Lecture 61

Editing file

Medicine Team

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Multiple sclerosis

Objectives:

- ★ Know the definition and types of CNS demyelinating diseases.
- ★ Know when to suspect multiple sclerosis in a patient presenting with neurological deficit.
- ★ Identify the similarities and differences between MS and other demyelinating diseases.

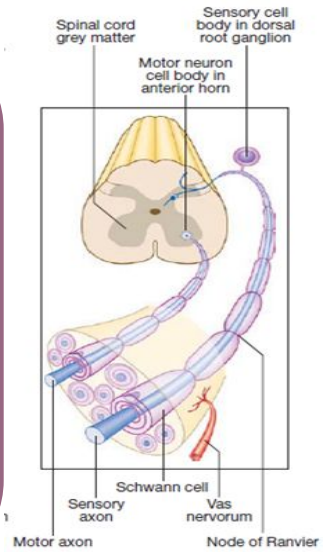
Color index:

Original text Females slides Males slides
Doctor's notes Textbook Important Golden notes Extra

Introduction

Myelin

- It's a **lipid dense layer** that surrounds the axon of the neurons.
- insulates the axons and **allows continuous propagation** of the electrical impulse.
- Myelin is essential for the speed of conduction and the level of myelination differs from a fiber to another depending on their function, for instance the fibers that conduct vibration and proprioception are usually more heavily myelinated than those that conduct pain and crude touch.
- **Myelin is produced by:**
  - **Schwann cells:** Peripheral nerves.
  - **Oligodendrocytes:** CNS.



Demyelinating Diseases

Acquired Demyelinating Diseases

- **How?** Damage of the myelin. **Depends on the site:**

1. **Central nervous system disease (CNS) :**
   - **Multiple sclerosis (MS) most common**
   - acute disseminated encephalomyelitis **(ADEM)**, usually in pediatrics
   - neuromyelitis optica spectrum disorder **(NMOSD)**. **it's common, and can mimic MS**

2. **Peripheral nervous system (PNS):**
   - **Acute inflammatory demyelinating polyneuropathy (Guillain Barre syndrome),** it's **very common,** and usually after infection, rarely after vaccination. typically presents as ascending weakness start from the legs, and develops in a few days
   - **Chronic** inflammatory demyelinating polyneuropathy (CIDP).

Note: It's very rare to see CNS and PNS involvement in the same person

Hereditary demyelinating disease

Rare disease and very specific, it is outside the scope of medical student

- Example:
  - Alexander disease
  - Canavan disease
  - Krabbe disease

Introduction to Multiple sclerosis (MS)

Definition

- Multiple sclerosis (MS) is a chronic autoimmune, **T-cell- mediated**, inflammatory disorder of the CNS.[1]
- MS is the most common chronic inflammatory, demyelinating and neurodegenerative disease of the CNS **in young adults** .
- The most common DISEASE causing disability is MS, and it is the second most common cause of disability after trauma in the young
- It is a heterogeneous, multifactorial, immune mediated disease that is **caused by complex gene environment interactions. but the exact etiology is still unknown**

Three factors are in effect:

1. **Population genetics**
2. **The interplay between genes and geographically determined physical environment.**
3. **Socioeconomic structure.**

◄ Risk factor

EBV Infection: most common

- History of infectious mononucleosis (EBV) is associated with higher risk of MS.
- Antibodies to **EBV were higher in people who developed MS** than in control samples (Studies showed that **100%** of MS patients are seropositive to EBV)

Vitamin D:

- Sunlight may be protective (ultraviolet radiation or vitamin D), some say it is the Vit D that is protective, other say even if you take supplemental Vit D it will not be protective, suggesting that the UV rays themselves are the protective factor.
- **Sun exposure & serum vitamin D are inversely related** to risk/prevalence of MS.
- Vitamin D levels are inversely related to MS disease activity.

