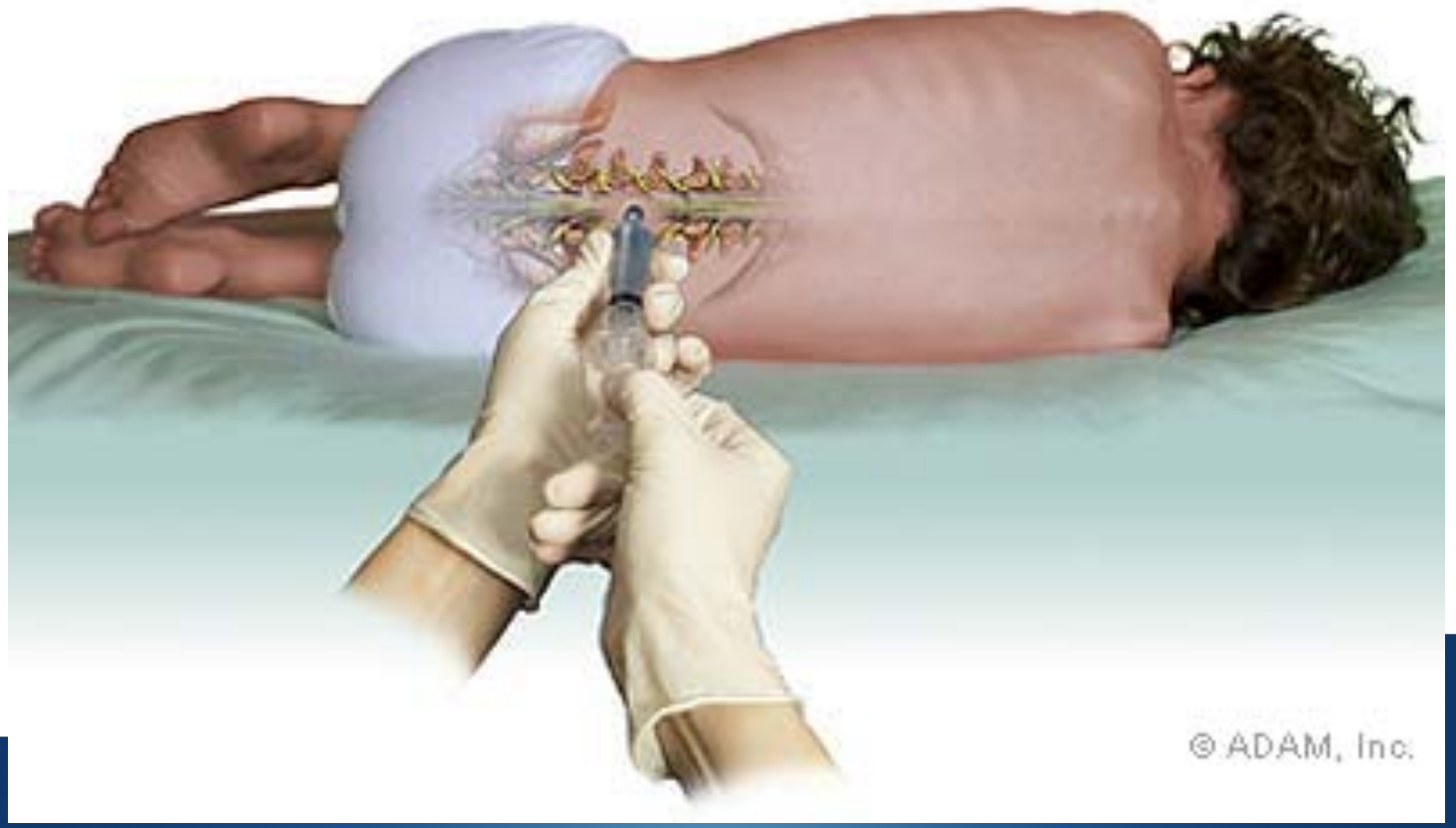




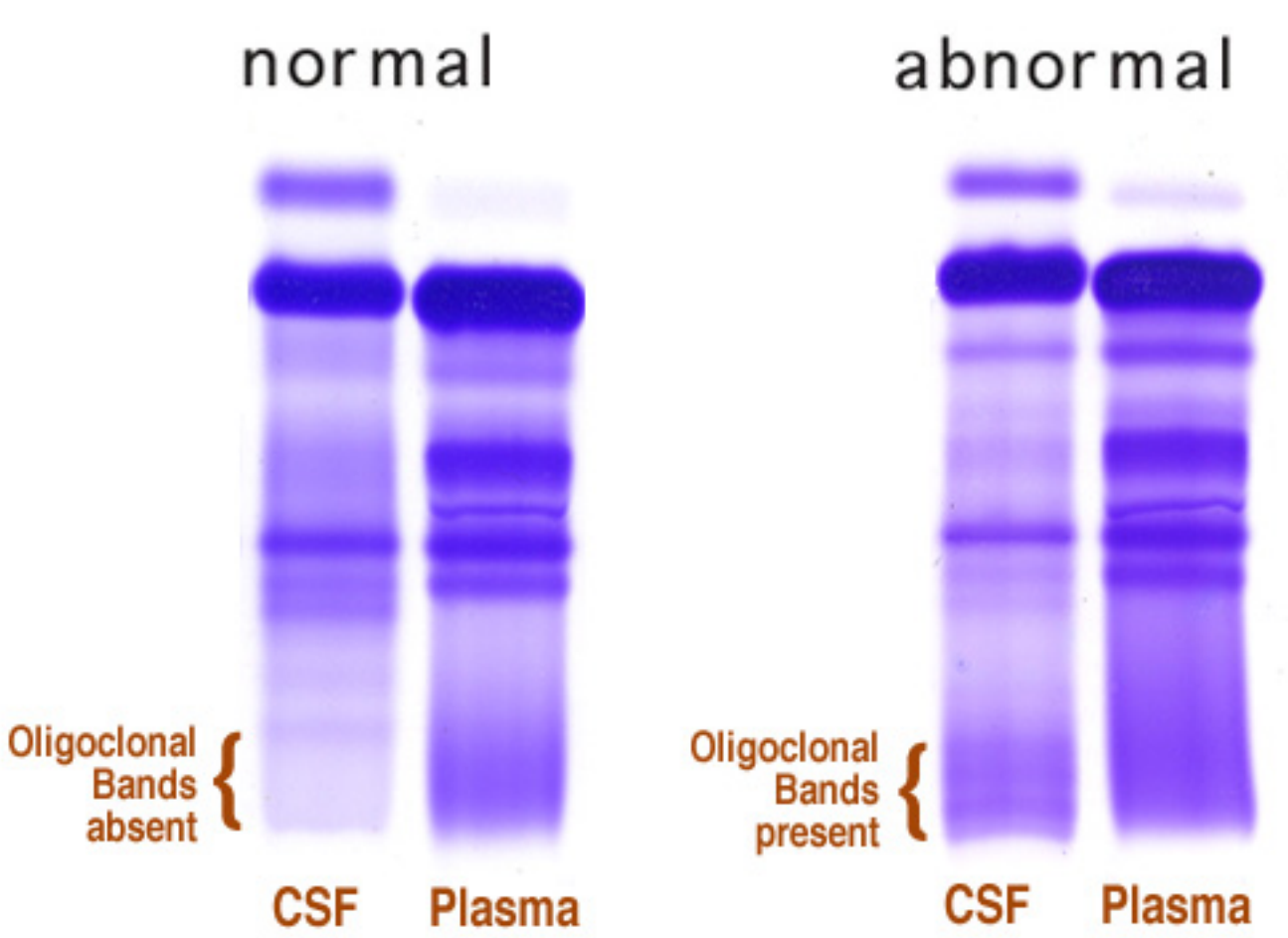


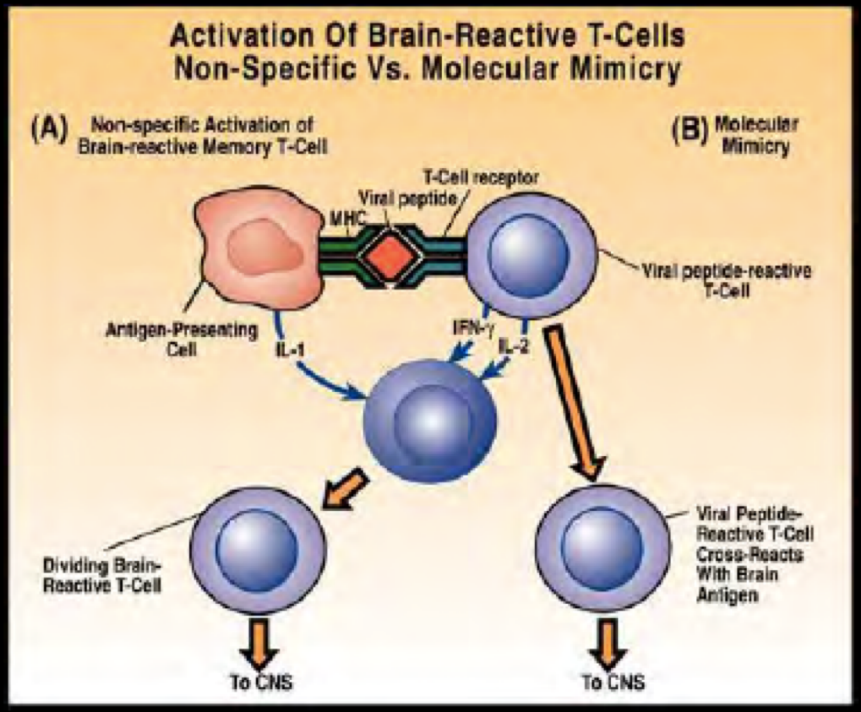


