MEDICINE

432 Team

48

CNS Demyelinating Diseases

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

Not given

CNS Demyelinating diseases

Classification of the Demyelinating diseases:

1- **Multiple sclerosis:**
   - A- Chronic relapsing encephalomyelopathic form.
   - B- Acute multiple sclerosis.
   - C- Diffuse cerebral sclerosis (encephalitis periaxalis diffusa) of Schilder and concentric sclerosis of Balo.
2- **Neuromyelitis optica (NMO), also known as Devic's disease.**
3- **Acute and sub-acute necrotizing hemorrhagic encephalitis.**
   - A- Acute encephalopathic form (hemorrhagic leukoencephalitis of Hurst).
   - B- Sub-acute necrotic myelopathy.
   - C- Acute brain purpura (acute pericapillary encephalorrhagia)

Some facts about demyelinating diseases

- Could be Inherited or acquired.
- **CNS:** multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica.
- **PNS:** acute inflammatory demyelinating polyneuropathy (Guillain Barre Syndrome), chronic inflammatory demyelinating polyneuropathy.

Multiple Sclerosis (MS):

Definition:

A chronic inflammatory disease of the CNS (primarily the white matter) characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination and axonal degeneration (Damage to the myelin).

Facts about MS:

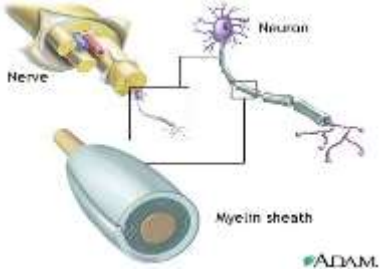
- Chronic autoimmune disease.
- Progressive disease.
- Involves Immune System & Neurological System.
- Multifocal areas of demyelination.
- Disrupts ability of the nerve to conduct electrical impulses.
- Leads to symptoms.

Note(s):

*Recent studies showed that MS can also affect the **grey matter** of the CNS.*

Myelin

- A lipid dense layer that surrounds the axon of the neuron.
- Insulates the axon and allows continuous propagation of the electrical impulse.
- Schwan cells → peripheral nervous system (PNS) neurons.
- Oligodendrocytes → central nervous system (CNS).



Types of MS:

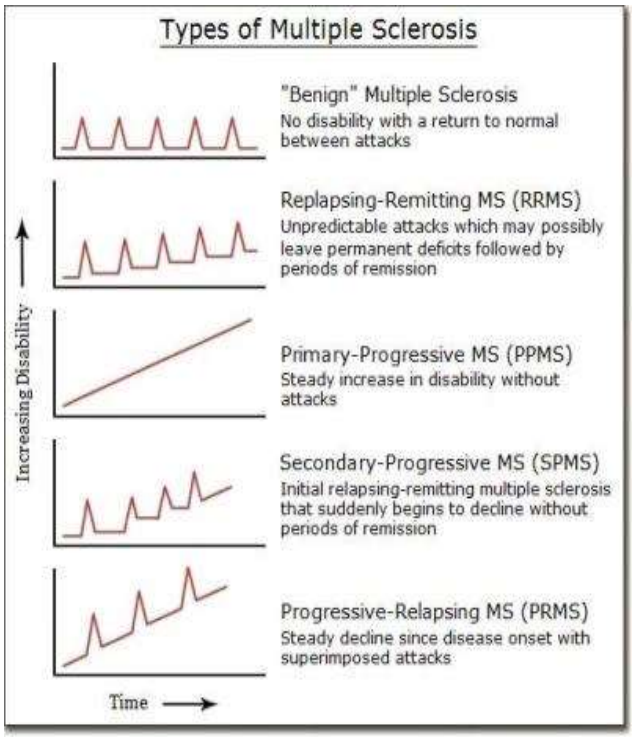
A. **Relapsing remitting (RRMS) 85%**
   a) Attacks followed by partial or complete recovery "back to baseline".
   b) Symptoms may be inactive for months or years.
   c) Most RRMS goes on to become SPMS.

B. **Primary progressive (PPMS) 10%**

C. **Progressive relapsing (PRMS) 5%**

D. **secondary progressive (SPMS)**
   a) Occasional relapses but symptoms remain constant, no remission.
   b) Progressive disability late in disease course.
   c) 50% of RRMS will progress to SPMS.

