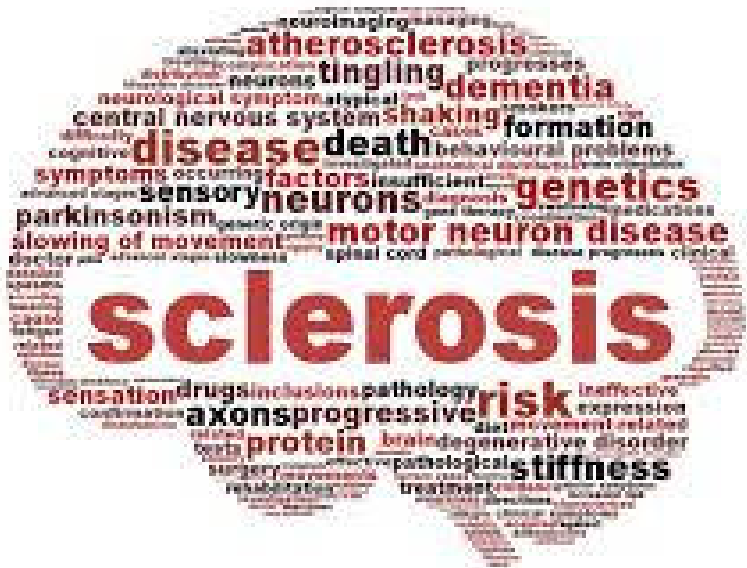


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AUB
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- Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees
- It is characterized by a triad of inflammation, demyelination, and gliosis (scarring) of the CNS

Infectious agents

- Viral or bacterial infections may be an important environmental cause of MS. Although no clear association has been identified
- Evidence for a virus as a cause include: the presence of oligoclonal bands in the brain and cerebrospinal fluid of most people with MS, increased immunoglobulin G (IgG) synthesis in the CNS and increased antibody titers to viruses
- Many possible agents have been implicated, including mycoplasma, *Chlamydia pneumoniae*, spirochetes, rabies virus, herpes simplex virus, coronavirus, human T-cell leukemia virus type I (HTLV-I), MS-associated retrovirus, measles, most recently, human herpes virus type 6 (HHV-6)^{10,11} and Epstein-Barr virus.

Epstein-Barr virus shows the strongest and most consistent association with multiple sclerosis.

- Elevated anti-EBNA-1 antibodies and infectious mononucleosis are linked to increased MS risk.

- HHV-6 and endogenous retroviruses may enhance EBV-related immune dysregulation.

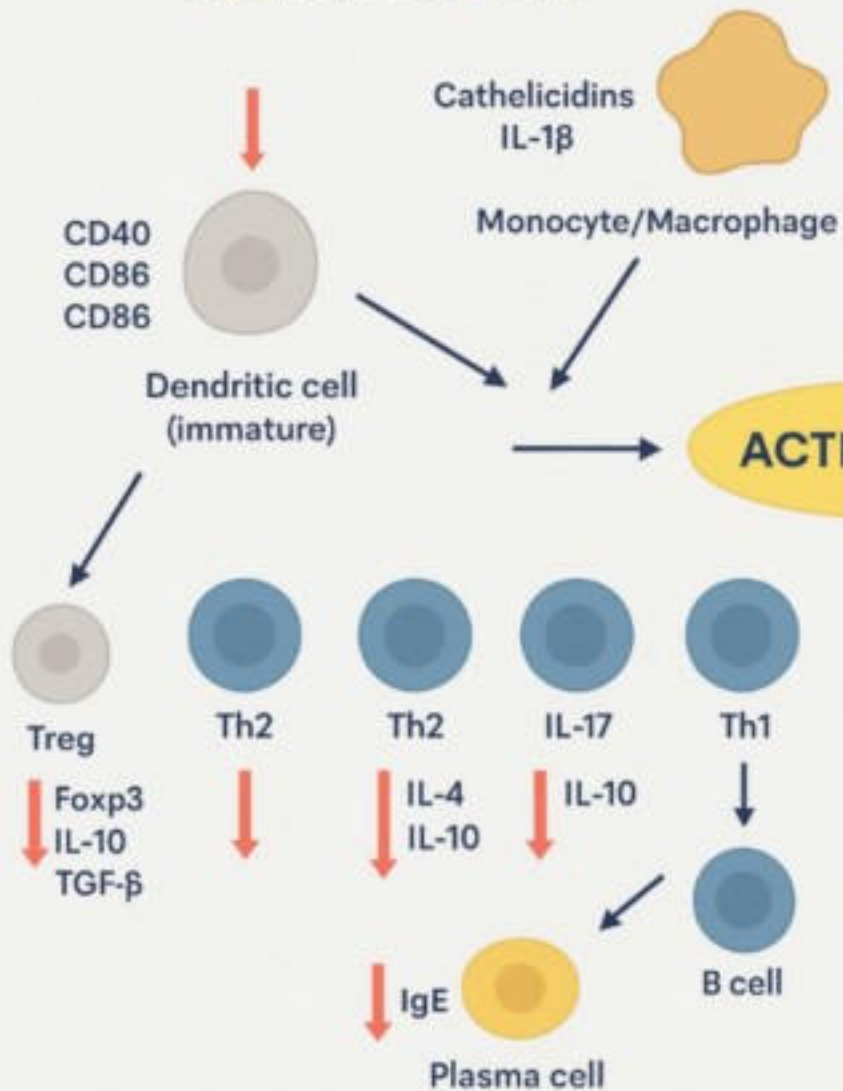
- Accumulating evidence suggests that alterations in the gut microbiota may contribute to MS pathogenesis.