Smoking: also increase the severity of MS

- A higher risk of MS in ever-smokers than in never-smokers, but stopping smoking is still decreases MS risk
- Smoking may also be a risk factor for disease progression

Obesity:

- In adolescence or early adulthood is associated with increased risk for MS, because obesity in youth increase the *number* of adeposite, while obesity later in life causes increase in the side only.
- **How?** leptin increases the proliferation of auto-aggressive cells responsible for myelin damage.

Genetics:

- Variations in some 60 different genes have been identified so far as conferring an increased risk of MS; 80% of these are genes relating to immune system function and regulation, including **HLA** and MHC polymorphisms.

1- The clinical course of MS is unpredictable: a high MR lesion load at initial presentation, high relapse rate, male gender and late presentation are poor prognostic features but not invariably so.

Epidemiology

◄ Epidemiology of MS

of patients experience their **initial** demyelinating **event** during **childhood**[1] **or adolescence**.

10%

0.1%

Is the **risk in the general population.**

The risk of familial **occurrence in first-degree relatives**[2]

2-4%

30%-50%

Monozygotic twins have a concordance rate[2]

- The life expectancy of patients **is reduced by 7–14 years.**
- MS is the main cause of death in more than 50% of patients. Mostly due to MS complications e.g. aspiration pneumonia or Neurogenic bladder (→ Infections → sepsis)
- Suicide is particularly substantially increased in MS (Depression is more common in MS pts).
- The prevalence of MS has increased since the 1950s, **especially in women.**
- **The female to male ratio of MS, has increased to ~3:1,** previously was 2:1
- **Why did the ratio change? This suggests a possible role of environmental risk factors:**

01 Occupation.

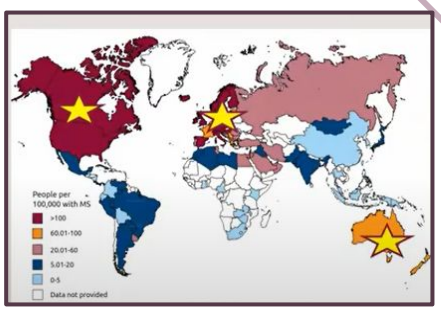
02 Increased cigarette smoking.

03 Obesity.

04 Birth control and childbirth.[3]

◄ Prevalence By Country

- MS is mainly found in individuals of European descent and is rare in Asian, black, Native Americans and Māori individuals.
- Prevalence varies greatly, being highest in North America and Europe and Australia (areas indicated in yellow stars) and lowest in Sub-Saharan Africa and East Asia. **more common in white women who live in colder climates.** Some theories as to why these certain areas have higher prevalence include:
  - Further away from the equator → Less sun exposure.
  - Higher socioeconomic status → better hygiene → less exposure to pathogen in childhood → more autoimmune diseases
- The most striking epidemiological characteristic is the apparent uneven distribution of the disease across the world

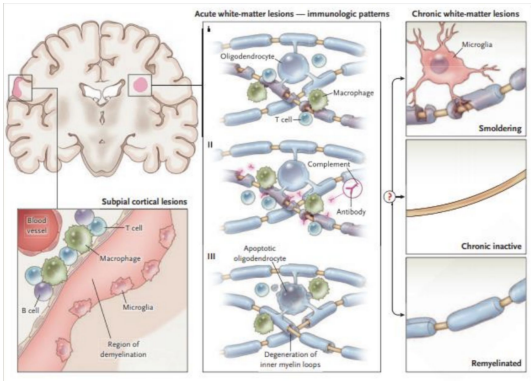


In KSA, the prevalence of MS is 60 per 100000

1- at five years or even younger
2- suggesting **genetic susceptibility**
3- The more women give childbirth the lower risk of MS (Just a theory) & there are conflicting data on the role of birth controls in MS

Pathogenesis of MS

◄ Pathophysiology



- These recognise myelin-derived antigens on the surface the microglia, and undergo clonal proliferation.
- The resulting inflammatory cascade releases cytokines and **initiates destruction** of the oligodendrocyte–myelin unit **by macrophages**