E. **Benign MS**



MS Variants:

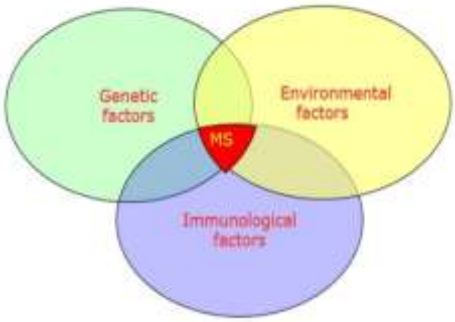
A- **Devic's = neuromyelitis optica (NMO):** severe optic neuritis and extensive transverse myelitis (explained in page 6) extending >3 vertebral segments (NMO antibody +ve). It was considered a variant but is now recognized as a distinct entity.
B- **Clinically isolated syndrome (CIS):** single MS-like episode, which may progress to MS.
C- **Tumefactive MS:** solitary lesion >2 cm mimicking neoplasms on MRI.
D- **Fulminant MS (Marburg):** rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis.
E- **Acute disseminated encephalomyelitis (ADEM):** monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination.
F- **Diffuse cerebral sclerosis of Schilder.**
G- **Balo concentric sclerosis (BCS).**

Epidemiology:

- Age onset: 20 – 50 years old
- Women are 2-3 times more likely to develop MS.
- 500,000 cases in US.
- Mean age of presentation is 30 years (Most common in young adults).
- Over 2.5 million people around the world.
- 1st degree relatives are at 15-33 times greater risk (Father, mother, sister, etc.)

- More common in North America and Europe and rare in tropics (sun exposure)

Etiology:



A- Genetics

- HLA DRB2 *1503 allele 2x risk factor
- IL 2 receptor
- IL 7 receptor
- 50 new candidates' genes each with low risk factors.

B- Environmental

❖ **Associated with viruses such as EBV** (cause infectious mononucleosis)

- 99% of MS patients have EBV titers.
- 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.

❖ **More common in regions with less sun exposure and lower stores of vitamin D (vitamin D deficiency).**

- Less sun exposure such as Europe, Canada, US, New Zealand, SE Australia.
- Vitamin D3 receptor important in immune function.
- Present on T regulator cells.

❖ **Age of migration:**

- If you migrate from high prevalence area to low prevalence area before age of 15, you will acquire the risk of your new home.
- But after age of 15, you still have the same risk of your previous home.

❖ **Smoking:**

- A higher risk if MS in ever-smoker that in never-smokers.
- Smoking may also be a risk factor for disease progression.

❖ **Dietary Salts:** "its relation to MS still under research"

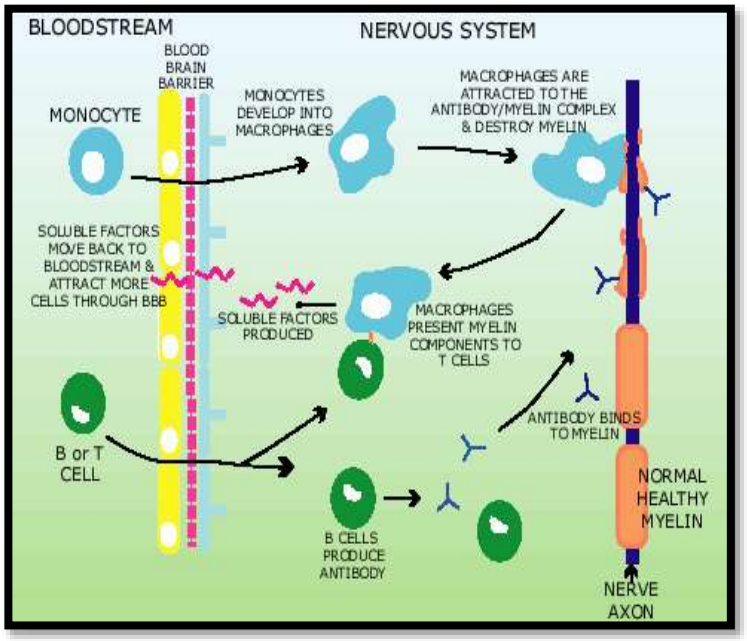
❖ **Obesity: ≤ 30**

- In adolescence or early adulthood is associated with increased risk of MS.
- Leptin increases the proliferation of auto-aggressive cells responsible for myelin damage and decrease regulatory cells.
- Obese patients usually have low Vitamin D due to lack of outdoor activities.

