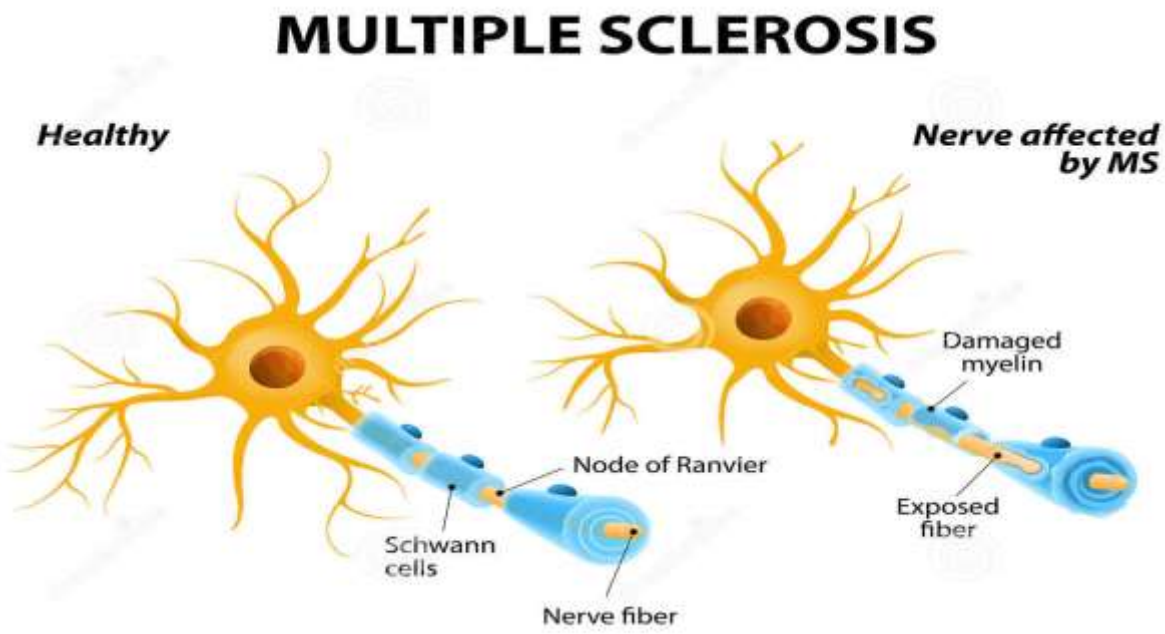


Multiple sclerosis (MS) is an inflammatory, demyelinating neurodegenerative, autoimmune disease of the central nervous system.

- MS associated with Demyelination and axonal damage occur.
- Diagnosis typically occurs between 20 and 50 years, with the mean age at onset of 30 years.
- The name refers to two featuresof the disease: multiple describes the number of CNS lesions; and sclerosis refers to the demyelinated lesions. Today, these lesions are usually called **plaques**, rather than scleroses.
- The etiology of multiple sclerosis (MS) is unknown, but it appears to be autoimmune in nature.Currently there is no cure.