01

- Initial CNS inflammation in MS involves entry of **activated T lymphocytes** across the blood– barrier.
- **Characterized by breakdown of the blood—brain barrier (BBB),** which introduces inflammatory cells into the CSF **(1st change in MS)**

02

03

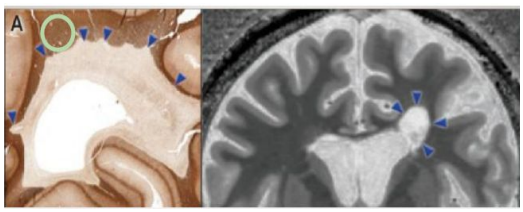
- Most easily recognized **in the white matter** as focal areas of demyelination, inflammation, and glial (astrocytes) reaction → **Plaques**
- the earliest stages of white-matter demyelination are heterogeneous and evolve over the course of months.
- Recurrent relapses lead to permanent myelin and axonal damage and oligodendrocytes loss. [1]

◄ Pathology

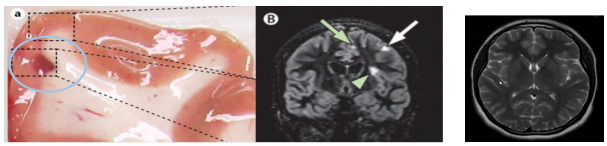
- **Plaques of demyelination**, 2–10 mm in size, are the **cardinal features**.
- Lesions are most easily recognized **in the white matter.** There has to be multiple lesions, if only one then it's not MS.
- Demyelination also involves gray matter. it's usually a white matter disease but can also involve gray matter.
- Cortical lesions are less inflammatory than their white-matter counterparts and have substantially less permeability of BBB.
- **Plaques occur anywhere in CNS white matter but most commonly sites:**

Optic nerves	Periventricular region	Corpus callosum	The brainstem and its cerebellar connections	Cervical cord (corticospinal tracts and posterior columns)

- **Right pic:** An MRI showing a (focal **plaque**) arrows [2]
- **Left pic:** the area in brown is normal white matter (normal staining dark brown) compare it to the areas of arrowheads (**light brown**) because it's devoid of myelin, no enough myelin to take the stain. In the middle (the white thing) is an area of axonal loss.



- **Right pic:** normal brain MRI
- **Left MRI pic:** MRI shows multiple plaques (white dots)
- This lesion involves both the gray and the white matter.



1- If only demyelination occurs, the oligodendrocytes can repair some the myelin that's lost but if axonal damage occurs they will develop SPMS (irreversible)
2- Remember in MRI, the **GREY color** is the **WHITE matter**, **WHITE color** is the **GREY matter**

Clinical Patterns of MS

◀ Clinically isolated syndrome (Pre-MS)

★ **CIS is the first clinical episode that is suggestive of MS**

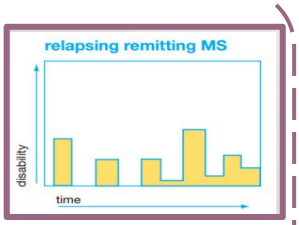
- **Why don't we classify them under MS?** Bc it's only one episode and not all of them develop MS (Many ppl in their 20s may get this attack and then live normal for the rest of their lives)
- A second clinical event indicative of a new lesion in a different anatomical location allows the diagnosis of MS to be confirmed. Alternatively, a repeat MRI brain scan at least 1 month later showing either a new lesion or a gadolinium enhancing lesion is sufficient to show dissemination in time and space and confirm the diagnosis even in the absence of new symptoms.
- **Characterized by:**

1. **Monophasic episode with symptoms and objective findings that reflect inflammatory demyelinating event in the CNS.**
2. **Acute or subacute (2-3wks), lasting for at least 24 hrs. (If less than 24hrs then it's NOT an MS attack)**
3. **Occurs in the absence of fever or infection.** (Why? Fever can precipitate **pseudo-relapse (Pseudo-exacerbations)** due to physiological slowing in the conduction across the axons that will lead to certain manifestations)
4. **Resembles a typical MS relapse (attack) but occurs in a patient not known to have MS** such as optic neuritis, weakness in one limb, symmetrical tingling.