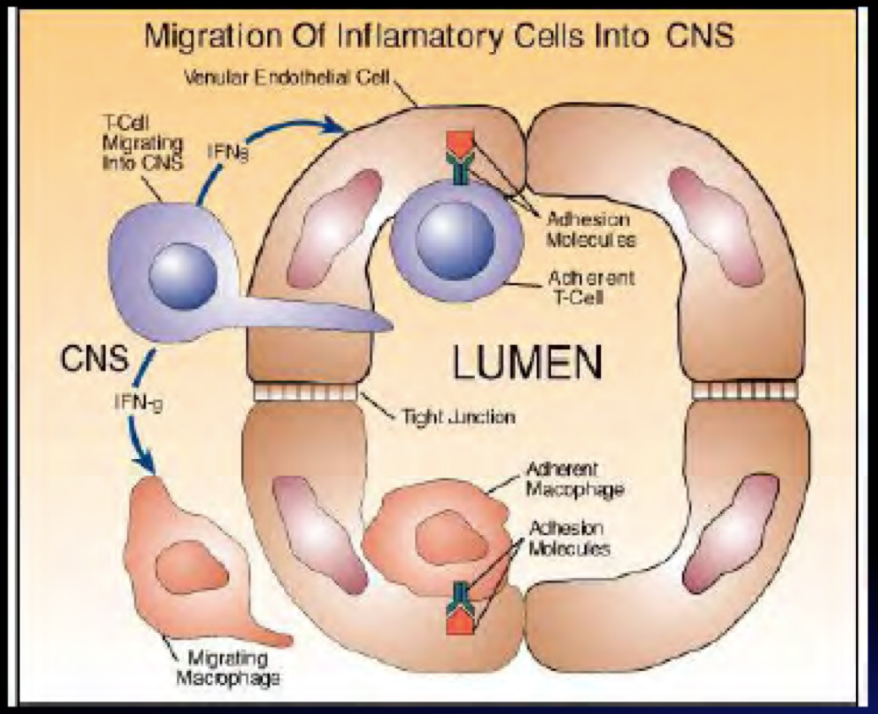
Cerebrospinal fluid drawn from between two vertebrae