Classification

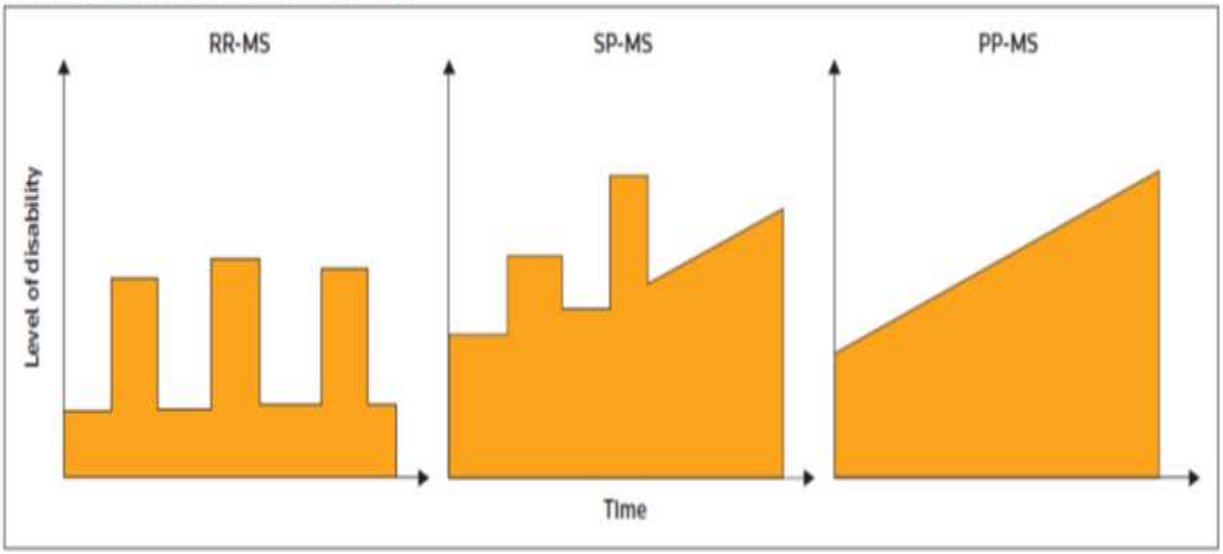
• MS is classified by the nature of progression over time into several categories, which have different clinical presentations and responses to therapy

• ***Relapsing-Remitting MS (RRMS):*** the most common initial diagnosis of MS (80%–90% of patients) in which clinical disease activity alternates with periods of symptom remission

• ***Secondary-Progressive MS:*** occurs in approximately 80% of patients with RRMS and is characterized by fewer relapses as disability continues to progress

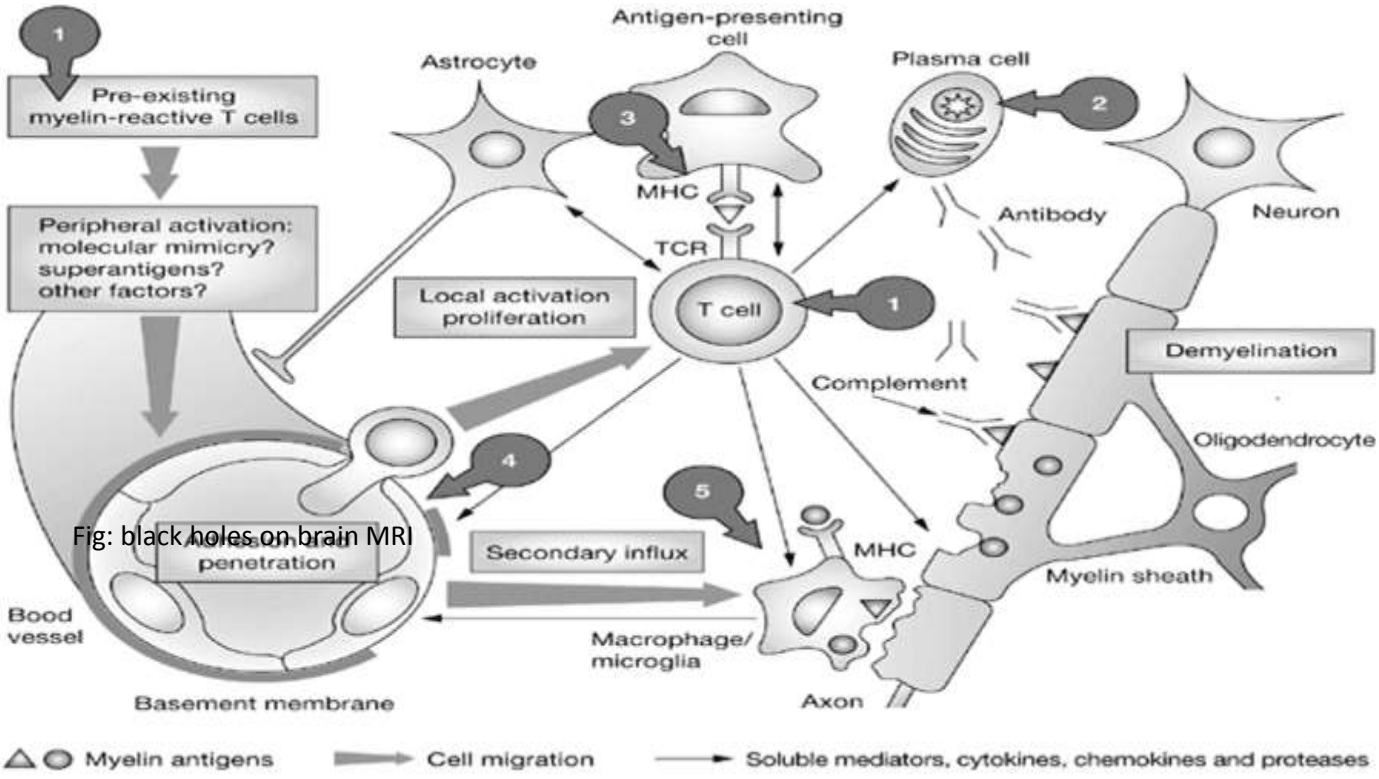
• ***Primary-Progressive MS:*** occurs in approximately 10% to 15% of patients and is progressive from onset with occasional minor improvements or periods of stabilization.