Four main clinical pattern

1. **Relapsing-remitting (RRMS)**
2. **Secondary progressive SPMS**
3. **Primary progressive (PPMS)**
4. **Relapsing-progressive RPMS**

1 Relapsing-remitting MS (RRMS) (85–90%)

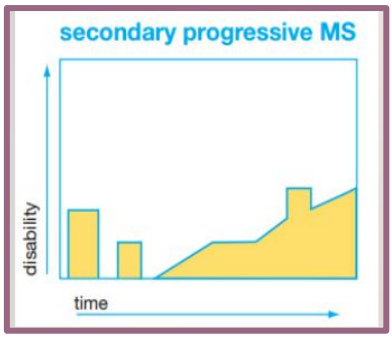


- **The typical and most common pattern of MS[1]**
- **RRMS has an onset between 20-35 years.**
- A purely RRMS is characterized by the **absence of worsening** neurological function outside of individual relapses
- About one third of RRMS patients may never develop a progressive disease course. About two thirds will develop SPMS.
- Symptoms occur in attacks (relapses) with a characteristic time course: **onset over days and typically recovery,** either partial or complete, over weeks.
- On average, patients have **one relapse per year** but occasionally many years depending on the activity of the disease.
- Patients may fully recover from a relapse, or may accumulate disability over time if they do not recover fully after relapses. However, the disability is constant through our the "remitting" phase.
- **the majority will eventually enter a secondary progressive phase,** The median time to conversion to SPMS is 21 years and median age at onset is 54.

1- Usually the patient is well and healthy, then they have a relapse, the relapse will cause disability and then they improve completely or sometimes there will be residual disability (sometimes the relapses resolve without treatment) (Recall if only one relapse (episode) occured then it's CIS NOT RRMS.) Acute relapses are caused by focal inflammation causing myelin damage and conduction block. Recovery follows as inflammation subsides and remyelination occurs. When damage is severe, secondary permanent axonal destruction occurs. Progressive axonal damage is the pathological basis of the progressive disability seen in progressive forms of MS.

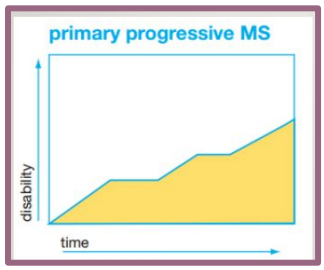
Clinical Patterns of MS *cont.*

2 Secondary progressive SPMS



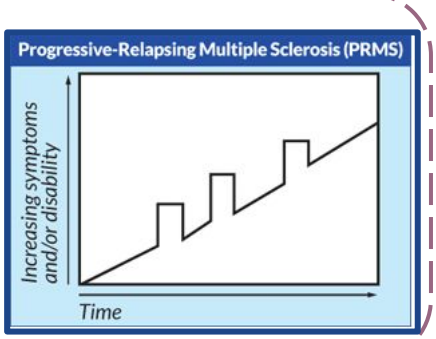
- **Worsening irreversible** neurological function, **preceded by RRMS** that cannot be explained purely by worsening associated with ongoing relapses (Some studies suggest that up to 60% of those with RRMS, develop SPMS eventually)
- This late stage of MS consists of **gradually worsening** disability progressing slowly over years.
- Periods of *plateau* may happen or no further disability is developing, but existing disabilities never get better.
- Some 75% of patients with relapsing–remitting MS will eventually evolve into a secondary progressive phase by 35 years after onset.
- Relapses may sometimes occur in this progressive phase (relapsing–progressive MS).
- Starting early treatment in RRMS can delay the onset of SPMS and hopefully even prevent it.

3 Primary progressive (PPMS) (10-15%)



- **Irreversibly continuous** worsening neurological function, **without preceding relapses**
- PPMS begins **at 40 years of age**
- Patients older at onset or with PPMS **have shorter survival.**
- It typically presents later and is associated with fewer inflammatory changes on MRI.
- Example: a 40 years old lady presenting with slowly progressing weakness in the lower limb. At first she was able to walk independently, then she depended on a cane to help her walk for months, afterwards she noticed that she needs a walker (bilateral support) to walk, which she kept using for a few months to years, and now she needs a wheelchair.