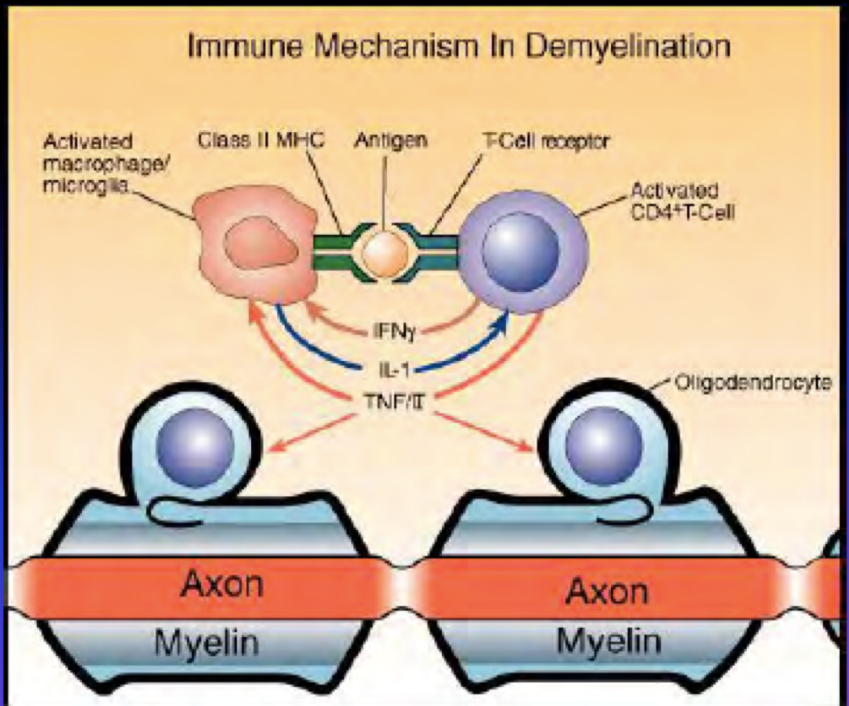


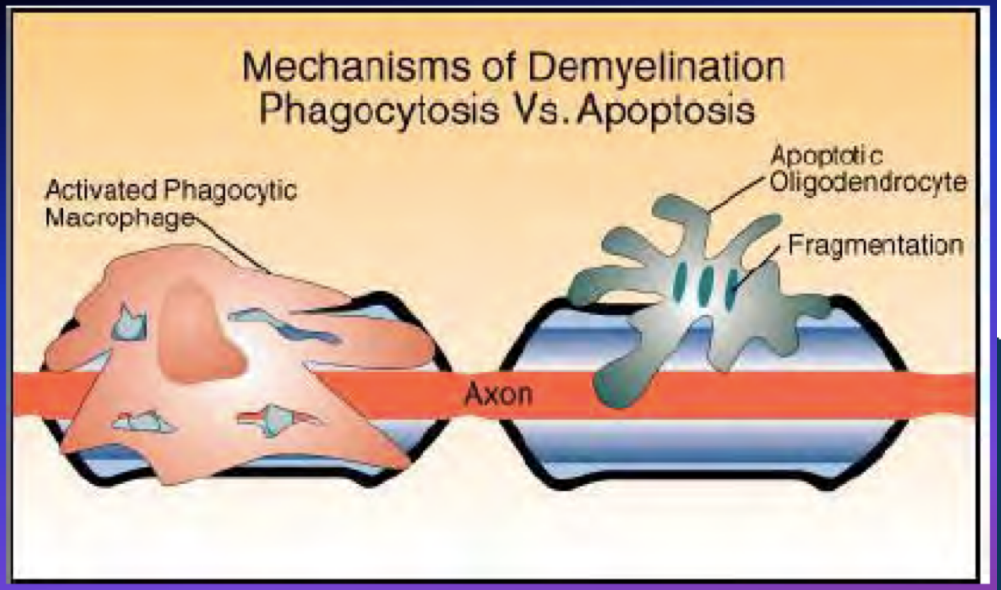
Oligoclonal Bands in CSF



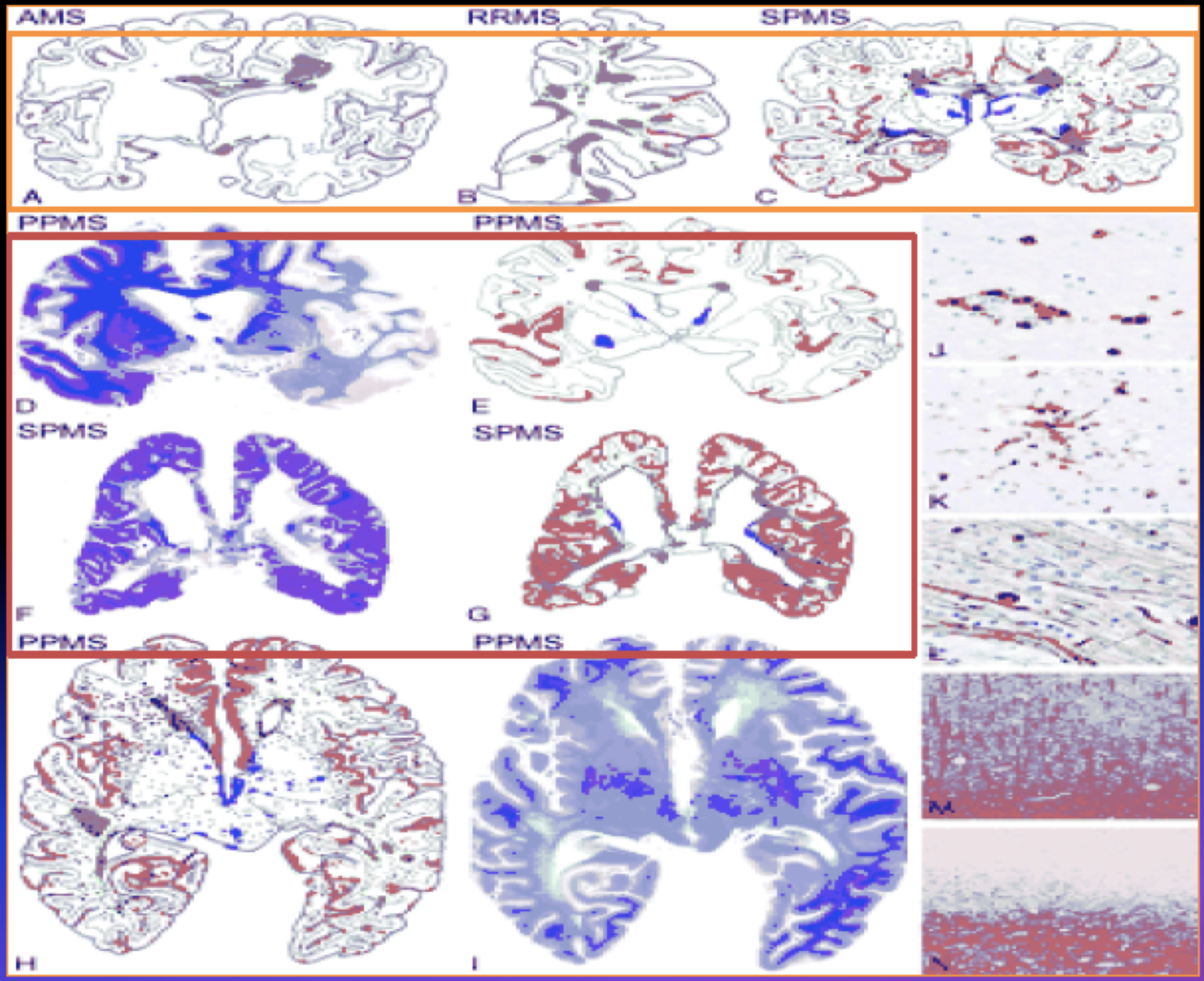

Activation Of Brain-Reactive T-Cells
Non-Specific Vs. Molecular Mimicry
(A) Non-specific Activation of Brain-reactive Memory T-Cell
(B) Molecular Mimicry
T-Cell receptor
Viral peptide
MHC
Viral peptide-reactive T-Cell
Antigen-Presenting Cell
IL-1
IFN-γ
IL-2
Dividing Brain-Reactive T-Cell
Viral Peptide-Reactive T-Cell Cross-Reacts With Brain Antigen
To CNS
To CNS


Migration Of Inflamatory Cells Into CNS
Venular Endothelial Cell
T-Cell Migrating Into CNS
IFNs
Adhesion Molecules
Adherent T-Cell
CNS
LUMEN
IFN-g
Tight Junction
Adherent Macrophage
Adhesion Molecules
Migrating Macrophage


Immune Mechanism In Demyelination
Activated macrophage/ microglia
Class II MHC
Antigen
T-Cell receptor
Activated CD4+T-Cell
IFNγ
IL-1
TNF/lt
Oligodendrocyte
Axon
Myelin
Axon
Myelin


Mechanisms of Demyelination
Phagocytosis Vs. Apoptosis
Activated Phagocytic Macrophage
Apoptotic Oligodendrocyte
Fragmentation
Axon

Pathology in MS



Symptoms of MS

- Vision problems
- Numbness
- Difficulty walking
- Fatigue
- Depression
- Emotional changes
- Vertigo & dizziness
- Sexual dysfunction
- Coordination problems
- Balance problems
- Pain
- Changes in cognitive function
- Bowel/bladder dysfunction
- Spasticity

FATIGUE IN MS

- Most common symptom of MS-MS Society estimates that 90% are affected
- Patients rate fatigue as overwhelming and having the biggest impact on their quality of life with 75% saying it is their most bothersome symptom and completely out of proportion to their activity level and can make even the simplest tasks impossible.

