Demyelinating disease of the CNS:

1-multiple sclerosis

2-Acure disseminated encephalomyelitis

3-neuromyelitis potica (Device disease)

4-leukoencephalopaties

5-inherited disorder: Device disease

1-multiple sclerosis:

introduction	-**demyelinating disease of the CNS:** acquired **loss of myelin** with relative **preservation of axons** **-MS is the most common (inflammatory demyelination)** -MS fears diagnosis? 1-effect young healthy 2-unpredictable relapses 3-any neurological function can be affected 5-life long motor disability (wheelchair)
epidemiology	-MS starts in **young adulthood**, peak incidence **(20-30 years)**, **2F>M** -**environmental factor:** 1- more common in north latitudes + Scandinavian countries compared to southern Europe (sunlight and vit-D levels) 2-higher in white population (racial differences) 3-migration before 15 (new home), after 15 (childhood home) 4-childhood viral infection -**genetic factors:** 1-higer incidence in homozygous twins compared to dizygotic 2-increse incidence with specific human leukocyte antigen alleles
Clinical manifestation	-diagnosed: finding **multiple white matter lesions** separated in **spaces** and **time** ***Multiple distinct areas** of the CNS (rather than one area recurrently) * It is **not** a simple monophasic illness (multiple areas affected simultaneously but **not recurring**) **-Clinal feature:** ***Defined by the location:** 1-right occipital lesion > left homonymous hemianopia 2-right cervical cord lesion > ipsilateral (hemiparesis + lose of joint position sense) + contralateral (loss of pain + temperature sensation) ***Common clinical feature** 1-corticospinal tract signs (weakness + spasticity) 2-cerebellar (intention tremor + ataxia) 3-sensory (loss of vibration + loss proprioception +paresthesia) 4-bladder dysfunction 5-fatigue is a common complain 6-cognitive and behavior abnormalities (later stages) -almost **any neurological symptoms** can be produced in **MS** Another clinical feature 1-**Lhermitte`s sign: tingling** and **electrical shock** sensation down neck and spine into limbs while **flexing the neck**. 2-**Ugthoff`s sign**: worsening of symptoms with **heat.**

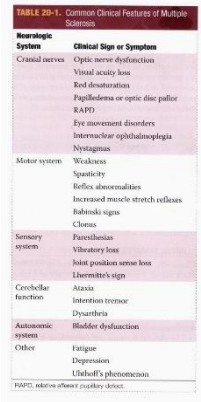


TABLE 20-1. Common Clinical Features of Multiple Sclerosis

Neurologic System	Clinical Sign or Symptom
Cranial nerves	Optic nerve dysfunction
	Visual acuity loss
	Red desaturation
	Papilledema or optic disc pallor
	RAPD
	Eye movement disorders
	Internuclear ophthalmoplegia
	Nystagmus
Motor system	Weakness
	Spasticity
	Reflex abnormalities
	Increased muscle stretch reflexes
	Babinski signs
	Clonus
Sensory system	Paresthesias
	Vibratory loss
	Joint position sense loss
	Lhermitte's sign
Cerebellar function	Ataxia
	Intention tremor
	Dysarthria
Autonomic system	Bladder dysfunction
Other	Fatigue
	Depression
	Uhthoff's phenomenon

RAPD, relative afferent pupillary defect.

<table>
<tr><th></th><th>Optic neuritis (ON)</th><th>Internuclear ophthalmoplegia (INO)</th><th>Transverse myelitis</th></tr>
<tr><td></td><td>-common initial presentation of MS
-inflammatory demyelination of optic nerve
-mostly retrobulbar optic neuritis and the optic disc appears normal (acute stage) but in severe cases optic disc may swollen with indistinct margins (papilledema of papillitis)

- ON characterized by:
1-painful loss of visual acuity in one eye worsens with heat (Uhthoff’s phenomenon)
2-visual loss range from:
a. mild blurriness + loss of color discrimination
b. severe episode of complete blindness
3-pulling or tugging pain with eye movement

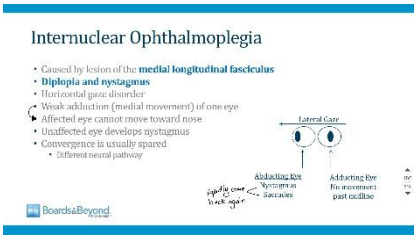
-On Px: loss of acuity and color vision

-past history of ON suggests the presence of:
1-red desaturation
2-optic disc pallor or atrophy
3-relative afferent pupillary defect (RAPD)</td><td>-caused by a lesion in the medial longitudinal fasciculus