4 Relapsing–progressive MS (<5%).



- This is the least common form of MS.
- It is similar to PPMS but with occasional supra-added relapses on a background of progressive disability from the outset.

Clinical feature of MS

◄ MS clinical features symptoms

MS Symptoms

- Optic Neuritis
- Brain Stem Related Symptoms
- Cerebellum Related Symptoms
- Brain And Spinal Cord Symptoms
- Uhthoff's Phenomena
- Transverse Myelitis

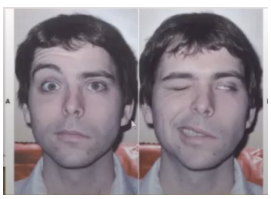
1 Optic Neuritis ★

- Optic neuritis is one of the most common causes of subacute visual loss. Symptoms may vary from a mild fogging of central vision with colour desaturation to a dense central scotoma, but very rarely complete blindness.
- Optic neuritis is not specific to MS, it can also happen with: IDAM, NMOSD, SLE, TB, Behcet.
- **The patient usually had :**
  - ★ **Blurred vision** usually in one eye. **NOT double vision**, seeing black dots, can't see clear in the dark.
  - ★ **Pain exacerbated by eyes movement**.
  - Reduced perception of **colors**. (red desaturation, the color will be pale in the affected eye)
  - Flashes of light on moving the eyes.
  - Enlarged blind spot. because the optic nerve is inflamed and swollen

Note: Blurred vision in one eye + Pain on eye movement = Almost always optic neuritis

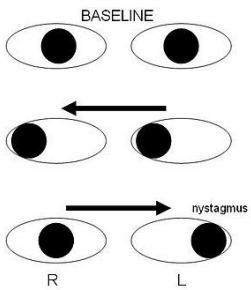
2 Brain Stem Related Symptoms

- Any area of the brain stem can be affected
- **Diplopia** if the nucleus of 3rd,4th and 6th nerves affected (the CNs themselves aren't affected, what's affected is their nucleus)
- **Trigeminal neuralgia:** is a severe pain that happen when one of the divisions of V CN distribution is touched and lasts for a few seconds, happens if involve trigeminal nerve (sensory).
- **Vertigo (spinning sensation) and nystagmus,** happens if there is a plaque in the cerebellum
- A typical picture is sudden diplopia, and vertigo with nystagmus, **but without tinnitus or deafness**.
  Bilateral internuclear ophthalmoplegia is pathognomonic of MS
- **Facial numbness and weakness:** if the facial nerve is involved. Note in pic (A); The pt has left sided facial weakness (LMN lesion not UMN), there's flattening of the frontalis muscle, the left eye is slightly bigger with mouth drooping. On the right pic, note that he couldn't close his left eye and his smile went to the right side.



★ **Internuclear ophthalmoplegia (INO):**

- Internuclear ophthalmoplegia (INO) is a specific gaze abnormality, characterized by impaired horizontal eye movement with weak adduction of the affected eye and abduction nystagmus of the contralateral eye. An INO is one of the most localizing brainstem syndromes, resulting from a lesion in the **medial longitudinal fasciculus** in the dorsomedial brainstem tegmentum of either the pons or the midbrain. The medial longitudinal fasciculus coordinates eye movements between the nuclei of the abducens and oculomotor nuclei to align lateral gaze. When attempting a left gaze, the right MLF sends fibers from the left abducens nucleus to the right oculomotor nucleus. This stimulates the right medial rectus, thus causing adduction of the right eye(right eye gazes left). If it is damaged, the right eye cannot adduct to the left when attempting a left gaze. The left eye (the functioning eye) will exhibit nystagmus. The opposite is true when attempting a right gaze.
- IF you see it in young patient almost always MS (If elderly, think stroke)



Clinical feature of MS *cont.*

◄ MS clinical features symptoms cont.