- No clear association has been established for fungal or parasitic infections.

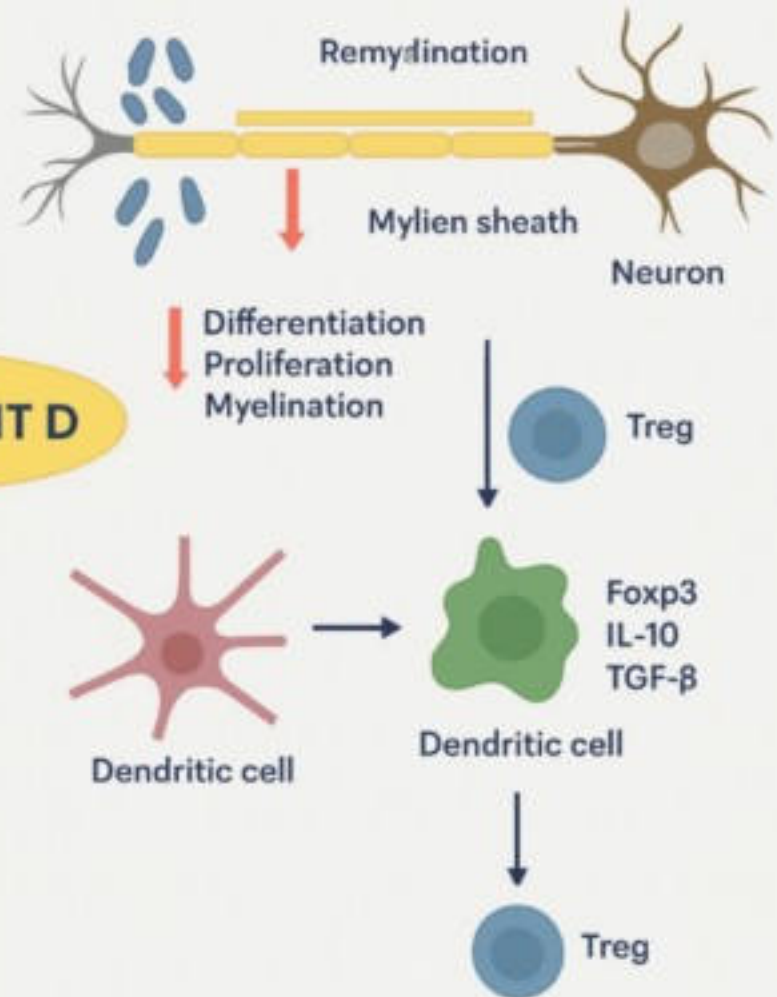
PATHOPHYSIOLOGY:

- The three main characteristics of MS are the formation of lesions in the central nervous system, inflammation, and the destruction of myelin sheaths of neurons.
- The lesions most commonly affect the white matter in the optic nerve, brain stem, basal ganglia, and spinal cord, or white matter tracts close to the lateral ventricles
- To be specific, MS involves the loss of oligodendrocytes, the cells responsible for creating and maintaining a fatty layer—known as the myelin sheath—which helps the neurons carry electrical signals (action potentials)

