433 Teams

MEDICINE

20|MS and Demyelinating Diseases of CNS

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Objectives:

1 Describe the function and components of myelin.

2 Define demyelinating diseases and give examples.

3 Understand the pathology of multiple sclerosis.

4 Describe the various presentations and the course of multiple sclerosis.

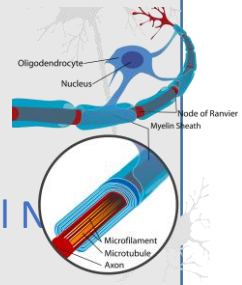
5 Understand that there are different treatment options for the disease.

6 Differentiate multiple sclerosis from other similar neurological diseases.

MS and Demyelinating Disease of CN

Myelin sheath:

- A lipid dense layer surrounds the axon of the neuron.
- **Function:** Insulation of the axon to allow continuous propagation of the electrical impulse.
- Myelin is synthesized by Schwann cells in the peripheral N
  And Oligodendrocytes in the central NS



CNS Demyelinating Diseases:
1. Multiple sclerosis
2. Acute disseminated encephalomyelitis (ADEM)
3. Neuromyelitis optica (NMO)

Multiple sclerosis

Definition	• An chronic autoimmune inflammatory demyelinating disorder of the CNS of uncertain etiology, likely autoimmune, • Destruction of myelin sheaths and axons • Progressive disease • Multifocal areas of demyelination • Disrupts ability of the nerve to conduct electrical impulses
Epidemiology:	• Peak age 15 to 45 – Mean presentation is 30 years old • Women : Men 2.5 : 1 (common scenario: 30-year-old female) • More people with MS where born in May and fewer were born in November. • First degree relatives are at 15-33 times greater risk. • More common in North America and Europe.

MS relapse or attack:

Patient reported symptoms and observed signs

Typical of CNS acute inflammatory demyelinating

lesion last at least 24 hrs –no fever no infection -

Transverse myelitis is an inflammation of the spinal cord, which often targets insulating material covering nerve cell fibers (myelin).

Other factors influencing MS	
1. **Vitamin D deficiency**	– Vitamin D3 receptor important in immune function – Present on T regulator cells
2. **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
3. **Genetic**	– HLA DRB2 *1503 allele 2x risk factor – IL 2 receptor – IL 7 receptor – 50 new candidates genes each with low risk factors 
4. **Smoking**	
5. **Obesity**	– Leptin increases the proliferation of auto-aggressive cells responsible for myelin damage.

Symptoms:

There are a variety of presenting symptoms in MS (depending on the affected site) that involves many areas of the CNS, and the inability to attribute them all to one localizing lesion is a characteristic feature of the disease. E.g. patient presents with difficulty in walking (frontal lobe) & coordination problems (cerebellum).

Common presentations:

Vision problems	Numbness (transient sensory deficit is the most common presentation)	Difficulty walking	Fatigue	Depression
Vertigo & dizziness	Sexual dysfunction	Coordination problems	Balance problems	Pain
Emotional changes	Bowel/bladder dysfunction	Spasticity		

Some details about the symptoms

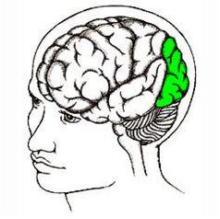
Motor:

- Mainly weakness and spasticity are due to pyramidal tract involvement.
- Weakness can progress to paraparesis, hemiparesis, or quadriparesis.
- Spasticity can impair patients ability to walk and maintain balance.

Visual disturbance:

INO is the inability to adduct one eye with nystagmus in the other eye

1. **Optic neuritis**
   - Monocular visual loss
   - Pain on movement of eyes
   - Central scotoma (black spot in center of vision)
   - Decreased pupillary reaction to light
2. **Internuclear ophthalmoplegia INO (Strongly suggest MS)**
   - A lesion in the medial longitudinal fasciculus → ipsilateral medial rectus palsy on attempted lateral gaze (adduction defect) and horizontal nystagmus of abducting eye (contralateral to side of lesion)

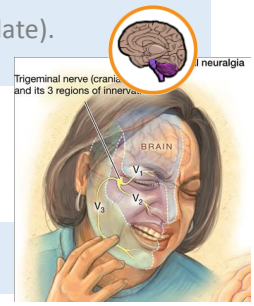


Cerebellum:

- Ataxia, Intension tremor, and Dysarthria, scillopsia (visual disturbance in which objects in the fields appears to oscillate).