3 Cerebellum Related Symptoms

Oscillopsia	Dysarthria	Imbalance
(A visual disturbance in which the object in the visual field appears to oscillate due to nystagmus)	(Slurred speech)	(Wide-based gait)

4 Brain And Spinal Cord Symptoms

Weakness (monoparesis, paraparesis, quadriparesis).

Sensory loss/numbness/pain

Sphincter dysfunction. urine incontinence, neurogenic bladder and stool incontinence**,** commonly seen if there is spinal cord lesion

Lhermitte's sign: electric like sensation induced by neck flexion, very serious almost always indicate spinal cord lesion (any **cervical** cord lesion, not specific to MS)

Cognitive dysfunction: memory, concentration, processing speed. (Uncommon in MS,and usually does not happen with the first attack**)**

5 Transverse Myelitis

- A general term that indicates inflammation of the spinal cord with cord swelling and loss of function. Typically, one or two spinal segments are affected with part or all of the cord area at that level involved [1]
- Spinal cord related motor, sensory &/or autonomic dysfunction. transverse in the name means involve more than one area of the spinal cord
- Could be caused by MS, infections, connective tissue diseases, behcet
- **Sensory level,** means the is loss of sensation in a specific level eg. patient has complete loss of sensation from mid abdomen and below, this sign i**ndicate a spinal cord lesion**
- Unilateral or bilateral.

6 Uhthoff phenomenon

- **Temporary worsening of pre-existing symptoms with increases in body temperature**, e.g. aft exercise or a hot bath
- Neurological dysfunction. Stereotyped.
- Less than 24 h, Reversible if last for more than 24h think about relapse
- Related to fluctuations in axonal conduction properties due to increasing body temperature.
- It does not indicate that there's ongoing damage, it only indicates that there was an area of inflammation and demyelination, so the conduction is slower than normal ppl, and with exposure to high temperatures the conduction becomes even slower. However, it doesn't affect the course of disease or anything, it's just annoying to some pt

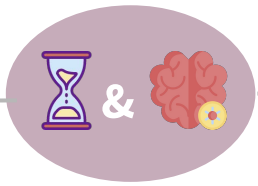
1- Clinically, a myelopathy evolves over days, and recovery (often partial) follows over weeks or months. MRI is sensitive and shows cord swelling and oedema with gadolinium enhancement at the affected level(s). Usually, images are also taken of the brain to look for evidence of demyelination.

Diagnosis of MS

To diagnosis of MS you must have both:

Dissemination in time

- History of **at least two attacks** separated by at least one month.
- **if 2 attacks occur in the same month it's counted as 1**
- **For example:** a pt presents with optic neuritis and it resolved, after 6mo he developed optic neuritis again. In this pt there's dissemination in time ONLY.



Dissemination in space

- Clinical evidence of involvement of **two CNS sites OR** of **one lesion with historical evidence of another site being affected.**
- **For example:** A pt presents with lesions in the optic nerve, cerebellum and cerebrum, but he didn't have any attacks later on (only one attack). In this pt there's dissemination in space ONLY. Dx? **CIS**

Example: patients comes to you with what seems to be a first episode of MS (optic neuritis) , after further history the patient describes to you an incidence that happened years ago where she had a right upper limb numbness, she was prescribed vitamin B12 by her family physician who said that it must be what is deficient. One month after taking supplementation the numbness disappeared. Does that mean the patient actually had a B12 deficiency? **Definitely NOT.** B12 deficiency will not be unilateral, and this spontaneous improvement is due to the remitting-relapsing nature of MS. This example shows **dissemination in space and time**

◀ Mc Donald's MS diagnostic criteria

Females Dr: Only know the name of the criteria, no need for any details

Attacks	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	none
≥2 clinical attacks	1(as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location)	none
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands

Notes:

- **The diagnosis of MS requires two or more attacks affecting different parts of the CNS, i.e. dissemination in time and space.**
- **However, the presence of multiple lesions on MRI (dissemination in space) or the demonstration of additional clinical attacks on MRI (by showing lesions of different densities (dissemination in time)) fulfills the criteria for MS despite the presence of one attack in the patient's history**