- DEFINITION: Extreme tiredness, typically resulting from mental or physical exertion or illness. Ask each of us to describe and we will define differently. Everyone experiences fatigue but persons with MS experience it profoundly.
- *You know you've got brain fog when ... I'm sorry, what were we talking about?*

FATIGUE IN MS

- Consortium of MS Centers and National MS Society defines as :a subjective loss of physical or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities.
- Three types: 1. Lassitude (overwhelming feeling of being tired) 2. Muscle fatigue (legs feel too heavy to move) 3. Mental fatigue (too tired to think or concentrate.

FATIGUE IN MS

- It occurs daily.
- It may be present in the morning, even after a good night's sleep. Sleep restores energy levels in the neurotypical person, not so in MS!!
- It worsens as the day progresses.
- Heat and humidity aggravate it.
- It comes on suddenly.
- It's more severe than normal fatigue and more likely to interfere with daily life and one's ability to cope and carry out their family/work responsibilities.
- Not only physical but mental fatigue-brain fog!
- Often not recognized or overlooked by health care professionals.

FATIGUE IN MS

- CAUSES:
- PRIMARY:
- 1. Damage to Central Nervous system causes the CNS to work harder.
- 2. May be related to decreased functioning or "hypometabolism".
- SECONDARY:
- 1. Other health conditions: thyroid disorders, diabetes, infections, heart disease etc.

FATIGUE IN MS

2. Side effects of medications: Interferons, medication for spasticity, pain, anxiety etc
3. Heat intolerance: saps energy
4. Depression: chicken and egg dilemma
5. Over exertion: must pace oneself. "Spoon Theory".

- *You know you've got chronic fatigue syndrome when you wake up in the morning to get ready for your nap.*

FATIGUE IN MS

What helps?

1. Get proper rest: Establish regular routines, avoid caffeine, alcohol, drinking before bedtime. Seek help for depression, anxiety, financial worries, bladder problems
2. Avoid heat: Get assistance for air conditioners, cooling vests. Swim, take cool showers.
3. Aerobic exercise

Symptoms

- Sensory

Impaired Vision

- Optic Neuritis

Muscle function

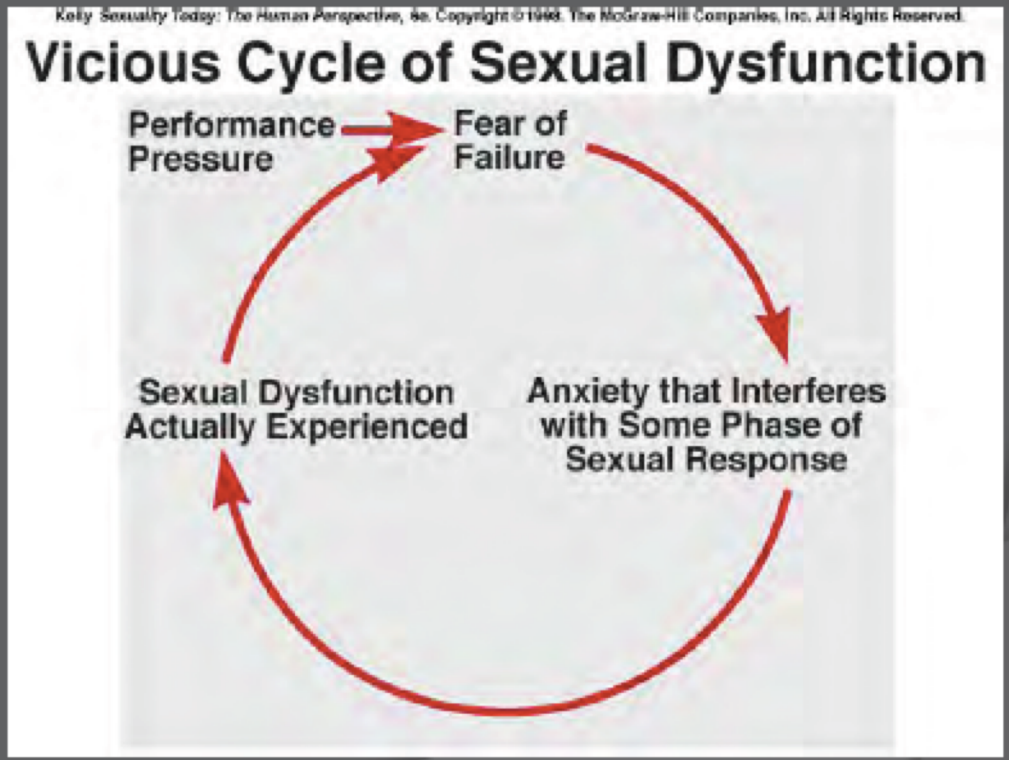
- Weakness
- Spasticity
- Foot Drop

Bowel and Bladder

- Urinary Urgency and Frequency
- Constipation

Sexual Disfunction

- Fatigue
- Decreased sensation
- Decreased Libido



Cognitive Function

- Short term Memory
- Multitasking
- Mood

Cognitive dysfunction in MS

- Discussed by Charcot 1877
- Difficult to study
  - population differences
  - clinical tools insensitive
  - neuropsychological tests expensive/unavailable
  - difficult to recognize by physicians/patients

My Early thoughts :

- 1 Occurs late in disease
- 2 Occurs after substantial disability
- 3 Not present in CIS

3 types of memory - 1

- Sensory memory - retention for less than 1/2 second; degraded quickly
- **Short-term memory**- allows recall for a period of several seconds to a minute ; typically approx. 4-5 items

  - dependent dorsolateral prefrontal cortex and parietal lobe. The hippocampus /limbic circuit is essential for learning new information

  -storage *short-term memory* have a strictly limited capacity and duration
- **Working memory**: temporary storage and manipulation of information required for complex tasks.