C- Immunological

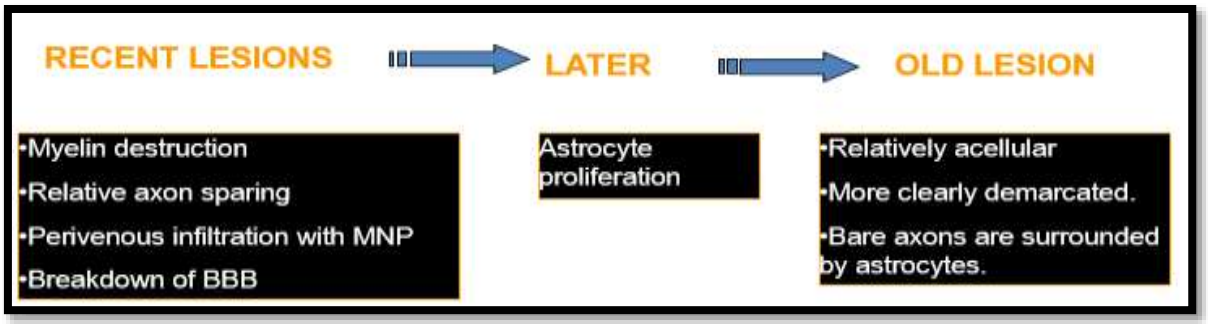
Pathophysiology: In MS, cells of the immune system attack myelin sheath of CNS and can cause permanent damage.

- Disease process consists of loss of myelin, disappearance of oligodendrocytes, and proliferation of astrocytes.
- Changes result in plaque formation (multi-focal zones of demyelination) with plaques scattered throughout the CNS (white matter). (Kumar: Plaques are perivenular –around veins– with a predilection for distinct CNS sites: optic nerves, the periventricular region, the brainstem and its cerebellar connections and the cervical cord (corticospinal tracts and posterior columns))



- Initially the myelin sheaths of the neurons in the brain and spinal cord are attacked, but the nerve fiber is not affected.
- Patient may complain of noticeable impairment of function.
- Myelin can regenerate, and symptoms disappear, resulting in a remission.
- Myelin can be replaced by glial scar tissue.
- Without myelin, nerve impulses slow down.
- With destruction of axons, impulses are totally blocked.
- Results in permanent loss of nerve function.

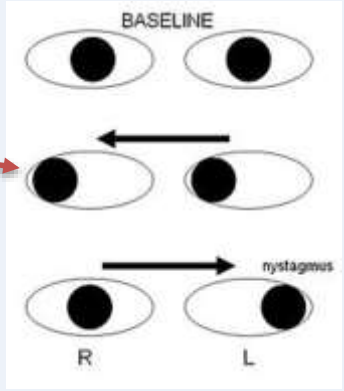
Disease Stage	Disease Stage	Main Clinical Outcome
Early	Inflammation and demyelination	Relapses
Late	Atrophy, axonal loss, and increasing tissue destruction (less Gd -defined inflammation, demyelination ongoing)	Disability



Clinical features: (Depend on anatomical sites of demyelination)

- **Transient sensory deficits:** (most common initial presentation)
  1) Decreased sensation or paresthesia (numbness)
- **Vision problems:**
  1) Optic neuritis: monocular visual loss (20%), central scotoma, pain on movement of eyes.
  2) Internuclear ophthalmoplegia (INO): (strongly suggest the diagnosis) is a specific gaze abnormality characterized by impaired horizontal eye movements with weak or no adduction of the affected eye, and abduction nystagmus of the contralateral eye. Can also cause diplopia.
- **Fatigue** (one of the most common complaints)
- **Motor symptoms:** weakness or spasticity (can cause difficulty walking) (monoparesis, paraparesis or quadriparesis).
- **Cerebellar involvement:** Balance & Coordination problems, walking problems, oscillopsia "visual disturbance of oscillation", dysarthria and ataxia.
- **Cerebral Involvement:** Memory loss, Emotional changes, Depression, Changes in cognitive function.
- **Inner ear involvement:** Vertigo, dizziness & Balance problems.
- **Neuropathic Pain:** hyperesthesia, trigeminal neuralgia.
- **Lhermitte's sign:** flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion.
- **Uhthoff's phenomenon**: neurological dysfunction, stereotyped, Less than 24 h, reversible and related to fluctuations in axonal conduction properties due to increasing body temperature "worsening of symptoms (classically optic neuritis) in heat".
- **Transverse myelitis:** a general term for spinal cord inflammation.