Neuropathic Pain:

- Hyperesthesia (excessive physical sensitivity, especially of the skin)
- Trigeminal neuralgia



spinal cord

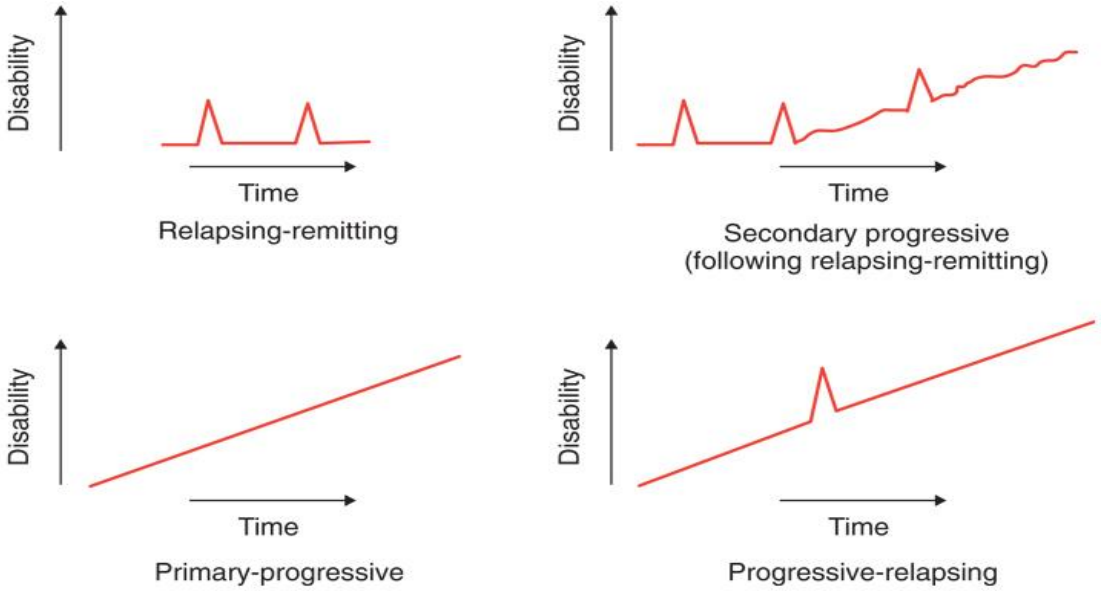
-Lhermitte's sign; electrical sensation that runs down the back and into the limbs by neck flexion

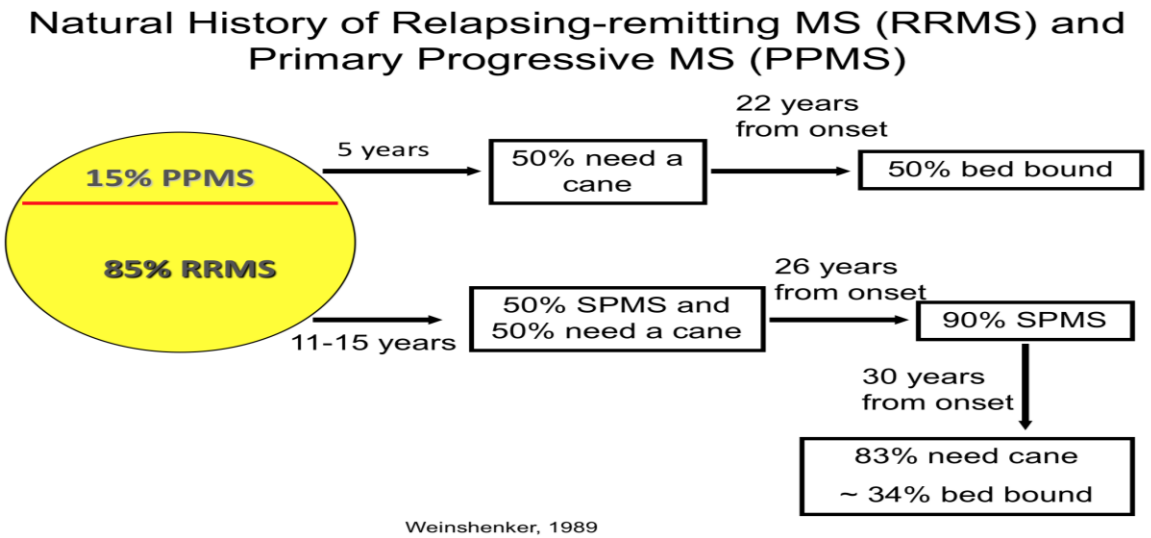
Pathophysioloigy

- Selective demyelination of CNS-Multifocal zones scattered throughout the white matter (of brain and spinal cord).
- Initially the myelin sheaths of the neurons in the brain and spinal cord are attacked, but the nerve fiber is not affected (CNS disease not PNS)
- 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
- Classical location of plaques is at the angels of lateral ventricles (periventricular)
- Commonly involves tracts are: pyramidal and cerebellar pathways, medial longitudinal fasiculus, optic nerve, posterior columns.