3 types of memory - 2

- long-term memory - stores large quantities of information for potentially unlimited duration
  - enhanced with repetition
- requires stable permanent neural connections widely throughout the brain.
- The hippocampus and limbic circuit is essential for consolidation from short-term to long-term memory

Cognitive dysfunction in MS

Epidemiology:

- MS clinics 53 – 65%
  - Community 43 – 48%
  - Increases over 10 yrs 26-56%

adapted from Amato MP et al J Neurol Sci 2006; 245(1-2):41-6

Arch Neurol 2001; 58(10):1602-6

- COGIMUS- community volunteers study ~35%
- MACFIMS- consecutive clinic attendees ~60%

- Little data on natural history over time but does not remit and may worsen at variable rate

Kujala et al 1997

Predictors of cognitive dysfunction

- Correlation :

  poor - with clinical indicators relapses or disability

  - good - with MRI burden of disease (83% of patients with > 30 cm2 lesion area were cognitively impaired
  - 22% if < 30 cm2 -Rao et al, 1989)

  - neuropathological substrate

- Studies tend to show impairment more severe with progressive disease ; but …..bias precludes conclusion on subtype relevance
- Signs of cognitive deterioration at onset of MS

MRI in Cognitive assessment

- Modest MRI correlation…….
  -lesion volume scores esp. left frontal lobe
- Stronger MRI correlation ……..
- global and regional cerebral atrophy :
  -third ventricle size
  - corpus callosum size
  -ventricular-brain ratios
  -neocortical grey volume loss (Amato et al Arch Neurol 2007;64(8):1157-61)

Cognitive Dysfunction: Domains Most Commonly Affected

(Rao et al, 1991)

- Short term memory
- Attention
- Concentration
- Verbal intelligence
- Visuospatial skills
- Information processing
- Less: language, long term memory

Cognitive domains affected in MS

- Slowed information processing (bradyphrenia)- most common deficit ; It may mirror EDDS status, but other deficits may not
- Impaired recent memory
  - "episodic " (visual and verbal) information that is seen, read, or heard
  - working
- Impaired retrieval
- Impaired visuospatial function

Multi-tasking is a problem

- Simple attention and verbal ability intact

Cognitive domain deficits in MS- Memory dysfunction *adapted from Amato MP et al J Neurol Sci 2006; 245(1-2):41-6*

Attention and concentration deficits

- "alternating attention" (shifting between two stimuli)
- "divided attention" (simultaneous attention to multiple stimuli)

Impaired executive functions such as concept formation, reasoning, problem-solving, planning and sequencing , abstraction

Risk factors for cognitive dysfunction:

adapted Benedict RHB, Zivadinov R Nat. Rev. Neurol. 2011 ;7 :332-42

- Early age of onset (data from pediatric neurology)
- Male sex
- Depression, fatigue, duration of disease poorly or not correlated (seen early or in CIS)
- Transition from RRMS to SPMS

Risk factors for cognitive dysfunction:

adapted Benedict RHB, Zivadinov R Nat. Rev. Neurol. 2011 ;7 :332-42

- Life style/behaviour
  - -Tobacco- Smoking is a MS susceptibility risk factor; associated with progression
  - -Cannabis- (Small studies +ve) -? ??
- Genetic factors – No association
  - - HLA-DR 15 (MS susceptibility risk factor)
  - -APOE4

Risk factors for cognitive dysfunction:

Julian L Neurol Clin 2011 ; 20: 507-25

- Depression/(anxiety)

  -independent risk factor(evidence from longitudinal studies)

  -affects attention & concentration, processing speed and impacts executive function in MS

  -both may occur for same neuropathological damage

  -cognitive impairment predicts poor response to antidepressants

Consequences of Cognitive impairment in functional domains

More likely to be :

- prone to psychiatric morbidity
- unemployed,
- socially withdrawn
- difficulty performing routine household tasks

Rao SM Neurology 1991;41(5):692–6.

- Affects several functional domains:

  social , occupational, educational , capacity for decision making (medical), driving, use of public transport, cooking

Chiaravalloti ND Lancet Neurol 2008;7(12):1139–51

Cognitive dysfunction in MS conclusions

- **Occurs in approx. 50% patients with consequence**
- **Cogitive domains most affected are *mental processing speed* and *episodic memory***
- **Specific Neuropsychological test are sensitive but not widely available to clinicians**
- **Risks factors include:**
  - **-males of low education or intelligence**
  - **-early onset of MS**
  - **-evidence of cerebral grey matter atrophy**
- **Evidence for effect of any medical therapy inconsistent**

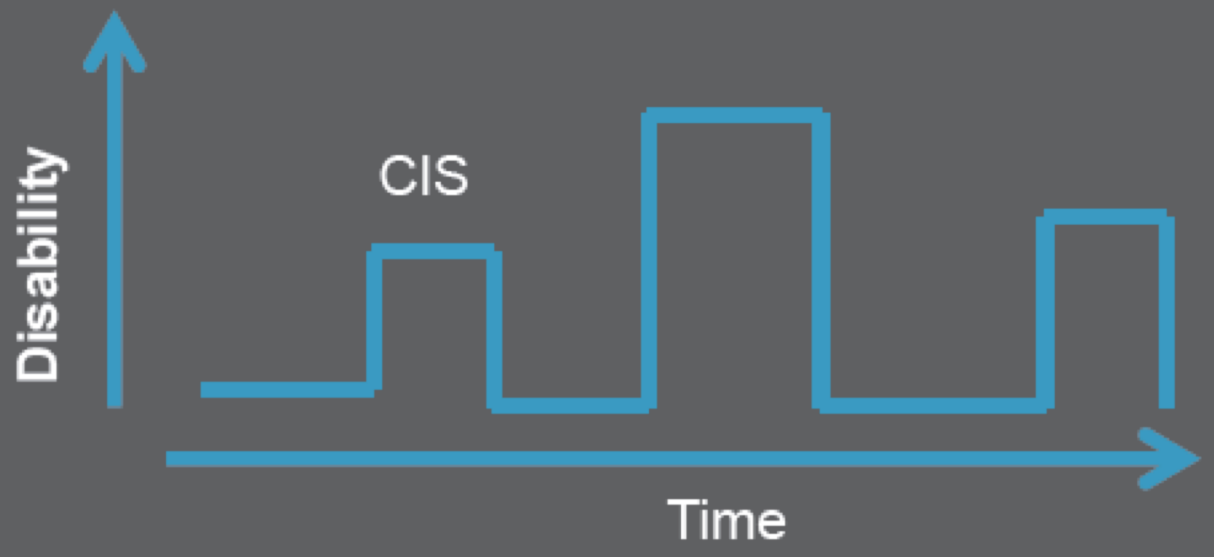
adapted Benedict RHB, Zivadinov R Nat. Rev. Neurol. 2011 ;7 :332-42

Types of MS

- Relapsing-remitting MS (RRMS)
  - Affects 85% of newly diagnosed
  - Attacks followed by partial or complete recovery
  - Symptoms may be inactive for months or years
- Secondary-progressive MS (SPMS)
  - Occasional relapses but symptoms remain constant, no remission
  - Progressive disability late in disease course