-cases:
1-inability to adduct one eye when looking toward the opposite side (eye on the affected side)
1-nystagmus of the abducting eye (eye on the opposite side)

-Preserved convergence (adduction of both eyes when observing a near target)

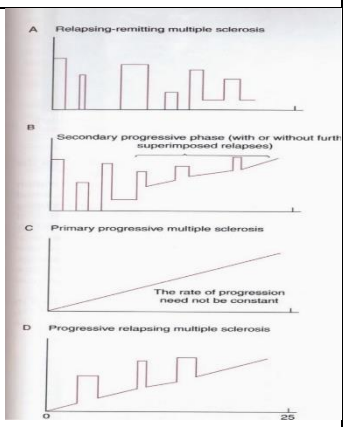
-characteristic findings in MS

  </td><td>-inflammatory demyelination of the spinal cord
-effect only particular tracts at the level of the lesion in a patch way rather than involving the whole spinal cord.

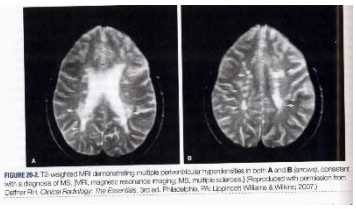
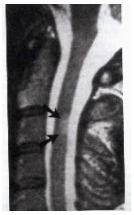
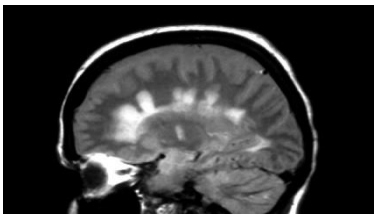
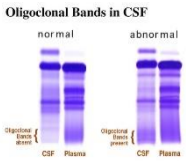
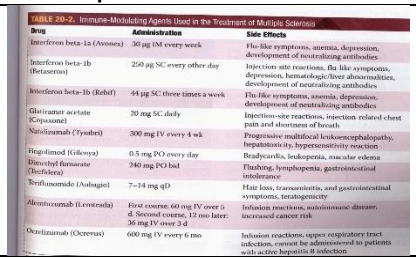
-characterized by:
1-unilateral or bilateral weakness or sensory loss below the lesion level
2-disrupted bowel and bladder function
3-hyperreflexia below the lesion and presence of Babinski sign.
4- patient may report a band of tingling or pain around the torso at the level of the lesion.</td></tr>
<tr><td>Clinical course and prognosis</td><td colspan="3">Clinical courses:
1-relapsing-remitting MS (RRMS)
-most patients begin with it
-characterized by discrete episodes of neurological dysfunction called relapses or flares
-followed by a period of partial or complete recovery where symptoms improve or resolve over weeks to months

2-secondary progressive MS (SPMS)
-over time, individuals with RRMS will transition to SPMS
-why? 1-incomplete recovery from relapse 2-baseline function deteriorates

3-progressive relapsing vs primary progressive
-relentlessly progressive (steadily worsening) course from the onset
1- with superimposed relapses (progressive relapsing) 2- without superimposed relapses (primary progressive)

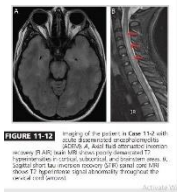
 
-Good prognosis:
1-young onset age 2-female sex 3-rapid emission of initial symptoms 4-mild relapses with no or residual deficits
5-presentation with sensory symptoms or ON rather than motor symptoms

-MS patients 60% (minimal disability), 20% (require walking aid remain ambulatory), 20% (sever disability need wheelchair)</td></tr>
<tr><td>Diagnostic evaluation</td><td colspan="3">1-clinical diagnosis (Hx, Px)
-Hx: - initially report single neurological episodes but may recall earlier symptoms indicating a prior lesion
- Inquire about past neurological symptoms like ON, transverse myelitis
-Px: signs of old optic nerve and other neurological lesions should be investigated</td></tr>
</table>