Internuclear ophthalmoplegia:



Affected eye

This phenomena happens when a person looks to the side opposite the affected eye

When you ask him to look to the side of affected eye, he will show a normal conjugate gaze. But when asking him to look to the opposite side of the affected eye, he will present with abnormal gaze:
1) No adduction of affected eye.
2) Abduction + Nystagmus of contralateral eye.

Diseases to rule out:

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

Relapse or Attack:

- Patient-reported symptoms or objectively observed signs
- Typical of CNS acute inflammatory demyelinating.
- At least 24 hrs.
- No fever or infection.

Diagnosis: Mainly by Hx and PEx

Clinically definite MS must meet criteria for:

- Dissemination in space: clinical evidence of involvement of 2 CNS sites OR of 1 lesion with reasonable historical evidence of another site being affected.
- Dissemination in time: Hx of at least 2 attacks.
  - A single episode of MS-like symptoms (clinically isolated syndrome [CIS]) will not meet these criteria.
  - But if MS is likely based on MRI, it still should be treated like MS.
  - Delaying treatment may be missing an important window of opportunity to delay the onset of irreversible disability.
  - Requires close monitoring over time to confirm diagnosis.

What Provides Evidence for Dissemination in Space?[2]

≥ 1 T2 lesion in at least two out of four areas of the CNS: periventricular, juxtacortical, infratentorial, or spinal cord

- Gadolinium enhancement of lesions is not required for DIS
- If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded and do not contribute to lesion count

What Provides MRI Evidence of Dissemination in Time?[3]

- A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI **OR**
- Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time

What is Positive CSF?

Oligoclonal IgG bands in CSF (and not serum) ***or*** elevated IgG index

2010 Revised McDonald Diagnostic Criteria for MS

Scenarios (Dx based on):	Clinical evidence		Need additional supporting evidence to make the dx	
	Attacks (represents dissemination in time)	Lesions (represents dissemination in space)	**Dissemination in**	
			Time	Space
Clinical evidence alone	2 or more attacks	2 or more lesions **OR** 1 lesion with historical evidence of a prior attack	None needed	None needed
Clinical evidence for time + clinical and MRI evidence for space	2 or more attacks	1 lesion	None needed	≥ 1 T2 MRI lesion in at least two MS typical CNS regions **OR** Await further clinical attack implicating a different CNS site
Clinical evidence for space + clinical and MRI evidence for time	1 attack	2 or more lesions	A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing **OR** Simultaneous asymptomatic contrast-enhancing and non-enhancing MRI lesions at any time **OR** Await a second clinical attack	None needed
Clinical and MRI evidence for both time and space	1 attack	1 lesion	A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing **OR** Simultaneous asymptomatic contrast-enhancing and non-enhancing MRI lesions at any time **OR** Await a second clinical attack	≥ 1 T2 MRI lesion in at least two MS typical CNS regions **OR** Await further clinical attack implicating a different CNS site
Only MRI and/or CSF evidence	None	None	1 year of disease progression	**At least 2 out of following 3:** **1)** ≥ 1 T2 MRI lesion in at least two MS typical CNS regions **2)** ≥ 2 T2 MRI lesions in spinal cord **3)** +ve CSF

2005 Revised McDonald Diagnostic Criteria for MS

Criteria for Dissemination in Space:

- At least 3 of the following:
  - ≥1 Gd-enhancing brain or spinal cord lesion or ≥9 T2 hyperintense brain and/or spinal cord lesions of ≥3 mm in size if none of the lesions are Gd-enhancing
  - ≥1 brain infratentorial lesion or spinal cord lesion ≥3 mm in size
  - ≥1 juxtacortical lesion ≥3 mm in size
  - ≥3 periventricular lesions ≥3 mm in size