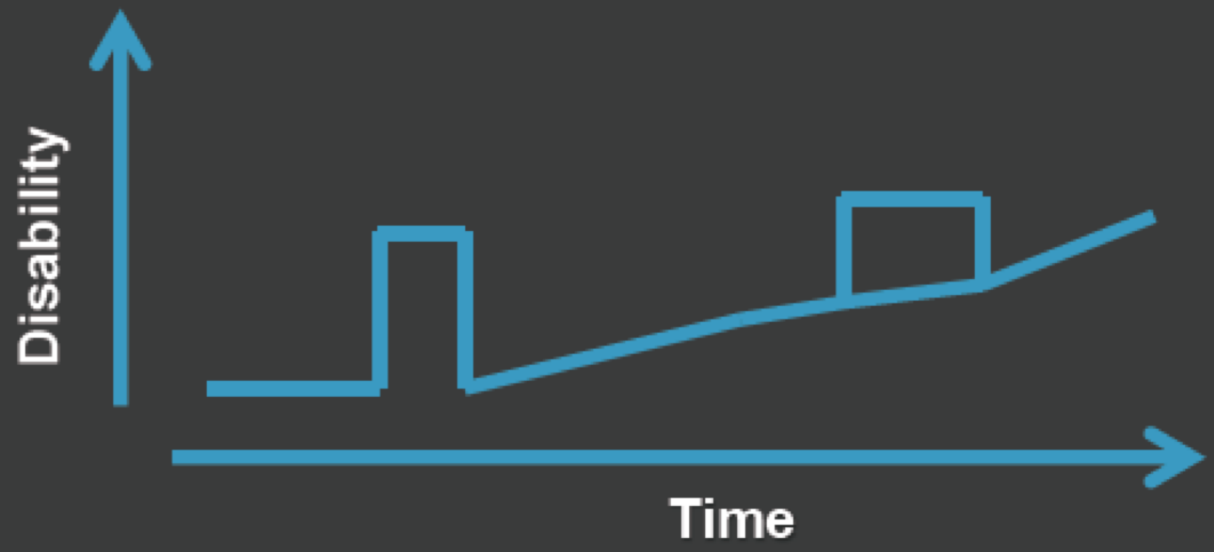
Types of MS

- Relapsing Remitting



Types of MS

- Secondary Progressive

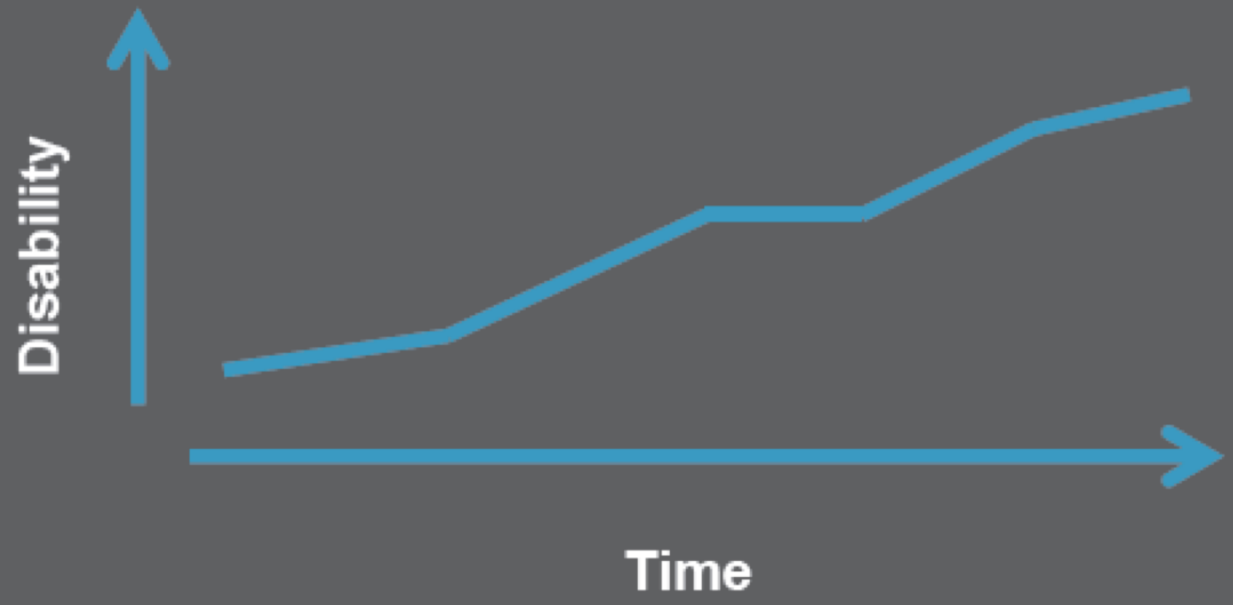


Types of MS

- Primary-progressive MS (PPMS)
  - Affects approximately 10% of MS population
  - Slow onset but continuous worsening condition
- Progressive-relapsing MS (PRMS)
  - Rarest form
  - Affects approx. 5%
  - Steady worsening of condition at onset