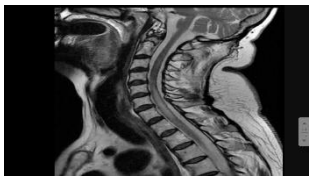
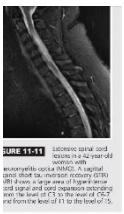
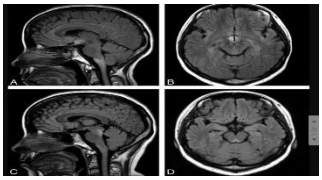
	2-MRI: -new MS lesion appears as a discrete **T2-hyperintense** (light color) area in the brain or spinal cord white matter -**FLAIR sequence** (Fluid-attenuated inversion recovery) also shows these lesions well -**acute lesion: not visible** on T1-weighted images (enhanced with **gadolinium**) -**old chronic lesion**: T**1-hypointense** (dark color) **black hole** appearance - **ovoid lesion** that favors certain areas like **periventricular white matter, juxtacortical regions**, **corpus callosum**, **cerebellar peduncles** **-Dawson`s fingers:** demyelination foci spreading perpendicular from the corpus callosum revile on sagittal images   
	3-CSF: **a-increase in oligoclonal bands (OCBs)** -90% of patient -indicate intrathecal production of **IgG antibodies** by plasma clone cells -can be detected in other neurological disorders **b-moderate pleocytosis and elevated proteins** **CSF index** calculation depends on **IgG** and **albumin** levels in CSF and serum (suggest intrathecal antibody production) 
	4-visual evoked potentials (VEP): **-**used to document evidence of **old ON** -increase the **latency** of the **p100 wave** on the affected side
Pathology	Histological appearance **1-Acute MS lesion:** a.sharply defied myelin loss with preserved axon b.perivascular inflammation (macrophages, lymphocytes and plasma cells) c.presence of reactive astrocytes **2-chronic MS lesion:** 1-axson loss 2-extensive glial proliferation
Treatment	**categories for treatment:** 1-acute therapies (relapses) 2-chronic therapies (treat underlying disease process) 3-symptomatic therapy (complication of the disease)
	1-acute MS relapses: -most commonly treated with **corticosteroids (IV methylprednisolone for 3 to 5 days +- oral prednisone taper)** -steroids **shorten the duration of acute relapses**, unclear role on long-term outcomes -IV steroids for **ON** patients **delayed** but **didn`t prevent** the eventual **onset of MS**
	2-Disease modifying agents: a-prevent relapses b-improving long-term outcome 

	Beta-1a and beta-1b interferon **-subcutaneous injection** -**Used** in (RRMS and some patient SPMS) **-SE:** (flu-like symptoms, depression, injection-site reaction) - **leukopenia** (check CBC) **-reversible transaminitis** (elevation of AST and ALT so check liver function test) -**neutralizing antibodies** (reduce drug effectiveness) -decrease: 1-rate of relapses 2-burden of MRI lesion 3-accumulated disability	**Glatiramer acetate** -**subcutaneous injection** -**polypeptide** formulation -used in **RRMS** When a patient no longer responds to interferons or glatiramer acetate or with progressive disease other drugs are used	**Natalizumab** -**monthly infusion** -monoclonal **antibody** against **alpha-4-integrin** (prevent lymphocytes and monocytes from crossing **BBB**) -**more effective than interferon** in preventing relapses and disease progression -risk of developing **progressive multifocal leukoencephalopathy (PML)** -higher risk in patients with **anti-JCV antibodies** (prior measure for antibodies is necessary) -**can't be used** with other immunomodulatory agents used to treat MS	**Fingolimod** -1st approved **oral** medication for MS -mixed **agonist/antagonist** of the **sphingosine-1p-receptor** -it **sequestrates** the autoreactive **T-cells** in lymph nodes **-SE:** 1-bradycardia (ECG monitor during first administration) 2-macular edema (optical coherence tomography (OTC))
	Dimethyl fumarate **-oral** **-SE:** 1-flushing 2-lymphopenia 3- gastrointestinal symptoms	**Teriflunomide** **-oral** -effective in reducing MS relapsing **-SE:** 1-hair loss 2-transaminitis 3-gastrointestinal symptoms **4-highly teratogenic**	**Alemtuzumab** -CD52 monoclonal **antibody** - used in **relapsing** forms of MS when **failing two other MS medication** **-SE:** 1-infusion reaction 2-precipitation of autoimmune disease 3-increase malignancy risk	**Ocrelizumab** -**IV** (dose 600mg every 6 months) -CD 20 monoclonal **antibody** -used in **RRMS and PPMS** -SE: 1-infusion reaction 2-URTI -contraindicated: **active hepatitis B infection**
	C- symptomatic complications: **1-Fatige:** the most disabling and persistent symptom of MS Tx:-Good sleep hygiene and gentile exercise -amantadine, aspirin, modafinil and amphetamines **2-spasticity:** TX: baclofen diazepam, tizanidine, or botulinum toxin infections **3-bladder disfunction:** TX: anticholinergic agent (for urgency), intermittent self-catheterization *It is important to address urinary problems to **prevent recurrent infections** which can **trigger MS relapses** or lead to chronic **renal disease** **4-Tremor and ataxia** (difficult TX)			