Example of dissemination in space & time:

Animation showing dissemination of multiple sclerosis lesions in time and space as demonstrated by monthly MRI studies along a year: http://upload.wikimedia.org/wikipedia/commons/6/6c/Monthly_multiple_sclerosis_anim_cropped_no_text.gif
Gd: gadolinium

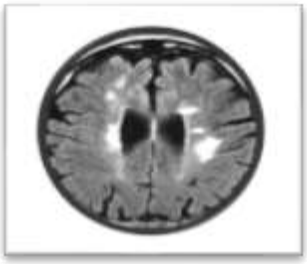
Criteria for Dissemination in Time:

- At least 1 of the following
  - A 2nd clinical episode
  - A Gd-enhancing lesion detected ≥3 months after onset of initial clinical event
    - Located at a site different from the one corresponding to the initial event
  - A new T2 lesion detected any time after a reference scan that was performed at least 30 days after the onset of an initial clinical event
- Thus, it is not always necessary to wait for 2 attacks to diagnose MS. A first attack plus changes on MRI may be enough

Investigation:

MRI: is both the best initial test and the most accurate test.

- Demyelinating plaques appear as hyper-intense lesions (bright spots) on T2 weighted MRI, with active lesions showing enhancement with gadolinium (contrast agent).
- Typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord.
- Dawson's fingers: periventricular lesions extending into corpus callosum.
- Radiologically isolated syndrome (RIS): an MRI findings suggestive of multiple sclerosis (MS) in asymptomatic ("clinically silent") patients.
- When a young female presents with trigeminal neuralgia do **MRI** to rule out tumor and MS.
- Notice the oval high signal lesion **around the ventricles** + **dawson's fingers.**



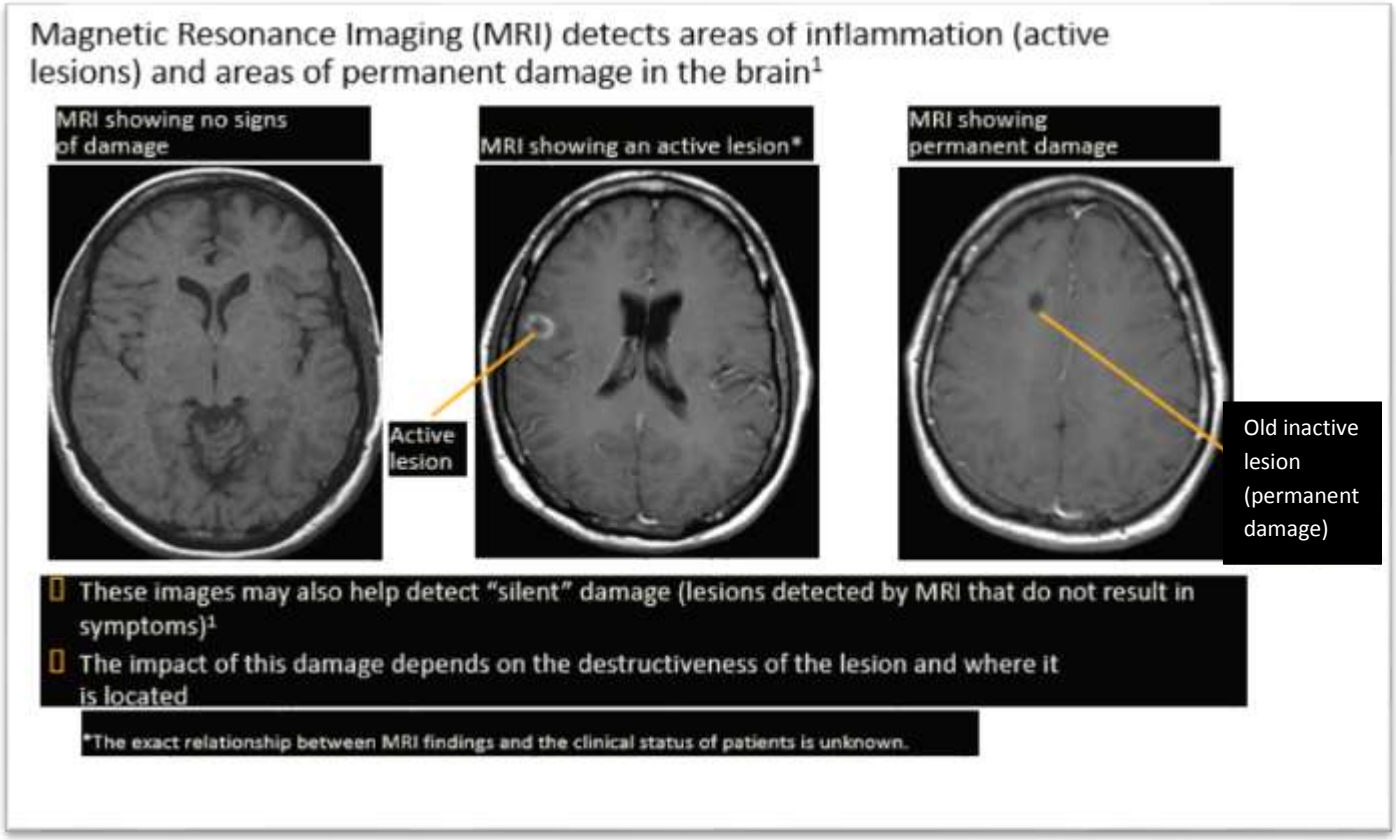
Lumber puncture (CSF):