Types of MS

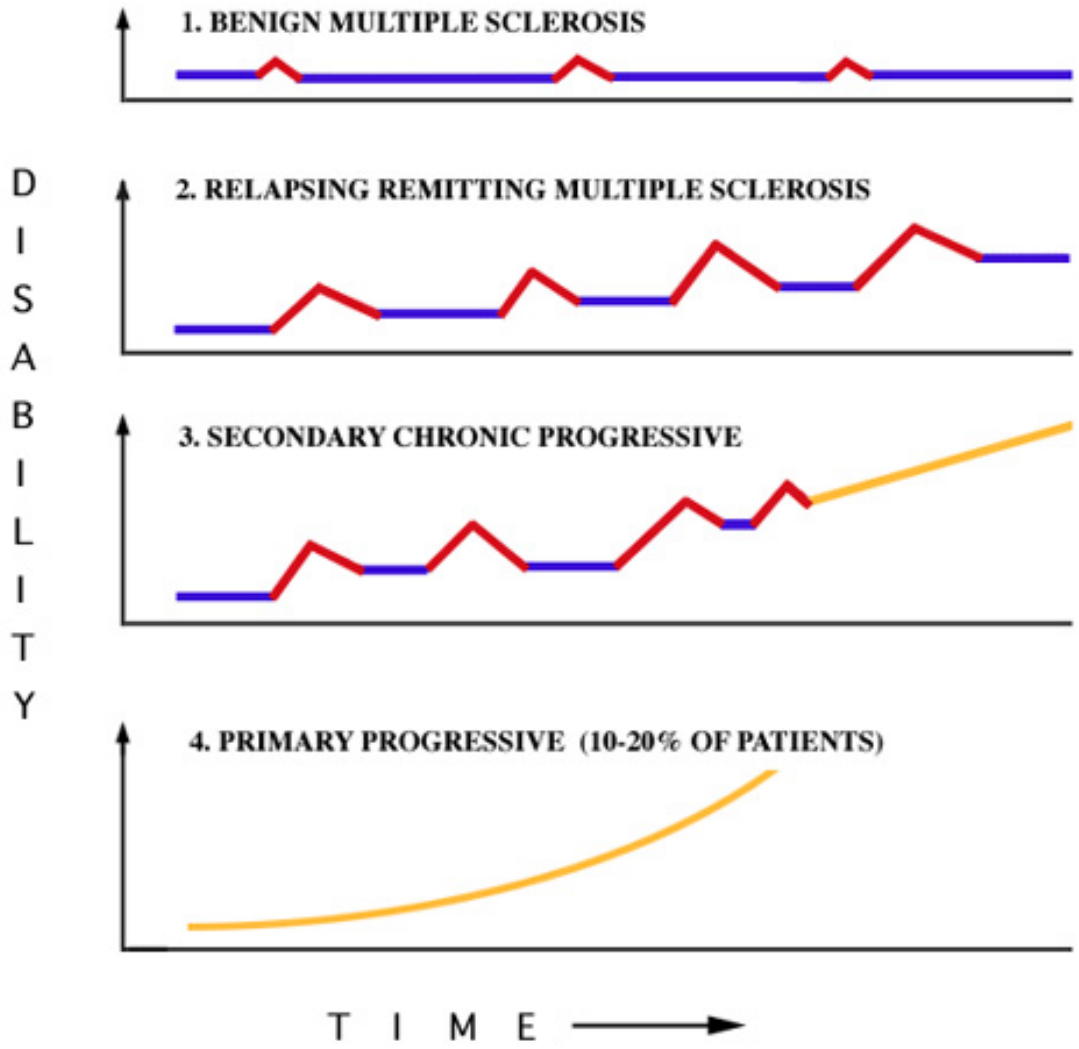
- Primary Progressive



Classification

Stable
Relapse
Progression

Click on graphs 1-4
for a description.



Other Factors Influencing MS

- Vitamin D deficiency
  - Vitamin D3 receptor important in immune function
  - Present on T regulator cells
- Infectious Mono/EBV
  - 99% of MS patients have EBV titers
  - Usually higher than in HC
  - Pseudo follicles in meninges containing B cells showing ENA antigen
  - EBER RNA found in inflammatory lesions
  - Protein stimulates Toll 3 receptors which release proinflammatory interferons
  - In inflammatory lesions T cells found surrounding B cells containing ENA antigen
- Genetics
  - HLA DRB2 *1503 allele 2x risk factor
  - IL 2 receptor
  - IL 7 receptor
  - 50 new candidates genes each with low risk factors

Vitamin D

- Vitamin D is a lipophilic vitamin synthesized by the conversion of 7 dehydrocholesterol to Vitamin D in the skin by ultraviolet radiation from the sun usually.

Role of Vitamin D in MS Background Information

1. US cohort study found that 3.5 times more women residing in northern states were diagnosed with MS than southern states
2. Incidence of MS highest in North Temporal Climate
3. MS more prominent in areas reporting less than 2000 hours of sunshine annually
4. MS displays seasonable variability with increased activity in the Spring and lowest in the Fall.
5. A Finnish study found in MS patients lower serum vitamin D levels in the Spring.
6. A line between dietary intake of vitamin D and the incidence of MS has been suggested in Norway along the coastal areas where fatty fish, dairy products, and cereals are all fish in vitamin D consumed in higher amounts. The incidence is lower then the rest of Norway.
7. Dietary information from the Nurse's Health Study of 187,000 women showed those with a history of vitamin D supplementation as low as 400 units daily had a 40% less chance of developing MS.
8. Levels of 1_1 25 hyroxy D_3 and 1

Diseases to rule out

- Viral infections
- Lyme disease
- B12 deficiency
- CVA
- Lupus
- Rheumatoid arthritis
- Other connective tissue disorders
- Vasculitis
- Syphilis
- Tuberculosis
- HIV
- Sarcoidosis

Medications and MS

Therapies	Administration	CLASS
Avonex	IM 1x a week	Interferon beta-1a
Betaseron	SC, every other day	Interferon beta-1b
Copaxone	SC 1x a day	Glatiramer acetate
Rebif	SC 3x a week	Interferon beta-1a
Gilenya	Oral capsule 1x day	Fingolimod
Tysabri	IV Monthly at Center	Natalizumab

Side effects of MS medication

- Local injection site irritation/reactions
- Flu like symptoms
- Rise in liver enzymes
- Decreased white cell count and platelets
- Opportunistic infections
- Depression
- Progressive multifocal leukoencephalopathy (PML)

Fatigue

- Medications
  - Amantadine
  - Ritalin drugs
  - Focalin
  - Adderall
  - Provigil/Nuvigil

Depression

- Selective Serotonin Reuptake Inhibitors
  - Paxil
  - Prozac
  - Zoloft
  - Lexapro
  - Celexa
- Tricyclic Antidepressants
  - Elavil
  - Pamelor
  - Tofranil
  - Norpramin
- Some other medications
  - Desyrel
  - Serzone
  - Welbutrin
  - Effexor
- Referral for counseling
- Psychologist
- Encourage expression of feelings will entire team and caregivers
- Work on solution together

Bladder problems

- Rule out UTI
- Bladder training
  - Strengthen pelvic muscles
- Medication
- Anti-spasticity
  - Vesicare
  - Detrol
  - Ditropan
- Referral to urologist for further evaluation and treatment

Sexual Dysfunction

- Medications
  - Viagra
  - Cialis
  - Levitra

Constipation

- Increase oral intake
- Increase fiber intake
- Miralax
- Metamucil
- Citrucel
- Colace

MCHUMOR.COM by T. McCracken

"In those four out of five doctors commercials, I'm the fifth doctor."

RIS (Radio logically Isolated Syndrome)

- White matter lesions suggestive of demyelinating disease on MRI
- Normal neuro exam
- No medical history compatible with MS
- Unclear whether RIS is subclinical MS or a separated entity
- About 33% of subjects with RIS develop a CIS especially with spinal cord lesions

Italian Group

- Tested 29 patients
- 23 had CSF analysis & 70% showed bands and elevated immunoglobulin G index
- Compared to 26 RRMS & 21 HC
- NPS performance showed 8 of RIS gr failed 2 studies and 5 failed one tests
- Results similar to RRMS group
- MR analysis showed comparable levels of lesion loads and cortical atrophy in RIS & RRMS groups which correlated with worse cognitive performance

OKADA et al

- OKADA et al showed presence of cervical lesions by MRI were associated with higher conversion to MS
- If negative for cord lesion conversions was 15% in 5 years but if positive 85% in 5 years.

Cortical Lesions

- Present on autopsy and biopsy studies
- Sometimes quite extensive
- Cause of cognitive dysfunction
- Amount of brain volume loss has been shown to be associated with cognitive impairment
- Inflammation not seen in chronic MS lesions in the cortex
- Luchinetti has shown cortical perivenular inflammation in acute lesion using cortical biopsy but response last only days, however.

MRI – Double Inversion Recovery (DIR)

- WM & CSF signals suppressed
- 3D DIR increases intracortical lesion detection by 500% compared to standard T2 spin echo and by more than 150% compared to FLAIR
- Post mortem brain slice lesion detection by using DIR & FLAIR & pathological exam
- DIR showed 35/198 total lesion i.e.: 18% detection (1.6 >FLAIR)
- Showed pathological specificity for 3D DIR was 90% & FLAIR 81%
- 9 more intracortical lesion seen by DIR but most missed by both techniques especially subpial and intracortical ones.