IMMUNE SYSTEM

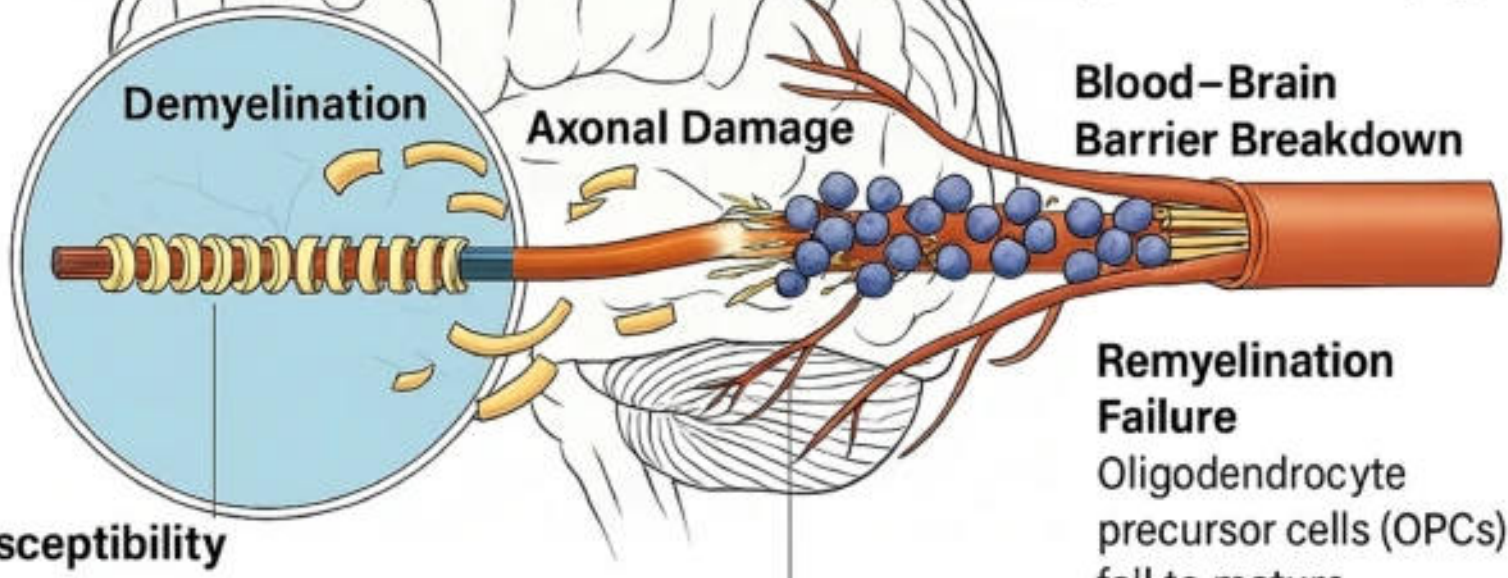


CENTRAL NERVOUS SYSTEM



EBV infection, vitamin D deficiency, and smoking increase MS risk

Chronic inflammation driven by cytokines (IL-17, IFN- γ , TNF- α) sustains CNS injury



Genetic Susceptibility
HLA-DRB1*15:01 allele confers a significant genetic susceptibility

Genetic Susceptibility
Activated T cells contribute significantly to genetic susceptibility in MS

Axonal Degeneration
Activated T cells (Th1/Th17)
B cells cross the BBB, releasing cytokines and autoantibodies

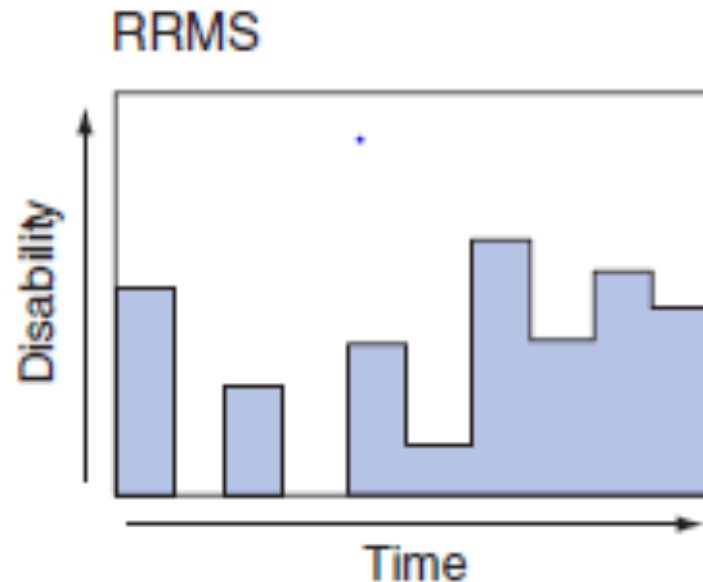
Remyelination Failure
Oligodendrocyte precursor cells (OPCs) fall to mature, limiting repair

Remyelination Failure
Oligodendrocyte precursor cells (OPCs) fails to

DISEASE COURSE

Four clinical types of MS have been described

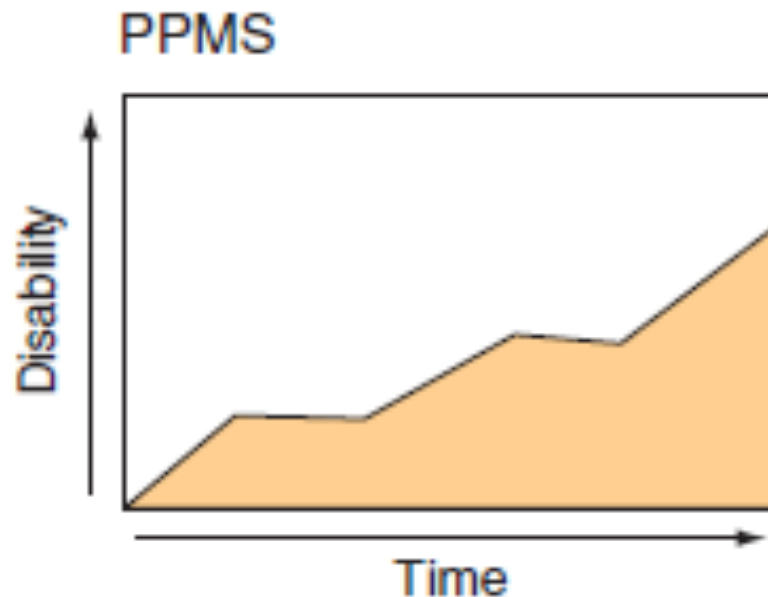
1. *Relapsing/remitting MS (RRMS)* accounts for 85% of MS cases at onset and is characterized by discrete attacks that generally evolve over days to weeks (rarely over hours). There is complete recovery over the ensuing weeks to months. Between attacks, patients are neurologically stable.