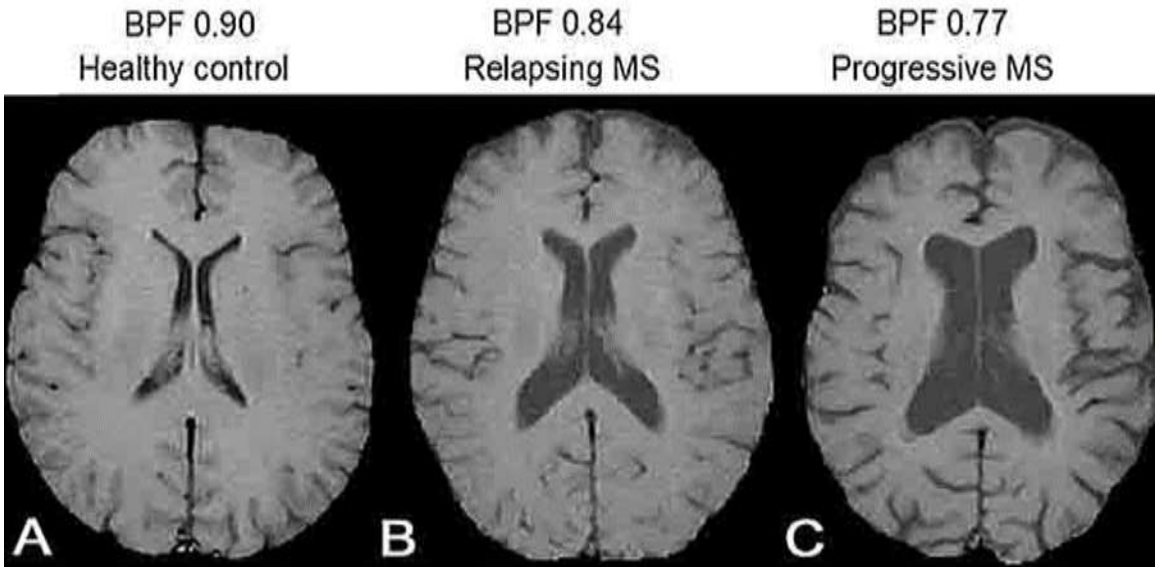
Figure 1. The different forms of MS progression.



PATHOPHYSIOLOGY

- While the actual causative agent of MS is not clear, the final result is the development of an autoimmune disorder with areas of CNS demyelination and axonal transection.
- The exact immune mechanism is not completely understood; however, T-helper1 cells and the inflammatory cytokines that they secrete (e.g., IFN-g) are strongly implicated.
- The basic physiologic derangement in MS is stripping of the myelin sheath surrounding CNS axons. This activity is associated with an inflammatory, perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement.
- Demyelination renders axons susceptible to damage, which becomes irreversible when they are severed. Irreversible axonal damage correlates with disability and can be visualized as hypo- intense lesions, or "black holes," on T1-weighted MRI.