- Oligoclonal bands are found in 90%, increased IgG concentration.
  - * Sensitive but not specific: other causes of CNS inflammation can yield similar findings
- Lymphocytic pleocytosis is rarely >50/mm3.
- Protein levels rarely exceed 100 mg/dL (mild elevation).
- Elevated myelin basic protein is not pathognomonic for MS.

Evoked potentials: not diagnostic test; only support the clinical suspicion

- Visual evoked potential: in optic nerve the latency of the large positive wave is delayed. The amplitude may also be reduced.
  - Provides evidence of a lesion associated with visual pathways.
  - Positive if shows delayed but well-preserved wave forms.
  - Can help establish dissemination in space.
- Somatosensory evoked response (SSEP): may detect central sensory pathway lesion.
- Brain stem auditory evoked potential (BAEP): may detect brain stem lesion.

How is MS monitored?



Treatment: An effective therapy administered early in the disease course can impact all of these goals.

Therapeutic Goals in MS:

- Prevent disability.
- Prevent relapses.
- Relieve symptoms.
- Maintain well-being.
- Optimize quality of life.

A- Acute treatment: high dose IV corticosteroid (methylprednisolone); if poor response to corticosteroids may consider plasma exchange.

B- Disease modifying therapy (DMT): to prevent replaces

First line: interferon-β, glatiramer acetate.

- Best first choice of prevention of relapse.

Second line: natalizumab, mitoxantrone.

- Generally indicated for persons with sub-optimal response to first-line agents.
- Require intravenous infusion.
- Associated with life-threatening adverse events.

Oral agents: fingolimod, fumarate, teriflunomide, laquinimod, cladribine.

Nonspecific immunosuppressive therapy: cyclophosphamide, azathioprine

- Should be reserved for rapidly progressive disease, because toxic side effects are too many.

C- Symptomatic treatment:

- Spasticity: baclofen, tizanidine, dantrolene
- Bladder dysfunction: oxybutynin
- Neuropathic pain: TCA, carbamazepine, gabapentin
- Fatigue: amantadine, modafinil, methylphenidate
- Depression: antidepressant, lithium
- Constipation: high fibers intake, stool softener, laxatives
- Sexual dysfunction: sildenafil, tadenafil, vardenafil

Prognosis:

- 50% of patients will require a cane 28 years after disease onset.
- 20% will require a wheelchair 44 years after disease onset.

Good prognostic indicators:

- Females
- Young
- PRMS
- Presenting with optic neuritis
- Low burden of disease on initial MRI
- Low rate of relapse early in disease

PPMS: poor prognosis, higher rates of disability, poor response to therapy

Clinically Isolated Syndromes (CIS):

- Is used to describe the first episode of neurological symptoms caused by inflammation or demyelination of nerve tissue.
- Can be monofocal in which symptoms present at a single site in the central nervous system, or multifocal, in which multiple sites exhibit symptoms.
- Individuals who experience a CIS may or may not go on to develop MS.