2. *Primary progressive MS (PPMS)* accounts for 15% of cases.

These patients do not experience attacks but only a steady functional decline from disease onset.

Compared to RRMS, the disease begins later in life (mean age, 40 years), and disability develops faster.

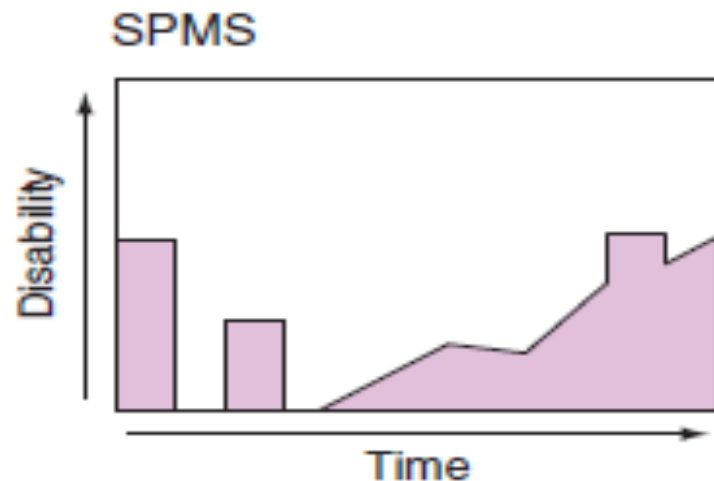


3. *Secondary progressive MS (SPMS)* always begins as RRMS.

At some point, however, the RRMS clinical course changes so that the patient experiences a steady deterioration in function unassociated with acute attacks (which may continue or cease during the progressive phase).

SPMS produces a greater amount of fixed neurologic disability than RRMS.

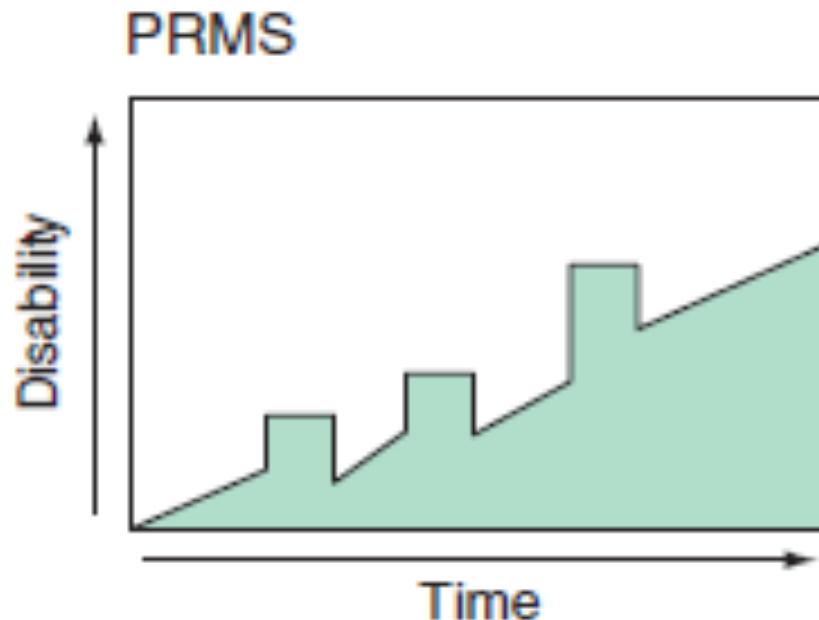
Approximately 50% of patients with RRMS will have developed SPMS after 15 years.



4. *Progressive/relapsing MS (PRMS)* overlaps PPMS and SPMS and accounts for 5% of MS patients.

Like patients with PPMS, these patients experience a steady deterioration in their condition from disease onset

The early stages of RPMS are indistinguishable from those of PPMS (i.e., until the first clinical attack).



CLINICAL PRESENTATION:



CLINICAL FEATURES

- INTERNUCLEAR
OPHTHALMOPLEGIA
- OPTIC NEURITIS
- RELAPSING AND REMITTING
SENSORY SYMPTOMS
- SUBACUTE PAINLESS SPINAL
CORD LESION
- ACUTE BRAIN STEM SYNDROME
- SUBACUTE LOSS OF UPPER LIMB
FXN(DOSAL COLUMN DEFICIT)
- CN6 PALSY
- UHTHOFF PHENOMENON
- LHERMITTE'S SYMPTOM

The McDonald Criteria

Developed by and named for neurologist W. Ian McDonald in 2001, these guidelines were revised in 2010 and again in 2017 to give us what's now the state of the art in diagnosis.