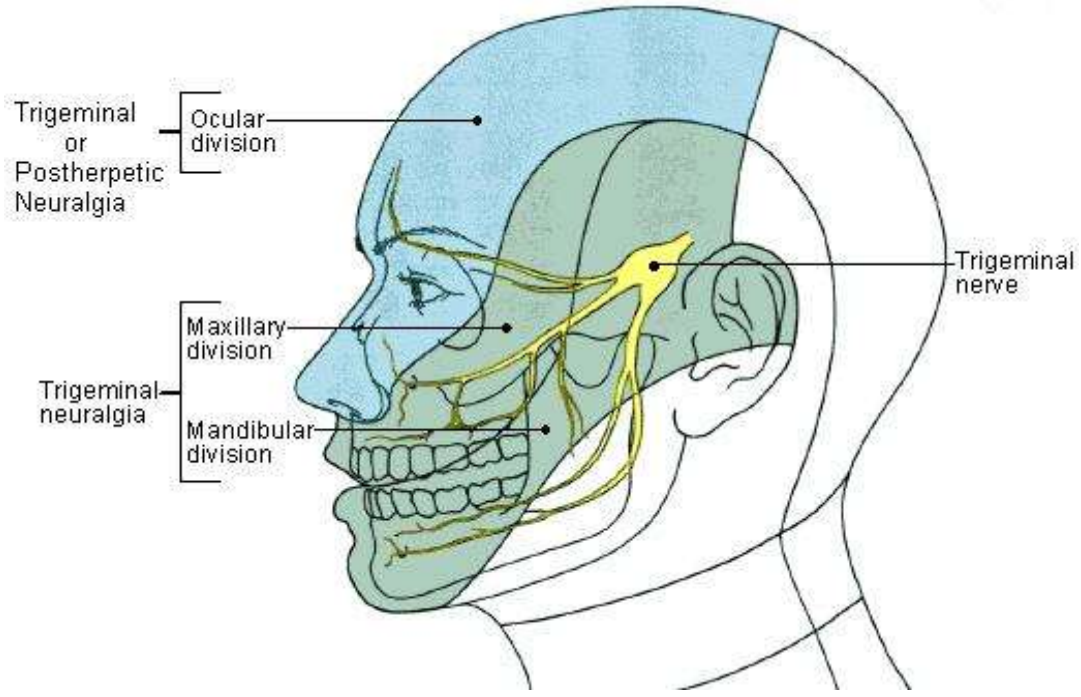


Patient Assessment

- ✓ The most common clinical symptoms are sensory disturbances (particularly of the extremities), partial or complete visual loss, motor dysfunction of the limbs, diplopia, and gait dysfunction.

Primary Symptoms /Signs	Secondary Symptoms	Tertiary Symptoms
Visual complaints/optic neuritis • Gait problems and falls • Paresthesia • Pain • Spasticity • Weakness • Ataxia • Speech difficulty • Psychological changes • Cognitive changes • Fatigue • Bowel/bladder dysfunction • Sexual dysfunction • Tremor	• Recurrent UTIs • Urinary calculi • Decubiti and osteomyelitis • Osteoporosis • Respiratory infections • Poor nutrition • Depression	· Financial problems · Personal/social problems · Vocational problems · Emotional problems