Variants (types) of MS:

Clinically silent	known as benign or stable
Relapsing/remitting (most common):	exacerbations followed by remissions
Secondary progressive:	gradual worsening of symptoms
Primary progressive:	steady progressive disease that appears later in life (after 40 yrs of age) + tends to have less visual and motor axonal invovment.





Uhthoff's Phenomenon?

Some people with multiple sclerosis (MS) can feel their symptoms worsen when they become overheated. When elevated body temperature impairs vision, it's called Uhthoff's phenomenon. Uhthoff's occurs because of damage to the optic nerve, which interferes with the transmission of signals between the eye and the brain. Symptoms include blurry or reduced vision

Summarization of the **Diagnostic MC Donald Criteria:**

1.Dissemination in space:	2. Dissemination in Time:	3. Rule out other explanations!
Objective evidence of neurological deficits localized to two separate parts of the CNS	Onset of neurological deficits separated by at least one month	• **Metabolic:** SCD (B12 def), Adrenomyeloneuropathy • **Connective Tissue Diseases:** Sjogren's, SLE • **Infectious:** HIV, HTLV1, Lyme disease, Syphillis • **Structural:** Chiari malformation, spinal cord compression • **Genetic:** ataxias, paraplegias, mitochondrial • **Neoplastic:** CNS lyphoma, paraneoplastic • **"MS variants":** ON, TM, ADEM, NMO • **Other:** Neurosarcoidosis, CNS vasculitis • **Psychiatric**
Finding a lesion in 3 or more of the following: • **9 T2 or 1** Gadolinum • 3 Periventricular • 1 Infratentorial • 1 Juxtacortical lesion		

MRI criteria for diagnosis of MS (Barkof criteria modified by Tintore et al):

Positive MS Diagnosis requires at least 3 of the 4 followings:

- One T2 GD-enhanced lesion Or 9 T2 lesions
- At least 1 infratentorial lesion
- At least 1 juxtacortical (subcortical) lesion
- At least 3 periventricular lesions

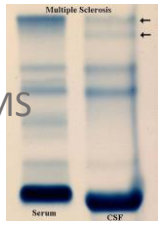
MRI is both best initial test and the most accurate test.

Lumber puncture:

Lumbar puncture shows CSF with mild elevation in protein and fewer than 50 to 100 WBCs.

- **Elevated IgG Index ≥0.7**: Increased CNS IgG synthesis, with normal serum IgG *consistent with MS*
- **Oligoclonal Bands**: Presence of ≥2 distinct bands in CSF is *consistent with* MS

Oligoclonal Bands is not specific for MS!



Management:

-Acute exacerbations:

1. high dose steroids is the best initial therapy
2. Plasma exchange

-Drugs that prevent relapse and progression:

- Glatiramer
- Beta interferon
- Fingolimod
- Fumarate
- Teriflunomide
- Laquinimod
- Cladribine

These two are the best first choice for prevention of relapse

Natalizumab worsening neurological deficit

Mitoxantrobe and Natalizumab are for aggressive MS

Other demyelinating diseases:

2- Neuromyelitis Optica

- also known as Devic's disease.
- Females to males 9:1
- Older group in comparusin to MS
- Common in Asian and African populations
- Affects the optic nerves and the spinal cord
- More sever attacks than MS
- Pathology : 1-targets aquaporin4 2-vasculocentric deposition of immunoglobulin and complement

Treatment:

Acute: Steriod or plasma exchange

Chronic: immunosuppression with azathioprine, rituximab, cyclophosphamide

IMPORTANT: **MS drugs worsen NMO**

3- Acute Disseminated Encephalomyelitis

- Acute disseminated encephalomyelitis
- CNS inflammatory demyelinating disease
- Frequently preceded by vaccination of infection
- Common in children
- A monophasic disease (no relapses)
- Pathophysiology: wide spread white and gray matter perivenous (sleeves) of inflammation and demyelination [Axons are relatively spared]

Treatment:

Acute: steroids, plasma exchange and intravenous immunoglobulins

ɔble 2. Differential features of relapsing NMO (opticospinal mu. tiple sclerosis) as compared with conventional multiple sclerosis.