A- Optic Neuritis: Is inflammation of the optic nerve. It is also called papillitis (when the head of the optic nerve is involved) and retrobulbar neuritis (when the posterior part of the nerve is involved).

- Risk factors for developing MS (60-75%):
  - History of minor neurologic symptoms
  - Unilateral optic neuritis
  - Brain MRI lesions
  - Abnormal CSF
  - Abnormal VERs

B- Transverse Myelitis: Is an inflammation of the spinal cord, which often targets myelin sheath. May result in injury across the spinal cord, affecting sensation below the injury.

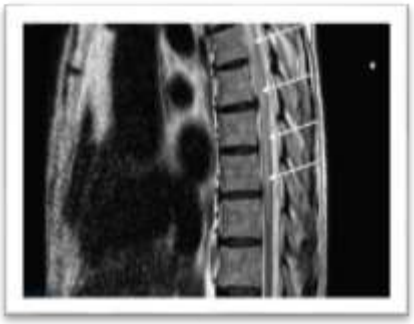
- Could be caused by MS, NMO, infections, and connective tissue diseases.
- Autonomic involvement: Sexual dysfunction, impotence and/or constipation.
- Upper motor neuron injury of spinal cord: Bowel/bladder dysfunction.
- Unilateral or bilateral.
- Sensory level.
- CSF: increased WBC count and proteins

  - Risk factors for developing MS:
    - Incomplete transverse myelitis
    - Asymmetric motor or sensory findings
    - Brain MRI lesions
    - Abnormal CSF
    - Abnormal VER and SSEPs

Others (Brainstem, Cerebellum)

Other demyelinating diseases

1- Neuromyelitis optica (NMO):



- More common in females (9:1).
- Mean age is 10 years later than MS.
- More common in Asian and African population.
- Affects mainly the optic nerve and the spinal cord.
- More severe attacks than in MS.
- Pathology:
  a. Astrocytopathy.
  b. Targets aquaporine 4 (a water channel) rich areas.
  c. Vasculocentric deposition of immunoglobulin and complement.
- Treatment:
  a. Acute relapses: steroids or plasma exchange.
  b. Relapses prevention: chronic immunosuppression with azathioprine, mycophenolate mefetil, cyclophosphamide.

2- Acute disseminated encephalomyelitis (ADEM):

- CNS inflammatory demyelination disease.
- Frequency preceded by vaccination or infection.
- More common in children.
- Usually a monophasic illness (no relapses).
- Pathology:
    a. Wide spread white and grey matter perivenous –around veins– "sleeves" of inflammation and demyelination.
    b. Axons are rarely spared.
- Symptoms:
    a. Encephalophathy (lethargy, stupor and coma).
    b. Multifocal neurological deficit (visual symptoms, ataxia, TM)
    c. May fluctuate over a 3 months period.
- Treatment:
    a. Steroids, plasma exchange and IV immunoglobulins.

SUMMARY

1. Pathologic hallmark is focal demyelinated plaques.
2. Variable degrees of inflammation, gliosis and neurodegeneration.
3. Recurrent relapses lead to permanent myelin damage and oligodendrocytes loss.

MS	NMO	ADEM
- Can affect any part of the CNS. - Disease of young adults. - Common in female. - RR course is the most common initial course.	- Affects mainly the optic nerve and spinal cord. - Older age group. - Common in females. - Relapsing course, progression is rare.	- Monophasic - Common in children. - Follows infection or vaccination. - Encephalopathy is a prerequisite for the diagnosis in children.

Approach to Multiple Sclerosis

Multiple Sclerosis

DIFFERENTIAL DIAGNOSIS OF PTOSIS

INFLAMMATORY DISEASES: Devic's neuromyelitis (neuromyelitis optica, combination of optic neuritis and cervical myelopathy), acute disseminated encephalomyelitis, SLE, PAN, Sjogren's, Behcet's disease, granulomatosis angiitis, paraneoplastic encephalomyelopathies
INFECTIONS: Lyme neuroborreliosis, neurosyphilis, HIV, HTLV 1, PML (JC virus)
GRANULOMATOUSDISEASES: sarcoidosis, Wegener granulomatosis, lymphomatoid granulomatosis
DISEASES OF MYELIN: adult metachromatic leukodystrophy, adreno-myeloleukodystrophy
OTHERS: vitamin B12 deficiency, Arnold Chiari malformation, spinocerebellar disorders