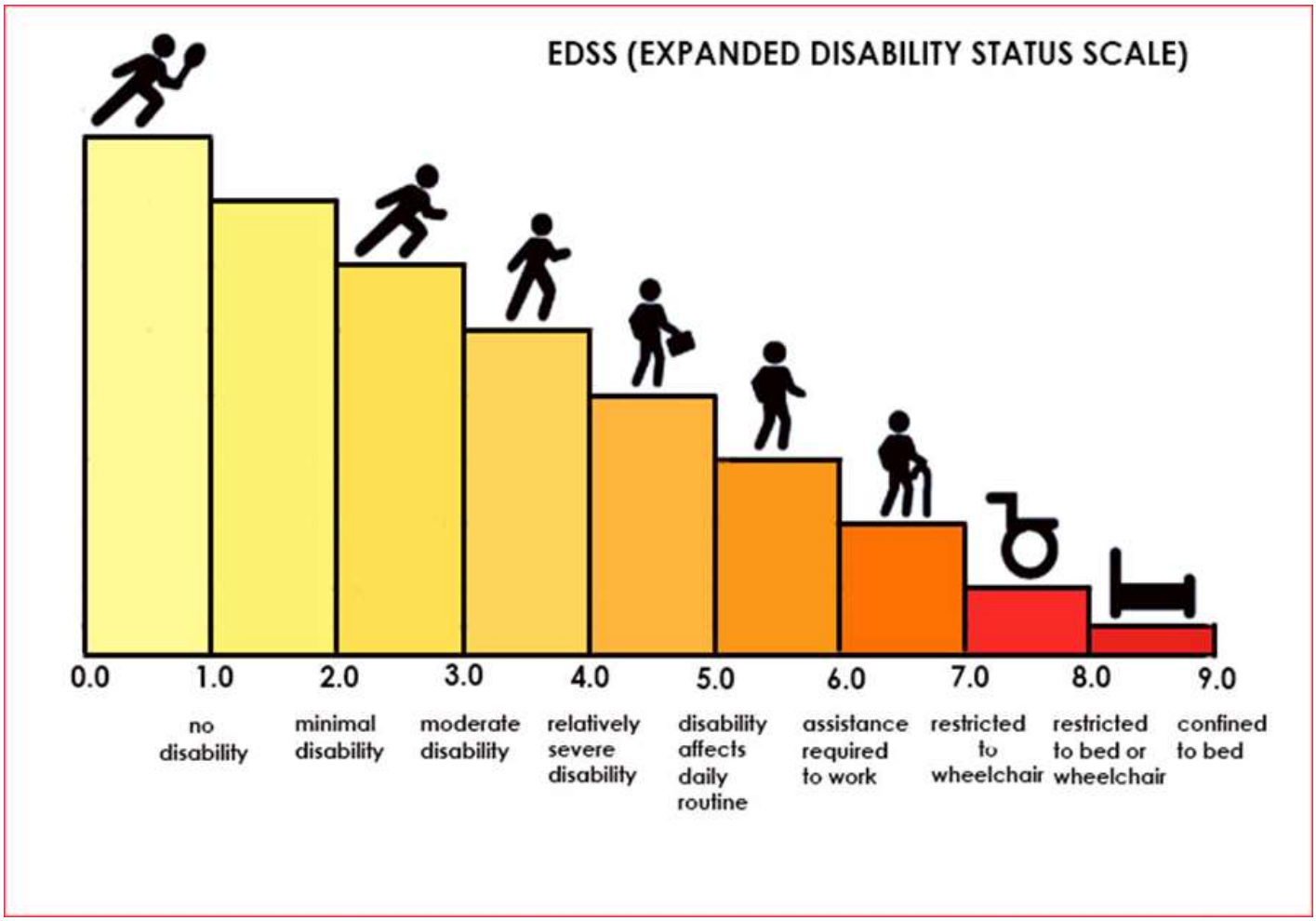
- ✓ A number of painful **neurogenic conditions** have been described in association with MS include:
  - **Trigeminal neuralgia**



Sudden, usually unilateral,severe, brief, stabbing, recurrent episodes of painin the distribution of one or more branches of the trigeminal nerve.

- **Lhermitte's phenomenon**—sudden onset, brief, electric shock-like sensation traveling rapidly down to the spine or into the arms or legs.Usually caused by flexing the neck. Sometimes occur occasionally for short periods
  - Tonic spasms
  - Burning dysesthesia of the limbs and trunk
  - Migraine headache.

✓ **The Expanded Disability Status Scale** (EDSS) may be used to measure the level of disability and progression of disease.



❖ **Diagnosis** الجدول للحفظ

TABLE 26–1. Diagnostic Tests for MS[21]

Test	Findings in Multiple Sclerosis
Magnetic resonance imaging	
T2 weighted	Demyelinated plaques, both active and inactive
Gadolinium enhanced	Active demyelinating plaques
Cerebrospinal fluid analysis	Oligoclonal bands of immunoglobulin G
	Elevated immunoglobulin G index
Evoked potentials	Slowed nerve impulse conduction

Abnormalities on magnetic resonance imaging (MRI) and cerebrospinal fluid findings may be used for diagnosis.MS diagnostic criteria were revised in 2001 and are known as the **McDonald criteria**which allow the clinician to use the clinical exam in combination with magnetic resonance imaging