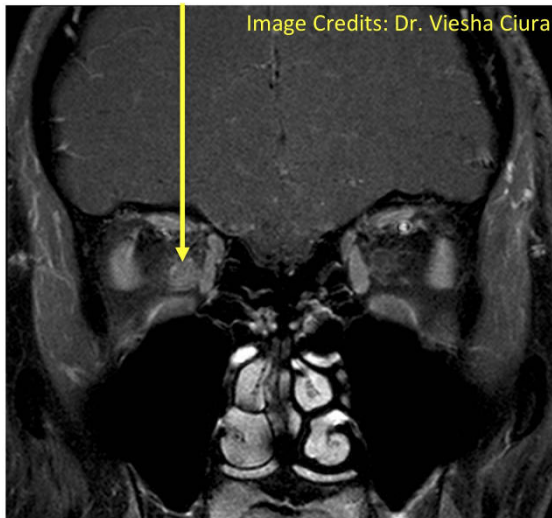
Clinical Attacks	Number of lesions with objective clinical evidence	Additional Data Needed for MS Diagnosis
Two or more	Two or more	None
Two or more	One with clear historical evidence of a previous attack	None
Two or more	One	Dissemination in Space (additional attack indicating effects on a different area of the Central Nervous System, OR lesions in different areas shown by MRI)
One	Two or more	Dissemination in Time (additional clinical attack, OR lesions detected by MRI, OR oligoclonal bands detected in spinal fluid)
One	One	Dissemination in Space (additional attack indicating effects on a different area of the Central Nervous System, OR lesions in different areas shown by MRI); AND Dissemination in Time (additional clinical attack, OR lesions detected by MRI, OR oligoclonal bands detected in spinal fluid)

findings shown here are not exhaustive but are some of the most common areas implicated on brain MRI in MS. Most common sites that lesions are observed are: juxtacortical regions, periventricular, infratentorial, spinal cord, and the optic nerve. However lesions can occur anywhere there is myelin in the CNS.

Active inflammation and destruction allows for gadolinium contrast to cross the blood-brain barrier, which can be visualized as a marker of active inflammation in MS

Classic optic nerve (CN II) lesion seen in optic neuritis. Gadolinium enhancement (↑ signal intensity of lesion after gadolinium injection) in this T1 image demonstrates active inflammation

Image Credits: Dr. Viesha Ciura



T-cell, B-cell, and macrophages infiltrate CNS

Infiltration occurs through veins → local inflammation

Perivenular infiltrates around the medullary veins (perpendicular to ventricles)

infiltrates in the infratentorial region

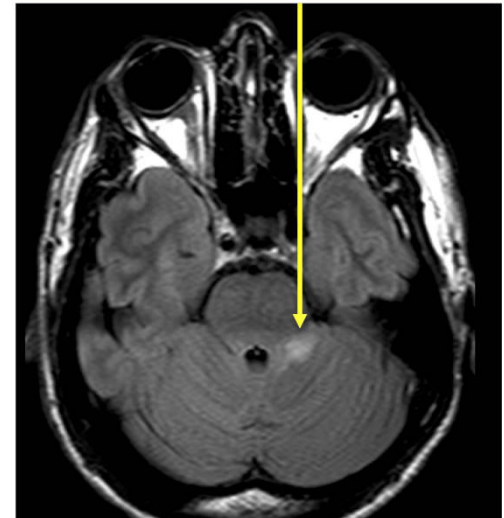
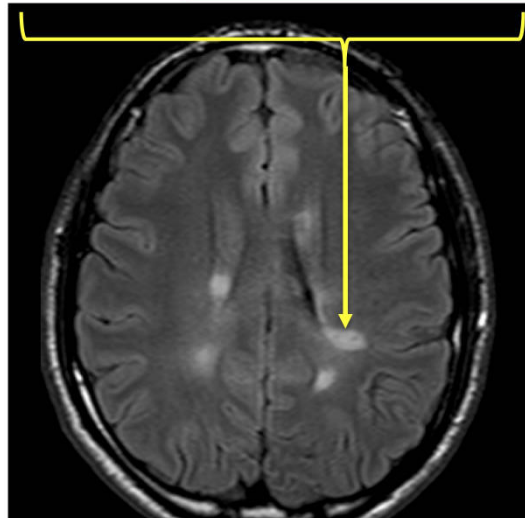
Inflammation and blood-brain barrier destruction ↑ extravascular inflammatory fluid around lesions, which appears hyperintense/bright

Loss of neuronal/axonal density in affected region, replaced by gliosis over time

Lesions extend out around veins, creating characteristic **ovoid lesions**

Classic hyperintense T2/FLAIR perpendicular periventricular plaques following the medullary veins – ‘**Dawson’s Fingers**’

Middle cerebellar peduncle T2/FLAIR hyperintense lesion in classic location for MS