CLINICAL FEATURES

CRANIAL NERVES: optic neuritis (afferent pupillary defect), diplopia (internuclear ophthalmoplegia, especially if bilateral), trigeminal neuralgia, other cranial nerves.
SENSORY: (most common) paresthesia, dysesthesia and hyperesthesia. Pain syndromes include trigeminal neuralgia, Lhermitte's sign (lightning bolt radiating down neck with flexion), dysesthetic pain, back pain, visceral pain, and painful tonic spasms. May be migratory (contralateral, ascending). Other sensory changes include useless hand syndrome (loss of discriminatory function and proprioception), ''cold water'' trickling feeling along limb, and pseudoathetosis (loss of sensory feedback from arm causing involuntary writhing movements of fingers and wrist when eyes closed)
TONE: spasms spells (maybe painful), spontaneous clonus
MOTOR: weakness, spasticity, and hyperreflexia. Upper motor neuron weakness in lower extremities characteristic of multiple sclerosis
AUTONOMIC: bladder,bowel,anderectiledysfunction
CEREBELLAR: loss of balance, action tremor, slurred speech, and incoordination
COGNITIVE: inattention, slowed information processing, memory loss, and difficulties with abstract concepts and complex reasoning
FATIGUE, DEPRESSION

INVESTIGATIONS

BASIC:

- **LABS:** CBCD, lytes, urea, Cr, Ca, Mg, PO4, CK, quantitative Ig, ANA, ENA
- **IMAGING:** MRI head/spine (sens 90%)
- **LUMBAR PUNCTURE:** with CSF IgG index and oligoclonal bands (mild lymphocytosis <50/mm3, mild ↑ protein with ≥2 oligoclonal bands)

SPECIAL:

- **EVOKED POTENTIAL STUDIES**

MANAGEMENT

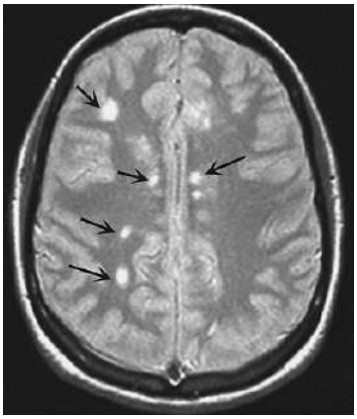
EXACERBATIONS: methylprednisolone 500 1000 mg IV daily _3 5 days. Plasma exchange
IMMUNOTHERAPY: **(ABCR)** drugs Avonex, Betaseron, Copaxone, Rebif. Natalizumab
SYMPTOM CONTROL: fatigue (amantadine 100 mg PO BID), spasticity (physiotherapy, baclofen, tizanidine, benzodiazepines), hyperreflexic bladder (fluid restriction, timed voiding, oxybutynin, propantheline, imipramine, intermittent catheterization)

Questions

1) A 30-year-old man complains of bilateral leg weakness and clumsiness of fine movements of the right hand. Five years previously he had an episode of transient visual loss. When the patient is asked to look to the right, the left eye does not move normally past the midline. Nystagmus is noted in the abducting eye. A more detailed history suggests the patient has had several episodes of gait difficulty that have resolved spontaneously. He appears to be stable between these episodes. He has no systemic symptoms of fever or weight loss. Which of the following is the most appropriate next test to order?

A. Lumbar puncture
B. MR scan with gadolinium infusion
C. Testing for oligoclonal bands in cerebrospinal fluid
D. Quantitative CSF IgG levels

2) A 26-year-old woman presents for follow-up of her multiple sclerosis. She has had two separate episodes of optic neuritis and has noticed stutteringly progressive weakness in her lower extremities. She has a mild neurogenic bladder. Her symptoms have been stable over the past 4 months. MRI scanning reveals several plaques in the periventricular white matter (MR scan shown here) and several other plaques in the brainstem. What is the best next step in her management?



A. Intravenous methylprednisolone
B. Oral cyclophosphamide
C. Interferon-beta
D. Oral cyclophosphamide

432 Medicine Team Leaders

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Answers:

1st Questions: B

2nd Questions: C