Mc Donald criteria for MS		
ATTACKS	**LESIONS**	**ADDITIONAL CRITERIA FOR DIAGNOSIS MS**
2 or more	**2 or more**	**None.** Clinical evidence alone will suffice
2 or more	**1 lesion**	**Dissemination in space on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**2 lesions**	**Dissemination in time on MR** (or await further clinical attack implicating a different CNS site)
1 attack	**1 lesion**	**Dissemination in space *and* time** (or await further clinical attack implicating a different CNS site)
0 attack progression from onset		One year of disease progression (retrospective or prospective) **AND** at least 2 out of 3 criteria: • Dissemination in space in the brain • Dissemination in space in the spinal cord based on 2 or more T2 lesions • Positive CSF

(MRI) and cerebrospinal fluid (CSF) data to make a diagnosis sooner, and thus begin treatment earlier.

❖ DIFFERENTIAL DIAGNOSIS

- Because a number of disorders can mimic MS, most patients are screened with blood tests for rheumatologic, collagen-vascular, infectious, and sometimes inherited metabolic diseases.
- Electromyography may help in diagnosing amyotrophic lateral sclerosis and neuropathies.
- MRI, used to rule out tumors and cervical spondylosis, may also lead to evaluations for MS in many patients with little or no clinical history of MS. While some of these patients may have MRI.

❖ Desired Outcomes

The main goals of treatment are to improve patients overall quality-of-life and minimize long-term disability. Treatment goals are attained by altering MS exacerbations or relapses, decreasing the number of white matter lesions and black holes on MRI, averting brain atrophy, and ultimately halting disease progression. This can be achieved by early recognition of the disease and immediate utilization of FDA-approved drugs.

❖ TREATMENT

- ✓ Treatment strategies focus on reducing the inflammation within the CNS.
- ✓ Treatment of MS falls into three broad categories:
  - **First**, acute relapses are treated with corticosteroids to speed recovery.
  - **Second**, disease-modifying therapies are used to decrease the number of relapses, prevent permanent neurologic damage, and prevent disability.
  - **Third**, symptomatic treatment minimizes the impact of MS on quality of life.
- ✓ Currently available therapies, loosely categorized as immunomodulating agents, target the inflammatory response of disease (rather than the neurodegeneration).
- ✓ Corticosteroids are used for treatment of acute relapses to control inflammation and reduce time to recovery.

- ✓ Although different treatment modalities have been studied in thelast 30 years, many older trials had flawed designs. As there are no universally accepted treatmentalgorithms, treatments vary among clinicians and centers. Perhaps more importantly, treatmentdecisions are frequently based on the wishes and goals of individual patients rather than evidencebasedalgorithms.
- ✓ FDA-approved agents for the treatment ofRelapsing-Remitting MS(RRMS) include beta-interferons, glatiramer acetate, mitoxantrone, natalizumab, and fingolimod.
- ✓ No treatment is FDA-approved for the treatment of primary-progressive MS.
- ✓ Rates of relapse for women with MS decreases during pregnancy, increases in the first 3 months after delivery, and then returns to the prepregnancy rate. No treatment for MS is recommended for use during pregnancy. In general, MS therapy should be discontinued before conception.

❖ Drug Therapy

• Beta-interferons

Work through several different mechanisms of immune modulation. Twotypes of beta-interferons are available: ***interferonβ -1a*** and ***interferonβ -1b***.

• **Interferon β -1a** (subcutaneous route) has a dose titration (20% of full dose for 2 weeks,50% of full dose for 2 weeks, and then 100% of full dose thereafter).

•**Interferonβ -1b** requires a dose titration (25% of the full dose for 2 weeks, 50% of full dosefor 2 weeks, 75% of full dose for 2 weeks, then full dose thereafter).