- Preponderance in non-white populations
- Higher preponderance in females
- Higher age at onset
- Greater disability (higher EDSS scores)
- Longitudinally-extensive spinal cord lesions (≥ vertebral segments in length)
- Lower proportion of secondary progressive disease
- Disability determined by relapses rather than by progression of the disease
- Lower number of brain MRI lesions
- Brain MRI lesions usually do not meet criteria for MS
- CSF with greater pleocytosis and higher protein content
- CSF may have neutrophils and eosinophils
- CSF usually with negative oligoclonal bands and normal IgG inde

Table III

Comparison of Clinical Characteristics in ADEM and MS

Features	ADEM	MS
Antecedent events	Infections or vaccination	No recognized antecedent infections or vaccination
Clinical characteristics	Meningism, stupor, focal signs	Focal signs
Course	Non progressive, monophasic	Relapsing and remitting or progressive
Recovery	Recovery is rapid and often complete	Recovery variable, may be rapid and complete

	MS	NMO	ADEM
AGE	30	40	5-8
GENDER	females 1:1.5-2.5	females 1:9	Equal or males 1-1.3:1
ETHNICITY	NA and Europe	Asia	all
SYMPTOMS	CNS	CNS (ON AND TM)	CNS
COURSE	RR/progressive	Relapsing	Monophasic
TRANSVERSE MYELITIS	Yes <3 v. segments	Yes > 3 v. segment	Yes <3 v. segments
ACUTE TREATMENT	Streoids and PLEX	Streoids and PLEX	Streoids and PLEX
Disease Modifying treatment	Yes	Yes	No need

MCQs

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. On physical examination, there is hyperreflexia with Babinski sign and cerebellar dysmetria with poor finger-to-nose movement. 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. Quantitative CSF IgG levels
d. Testing for oligoclonal bands in cerebrospinal fluid
e. CT scan of the head with intravenous contrast

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 1 g daily for 3 days
b. Oral cyclophosphamide
c. Oral anticholinergics for the urinary incontinence and observation of the demyelinating process
d. Interferon-beta
e. Intravenous mitoxantrone every 3 months

1-B 2-D

The answers :

1-The answer is b. This patient's episode of transient blindness was likely a result of optic neuritis. This transient loss of vision in one eye occurs in 25% to 40% of multiple sclerosis patients (a similar presentation can occur in SLE, sarcoidosis, or syphilis). In addition, the patient gives a history of a relapsing-remitting process. There are abnormal signs of cerebellar and upper motor neuron disease. Signs and symptoms therefore suggest multiple lesions in space and time, making multiple sclerosis the most likely diagnosis. All patients with suspected multiple sclerosis should have MRI scanning of the brain. MRI is sensitive in defining demyelinating lesions in the brain and spinal cord. Disease-related changes are found in more than 95% of patients who have definite evidence for MS. Most patients do not need lumbar puncture or spinal fluid analysis for diagnosis, although 70% have elevated IgG levels, and myelin basic protein does appear in the CSF during exacerbations. When the diagnosis is in doubt, lumbar puncture is indicated. Pleocytosis of greater than 75 cells per microliter or finding polymorphonuclear leukocytes in the CSF makes the diagnosis of MS unlikely. In some cases, chronic infection such as with syphilis or HIV may be in the differential of MS. Quantitative IgG levels would notbe specific enough for diagnosis. Oligoclonal banding of CSF IgG is determined by agarose gel electrophoresis, but this is not the first test chosen. Two or more bands are found in 70% to 90% of patients with MS. CT scans are much less sensitive than MRIs in detecting demyelinating lesions, especially in the posterior fossa and cervical cord.

2- The answer is d. (Interferon-beta is standard therapy used to prevent progressive disease in relapsing-remitting multiple sclerosis. Both interferon-beta 1b and several forms of interferon-beta 1a are available and are similarly effective. Glatiramer acetate (Copaxone) is also approved for MS. While patients who receive any one of these treatments have 30% fewer exacerbationsand fewer new MRI lesions, the treatments do not cure the disease. Interferon-beta can cause side effects, particularly a flulike syndrome that usually resolves within several months. Acute exacerbations of MS are treated with high-dose methylprednisolone followed by tapering oral prednisone. This treatment improves symptoms during a relapse but does not appear to affect the long-term course of the disease. This patient, however, is not having an acute exacerbation of her disease. Steadily progressive MS, especially primary progressive disease, when the disease never remits but worsens inexorably, is a difficult management problem. Immunosuppressives such as cyclophosphamide and mitoxantrone are often tried. Such patients often progress to debility and mortality from urinary infection, aspiration pneumonia, or infected pressure ulcers. Simply providing this patient who has worsening disease with symptomatic treatment would be inappropriate.

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