2-acute disseminated encephalomyelitis (ADEM):

definition	-**monophasic** illness leading to an area of demyelination within the CNS -commonly **followed viral infection or vaccination** -difficult to differentiate from the initial presentation of MS *diagnosis of MS should be done after the second episode*
diagnosis	**1-clinical:** -**Any** neurological symptom or sign can occur (depending on demyelination location) -**behavioral, and cognitive abnormalities and seizures** are often seen (uncommon in MS, until the late stage) **2-MRI:** -all areas of demyelination appear acute and may induced with gadolinium -lesions are **multiple, patchy, bilateral, and confluent** (blend together) contrasting with MS where lesions are more district and separated -common location: **posterior cerebral hemisphere white matter**  **3-CSF:** -**lymphocytic pleocytosis** (more elevation of WBC than in MS) and **elevated protein levels** but **OCB are rarely present**
Prognosis and treatment	-**favorable** outcome -Tx: **IV corticosteroids** (shorten the episodes and lessen the severity of the symptoms)

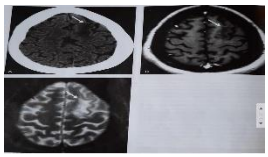
3-neuromyelitis Optica (Devic disease):

definition	-involves **transverse myelitis** and **optic neuritis** (simultaneously or with a delay of 1 or 2 years) -demyelination of the **brain** is relatively **absent or minor** -**pain and deficit** are more common and severe in NMO than in MS
diagnosis	**1-MRI:** -lesions that extend over **several segments** and involve an **individual (entire) level** of the cord (not patchy)    **2-CSF:** -**pleocytosis**, sometimes with **neutrophilic pleocytosis** (more common in NMO than MS) **3-antiboies to aquaporins-4 channels (NMO Ab)** -definitive diagnosis **4-myeline oligodendrocyte glycoprotein antibodies (MOG Ab)** -when (NMO AB) is negative
Prognosis and treatment	-**poor prognosis** (develop **paralysis** and **blindness** in the long term) -Tx: **1-acute treatment: steroids** but for patients who do not improve quickly we use **plasmapheresis** **2-prevent recurrence: chemotherapy agent** (azathioprine, mycophenolate mofetil, and rituximab) *it's important to differentiate NMO from MS because **MS Tx can worsen the case**)

3-leukoencephalopathies:

A-progressive multifocal leukoencephalopathy (PML)

-characterized by **dementia**, **focal cortical** dysfunction, and **cerebellar** abnormalities
-seen in **immunocompromised** patients (AIDS, leukemia, lymphoma) and patients treated with **natalizumab**
-causative agent **(JC virus)** leads to demyelination by infecting oligodendrocytes
-Brain MRI:
Multiple foci of white matter abnormalities (usually in the posterior region)
-CSF is normal
-Tx not been particularly effective



B-posterior reversible encephalopathy syndrome (PRES)

-**causes:**
1-sever and rapidly developing HTN
2-eclampsia
3-immunosuppressant medication (tacrolimus and cyclosporine)
-symptoms: acute **confusional** state and cortical **visual loss** (blindness with **preserved** pupillary reactivity)
-**MRI** (T2-weighted images): **posterior** white matter **hyperintensities**
-TX;
1-addressing and controlling the **underlying cause**
2-Ca++ channel blocker (may be effective)
-prognosis: not always reversible, can cause coma or death

C-central pontine myelinolysis

causes:
1-alcoholism
2- hyponatremia (over-rapid correction)
symptoms:
-present **acutely** over several days
-features of **pontine** and **medullary lesions (bulbar palsy, tetraparesis, eye movement disorder and coma)**
Tx:
-gradual correction of metabolic abnormalities
-vitamin supplement
Though Poor prognosis

5-inherited disorders:

-**genetic disorder** of **myelin** chemistry leads to its **abnormal formation** (**dysmyelination** rather than demyelination)

-also called **leukodystrophies**

-usually affects **infancy and childhood**

-may develop in **adults** with **(dementia, ataxia, spasticity, seizures, optic atrophy, and sometimes PNS involvement (polyneuropathy)**

-very rare, progressive, and fatal disorder

-no TX, but there is interest in the potential future treatments like enzyme replacement via bone marrow transplantation or gene therapy

Done by Maysana AL-yacoub