- ☒ These products exist as three different preparations
  - Interferon beta 1a, IM with Weekly dose.
  - Interferon beta 1a SQ, given Three times /week.
  - Interferon beta 1b SQ given Every other day
- ☒ **Neutralizing Antibodies** :Antibodies to beta interferons can form over time and reduce the clinical effect of beta interferons
- ☒ **Adverse effects** with interferon b include leucopenia, injection site reactions, necrosis, flulike symptoms, breakthrough menstrual bleeding, and increased liver function tests(alanine aminotransferase and aspartate aminotransferasemust be monitored)

• **Corticosteroids**:Corticosteroids hasten functional recovery after relapses. Intravenous adrenocorticotropic hormone, intravenousmethylprednisolone, or oral prednisone are used fortreatment of relapses. Generally, intravenous **methylprednisolone**is considered the drug of choice for acute relapses.Recent studies show equal efficacy of equivalent doses ofintravenous and oral dosage forms. Some clinicians arenow using oral prednisone for patients experiencing relapsesto avoid the discomfort, inconvenience, and expense ofintravenous therapy.

The most common IV regimen for acute relapses is methylprednisolone 500to 1,000 mg daily for 3 to 5 days with or without a subsequent regimen of tapering using oralsteroids for 1 to 3 weeks. The recommended oral dose for acute relapses is prednisone 1,250mg every other day for 5 doses.

• **Fingolimod** is the first oral medicine for MS that acts by suppressing T-cell activity. After the first dose of fingolimod, the heart rate decrease starts within an hour, so monitoringof heart rate is very important. Patientswith preexisting sinus bradycardia or heart block without pacemakers should not receivetherapy.

• Dalfampridineis an oral potassium channel blocker approved for the treatment in improvingwalking in patients with MS. Dalfampridine is associated with a dose-dependent risk ofseizure. Seizures may occur within days to weeks after treatment initiation and have beenreported more frequently in patients with no history of seizure.

• Glatiramer acetatedecreases type 1 helper T cells while increasing type 2 helper T cells.

• Glatiramer is dosed at 20 mg **SQ daily**, with no dosage titration needed.

• *Common adverse events* are injection site reactions and postinjection systemic reactions(facial flushing, chest tightness, dyspnea palpitations, tachycardia, and anxiety).

• Mitoxantrone is an antineoplastic agentused for:

Reducing disability and the number of relapses in certain patients with multiple sclerosis. It is used along with other medicines to treat acute

nonlymphocytic leukemia (ANLL) or advanced prostate cancer in certain patients.

It is thought to interfere with cell reproduction and growth, which helps reduce the number of cancer cells in the body. Also works as a general immunomodulator, decreasing monocytes and macrophagesand inhibiting T and B cells.

It is dosed at 12 mg/m2 given as a 5- to 15-minuteintravenous infusion every 3 months.

Cardiotoxicity limits the lifetime dose to 140 mg/m2.

Common adverse effects include nausea, menstrual abnormalities, alopecia, upper respiratoryand urinary tract infections, neutropenia, and temporary blue color change to urine andsclera.

• Natalizumabis a humanized monoclonal antibody that blocks T-cell entry into the CNS.

Natalizumab is used for:

Treating certain forms of multiple sclerosis (MS) by slowing the worsening of physical disability and reducing the number of symptom flare-ups. It is usually given to patients who cannot use other MS treatments or for whom other MS treatments have not worked well enough. Natalizumab is also used to treat moderate to severe Crohn disease in certain patients.

Adverse effects include fatigue, liverdysfunction, infections, hypersensitivity reactions, and infusion-related reactions.

IMPORTANT WARNING:

Receiving natalizumab injection may increase the risk of **progressive multifocal leukoencephalopathy (PML)**a rare infection of the brain that cannot be treated, prevented, or cured and that usually causes death or severe disability.

Symptomatic Therapies

Fatigue

There are nonpharmacological **(Appropriate rest: activity ratio,Regular aerobic exercise, Stress management techniques)** and pharmacologic strategiesfor decreasing the impact of fatigue on the lifestyle of MSpatients. Pharmacologic management of fatiguemay include **amantadine** or **stimulants**; however, evidence ofefficacy from randomized controlled trials is limited.

Spasticity

First line therapy is **Baclofen** 5 mg orally three times daily, or **Tizanidine**Centrally-acting α2-receptor agonist. Second-line is **Dantrolene** which is a direct inhibitor of muscle contraction by decreasing the release of calcium from skeletal muscle.
Botulinum toxin whichprevents release of acetylcholine in the neuromuscular junction are used for Focal spasticity.

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