Treatment Options

- Non FDA approved
  a) Cellcept
  b) Cytoxan
  c) Laquinomod
  d) Cladribine
  e) Fumarate (BG12)
  f) Terflunomide
  g) Monoclonal antibodies
     1. Alemtuzimab (Campath)
     2. Rituximab
     3. Dacluzimab
     4. Anti Lingo antibody
  h) Vaccines
     a) Tovaxin

Tysabri & PML

- Risk factors
  - JC antibody status
  - Length of treatment
  - Prior immunosuppressant use
    - Immuran (Azothrioprine)
    - Cytoxan
    - Novantrone
    - Methotrexate
    - Cellcept

Tysabri & PML

- Biogen Risk Ratios
  - JC negative 1/10,000

JC positive	NO IS	Prior IS
1-24 months	.35/1000	1.2/1000
25-48 months	2.5/1000	7.8/1000

- Rudick/Fox Risk Ratio

	IS	Overall	Up to 24 Months	> 24 Months
JC neg	No	1/17,000	1/50,000	1/9,629
JC neg	Yes	1/6,239	1/18,000	1/3,396
JC pos	No	1/442	1/1,288	1/241
JC pos	Yes	1/177	1/454	1/85

Gilenya “Fingolimide”

Blocks S1 Phosphate receptor keeping T & B cells in lymphoid tissue

First oral pill released by FDA two years ago for treatment of MS

Reduces relapse rate by 55-58%

Shows benefit on MRI endpoints as T2 lesion load and Gad enhancing lesions

Side effects:

- Macular Edema
- Heart Block
- Liver Function Abnormalities
- Sudden Death

Dimethyl Fumarate (BG12)

- Pilot study IIB vs. placebo
  - 240mg tid vs placebo
  - Week 24 decreased GD+ lesion by 69% and new or enlarging T2 lesions
- DEFINE TRIAL (phase III) 1200 pts
  - Results @ 2 years 240 mg BID or TID
  - 49% reduction in pts that relapse
  - Reduced ARR by 53%
  - Decreased GD+ lesion by 90%
  - Decreased new or enlarging T2 lesions by 85%

Dimethyl Fumarate (BG12)

- Reduced EDSS worsening by 38%
- Reduced number of T1 hypointense lesions by 72% and 63% with BID and TID dosing

- CONFIRM TRIAL (phase III)1200 pts
  - Randomized to 4 groups
    - BG12 240mg BID, TID, Copaxone, Placebo
  - Results:
    - 44% reduction ARR for BID & 51% reduction ARR for TID
    - Copaxone 29%

Dimethyl Fumarate (BG12)

- Side effects
  - Flushing
  - GI upset
  - No serious infections
  - ↑ QOL measurements @ 2 years

Laquinimod

- Induces cytokinin shift toward Th2 subset
- Allegro Trial (Phase III) 1106 pts
  - Laquinimod 0.6mg vs placebo for 2yrs
  - Results: ARR reduction by 23% confirmed EDSS worsening by 36%; GD+ lesions reduced by 37% and brain volume loss reduced by 33%
  - Safety good
    - Mostly back pain
    - GI upset
    - Transient LFT abnormalities

Laquinimod

- BRAVO Trial (Phase III)
  - Laquinimod or placebo added to Avonex
  - Results: ARR reduction not significant
    - Reduced EDSS progression by 33%
    - Reduced loss of brain volume by 27%
    - Results indicate may be neuroprotection & supported by animal models which showed better oligo survival & less axonal injury

Teriflunomide

- Inhibits pyridine synthesis with mild lymphopenia
- TEMSO Trial (Phase III) 1088 pts
  - Follow for 2 years
  - Randomized to 7 or 14mg tablets or placebo
  - Results
    - 31% reduction ARR
    - Decreased EDSS worsening by 30% (14mg)
    - Decreased new lesion by 39% in 7mg & 67% in 14mg
  - Safety: good
    - Mainly diarrhea and LFT abn.

Teriflunomide

- TENERE Trial (Phase III) 300pts
  - Compare 7mg to 14mg to Rebif
- TOWER (Phase III) 1200 pts
  - Compare 7mg & 14mg to placebo
- TOPIC (Phase III)
  - CIS trial

TENERE TRIAL

- Phase III Blocks proliferation of activated T&B cells
- Teriflunomide 7 mg & 14 mg vs. Rebif
  - 324 patients
  - Results ARR
    - 7mg- .410
    - 14mg- .259
    - Rebif- .216
  - S.E
    - URI
    - Diarrhea
    - Hair loss
    - Back pain
    - Abnormal LFT
- Other Trials in Progress
  - Tower 1200 pts 7 or 14 mg vs placebo
  - TOPIC CIS Trial
  - TERACLES adjunct added to B interferons

Daclizumab

- Humanized monoclonal antibody vs CD25 alpha subunit of the IL 2 receptor
- ↑ CD56 natural killer cells by 6-8X
- SELECT phase II trial 600 patients 1YR
  - 2 doses of drug 150 mg or 300mg SC monthly vs placebo
  - MRI study 300 monthly MRI's rest 4x for 1 year
  - Naïve with RR of 1.3-1.4 in the previous year 52% of 150mg group had 1 GEL, higher than other groups

Daclizumab

- Results:
  - ARR - 21 for 150mg group
    -23 for 300mg group
    - 46 placebo group
  - Free of relapse
    81% & 80% of Daclizumab vs 64% for placebo
  - Confirmed disability progression
    5.9% for 150mg
    7.8% for 300 mg
    13.3% for placebo

Daclizumab

- **MRI data**
  - 69-78% ↓ in new or enlarging GD lesions by 8-24 weeks
  - 79-86% by end of year
  - 1 death – infection in treated group

Firategrast

- Phase II for RRMS
- 343 patients 1:2: 2:2 ratio
  1) 150 mg drug BID (49)
  2) 600 mg drug BID (95)
  3) 900 mg women or 1200 mg (men BID 9100)
  4) Placebo (99)
- Oral gamma 4B integrin antagonist with very short half life of 2.5 to 4.5 hours
- Results:
  - 49% reduction in Gd + lesions for larger dose'
  - 22% in 600mg dose and
  - 79% increase for 150mg dose
  - Safety good
  - Well tolerated slight increase in UTI in higher dose group

AUTOLOGOUS Stem Cell Treatment

- 10 SPMS patients
- CDMS patient with HX of ON, abn VEPS, or clinical O. A. or HX of Uhthoffs phenomenon
- MRI of ON had a T2 lesion followed for 20 mo before IV of stem cells for 10 mo afterwards
  - Results
    - Improved V.A. and low contrast V.A.
    - But not in color vision or visual fields
    - Reduction in V.E. latency & improved amplitudes but no change OCT
    - Increased ON area
    - No change in macular volume, RFL, or MT ration
    - Reduction in general disability with improved in EDSS
    - No change in MSFC, depression , cognition
    - Dec. in T1 hypointense volume
  - S.E.
    - Infections
    - Rash
    - Pruritus