Sclerosis (MS): Pathogenesis and Clinical Findings

Viesha Ciura*
Reviewers:
Yan Yu*
* MD at time of publication

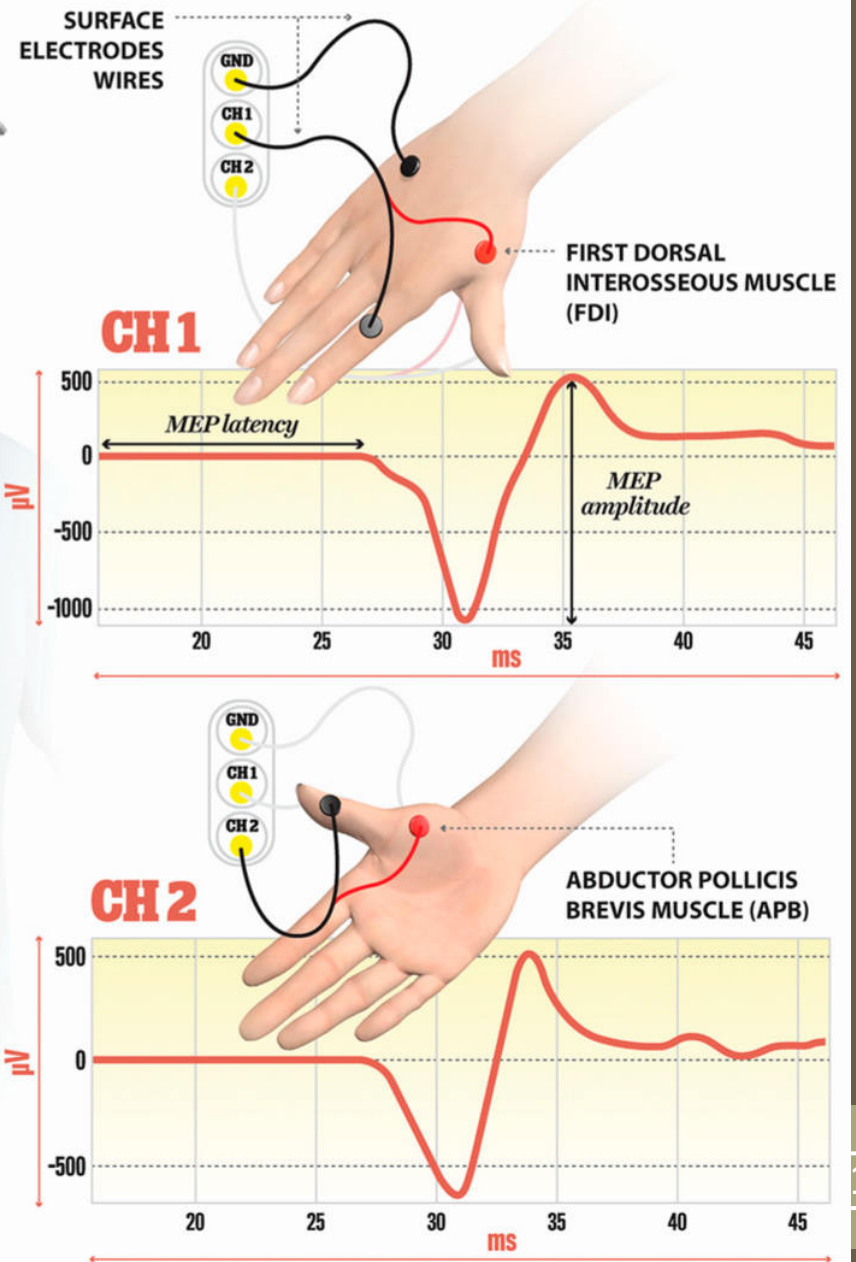
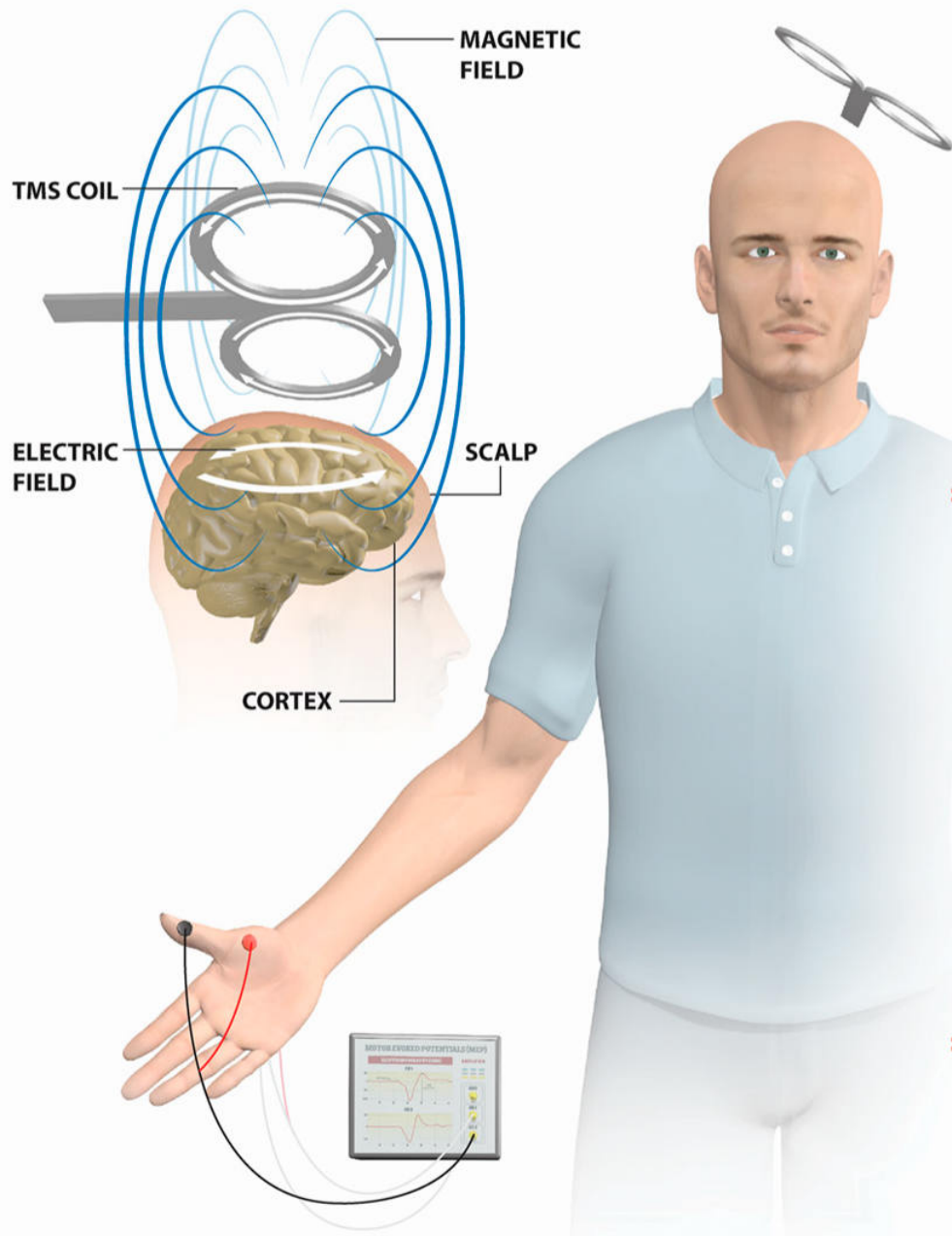
MS MRI FINDINGS

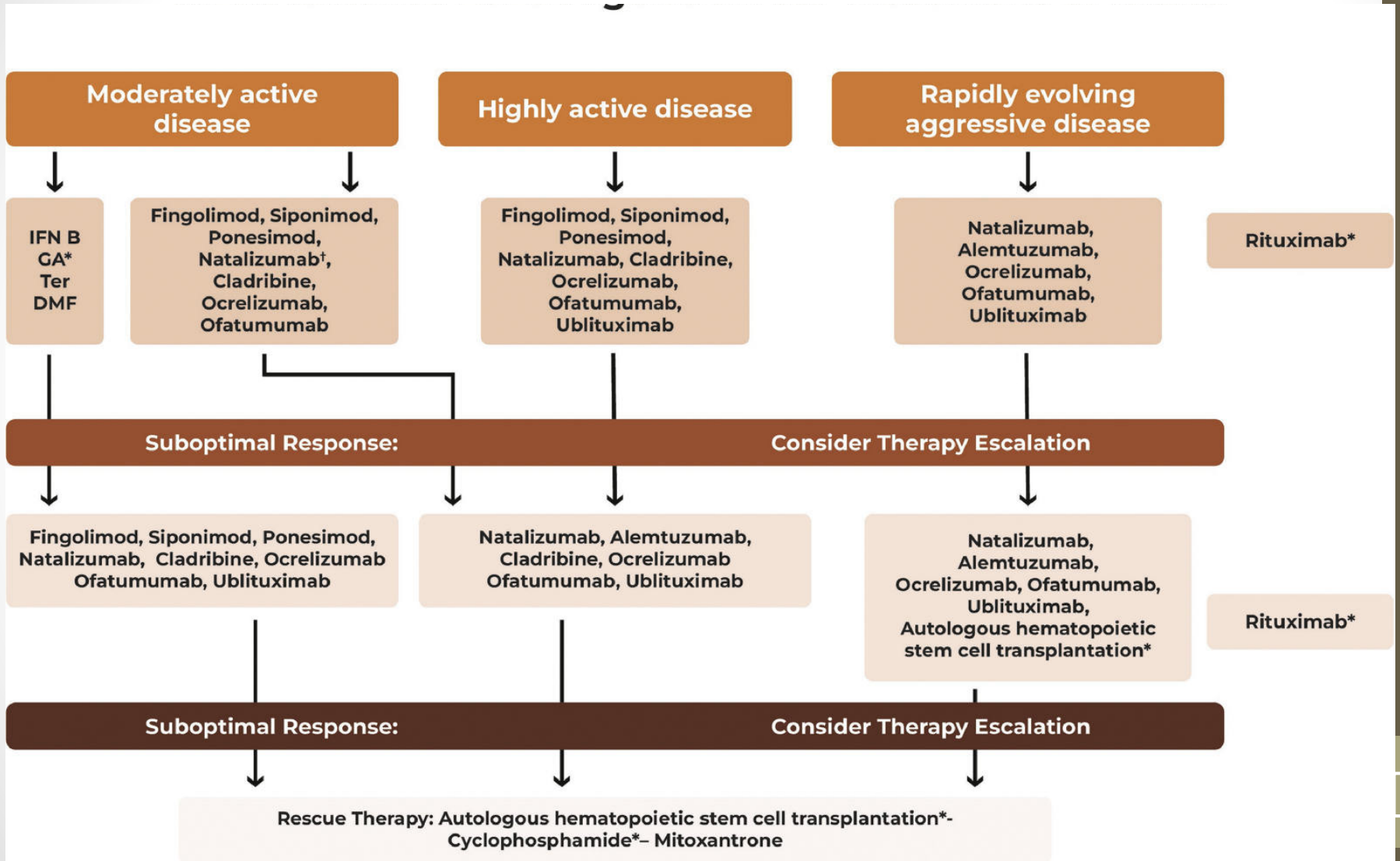
CSF FLUID ANALYSIS:

- Mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG.
- The total CSF protein is usually normal or slightly elevated and <50-100 WBCs
- The measurement of oligoclonal banding (OCB) in the CSF also assesses intrathecal production of IgG.

EVOKED POTENTIALS:

- EP testing assesses function in afferent (visual, auditory, and somatosensory) or efferent (motor) CNS pathways.
- Abnormalities on one or more EP modalities occur in 80 to 90% of MS patients.





TREATMENT:

Current therapy for MS can be divided into several categories:

- (1) treatment of acute attacks as they occur;
- (2) treatment with disease modifying agents that reduce the biological activity of MS, and
- (3) symptomatic therapy.

Acute Attacks or Initial Demyelinating Episodes:

- Glucocorticoids are used to manage either first attacks or acute exacerbations.
- **IV methylprednisolone, 500 to 1000 mg/day** for 3 to 5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60 to 80 mg/d and gradually tapered over 2 weeks.
- **ADRs:** fluid retention, potassium loss, weight gain, gastric disturbances, acne, and emotional lability.

Plasma exchange (7 exchanges: 54 mL/kg or 1.1 plasma volumes per exchange, every other day for 14 days) may benefit patients with fulminant attacks of demyelination (not only MS) that are unresponsive to glucocorticoids.

Disease-Modifying Therapies for Relapsing Forms of MS (RRMS SPMS with Exacerbations)

- (1) IFN β -1a (**Avonex**) : 30 mcg, is administered by intramuscular injection once every week.
- (2) IFN β -1b (**Betaseron**) : 250 mcg, is administered by subcutaneous injection every other day
- (3) Glatiramer acetate (**Copaxone**) : 20 mg, is administered by subcutaneous injection every day.

IFN- β :

IFN β shows immunomodulatory properties including:

- (1) downregulating expression of MHC molecules on antigen-presenting cells
- (2) inhibiting proinflammatory and increasing regulatory cytokine levels
- (3) inhibition of T cell proliferation and
- (4) limiting the trafficking of inflammatory cells in the CNS
- **ADRs:** flulike symptoms (e.g., fevers, chills, and myalgias) and mild abnormalities on routine laboratory evaluation (e.g., elevated liver function tests or lymphopenia)

GLATIMER ACETATE:

- It is a synthetic, random polypeptide composed of four amino acids (L-glutamic acid, L-lysine, L-alanine, and L-tyrosine).
- Its mechanism of action may include:
 - (1) induction of antigen-specific suppressor T cells
 - (2) binding to MHC molecules, thereby displacing bound MBP;
or
 - (3) altering the balance between proinflammatory and regulatory cytokines.
- Mild pain and pruritus at the injection site are the most frequent patient complaints.
- Approximately 10% of patients will experience a one-time transient reaction consisting of chest tightness, flushing, and dyspnea beginning several minutes after injection and lasting usually no longer than 20 minutes

NATALIZUMAB:

- Natalizumab is a partially humanized monoclonal antibody directed at the cell surface adhesion molecule $\alpha 4\beta$ -integrin (also known as verylate antigen 1, VLA-1).
- It works by attaching to VLA-1 and blocking its interaction with its ligand on CNS endothelium vascular cell adhesion molecule (VCAM)-1.
- Thus, activated lymphocytes are denied entry past the blood-brain barrier.
- It is indicated as monotherapy, 300 mg every 4 weeks as an infusion.
- **ADRs:** progressive multifocal leukoencephalopathy headache, fatigue, depression, arthralgia, rash, abdominal discomfort

Symptomatic Therapy:

- **WEAKNESS:** Potassium channel blockers (e.g., 4-aminopyridine, 10 to 40 mg/d;
3,4-di-aminopyridine, 40 to 80 mg/d)
- **ATAXIA/TREMOR:** Clonazepam (1.5 to 20 mg/d), mysoline (primidone) (50 to 250 mg/d), propranolol (40 to 200 mg/d)
- **SPASTICITY:** lioresal (baclofen)(20 to 120 mg/d), tizanidine (8 to 32 mg/d)
- **PAIN:** carbamazepine, 100 to 1000 mg/d; phenytoin, 300 to 600 mg/d; or gabapentin, 300 to 3600 mg/d)
- **BLADDER DYSFUNCTION:** *Bethanechol* up to 50mg/d
- **FATIGUE:** amantadine (200 mg/d)
- **COGNITIVE PROBLEMS:** cholinesterase inhibitor donepezil hydrochloride (10 mg/d).
- Vitamin D for everyone

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thank
you!