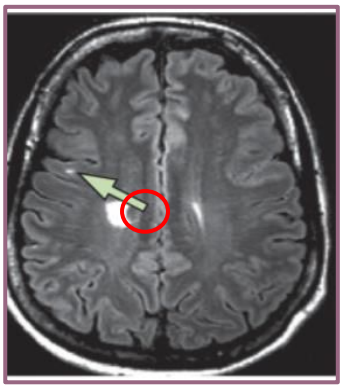
Diagnosis of MS *cont.*

01 History & Exam

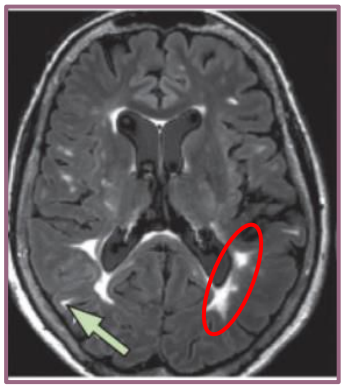
- When taking a history at the time of initial presentation, **it is essential to ask about previous episodes of neurological symptoms,** often years previously, that may represent episodes of unrecognized demyelination: for example, a severe episode of vertigo lasting weeks or loss of vision in one eye that gradually recovered.

02 Imaging: MRI of the brain and spinal cord

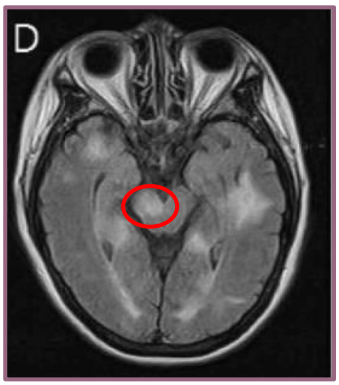
- MRI is both the **best initial test and the most accurate test.**
- MRI of brain and cord **is the definitive investigation**, as it demonstrates areas of demyelination with high sensitivity. Multiple scattered plaques are usually seen, demonstrating dissemination in space. Acute lesions show gadolinium enhancement for 6–8 weeks.
- **Plaques are rarely visible on CT.**
- MRI shows multiple plaques in different area. If you see multiple lesions this confirm dissemination in space. To confirm dissemination in time, check the enhancing (take up gadolinium) and nonenhancing lesions, enhancing are new, non-enhancing are old.



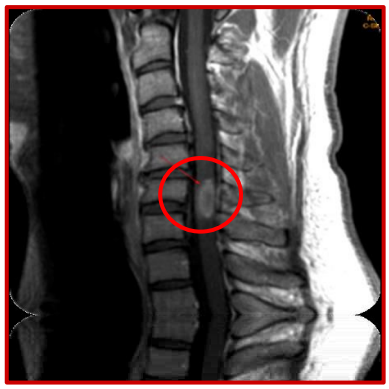
Green arrow: juxtacortical lesion (MS specific)
Red circle: non-specific



Red circle: periventricular lesion (MS specific)



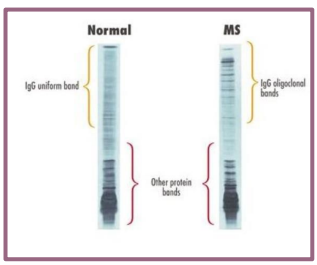
Red circle: brain stem lesion



Spinal lesions:
In MS: short and peripheral (visualized on axial images)
In NMO: long and central or circumferential.

03 Lumbar puncture and CSF analysis

- if you not sure about the diagnosis another way to confirm it is to do lumbar puncture and look for oligoclonal IgG bands, **BUT with presence of relapse and remitting symptoms.** Rarely used anymore
- The CSF may show a lymphocytic pleocytosis in the acute phase and unique (i.e. absent from the serum) oligoclonal bands of IgG in 70–90% of patients **but these are not specific for MS.**



Diagnosis of MS *cont.*

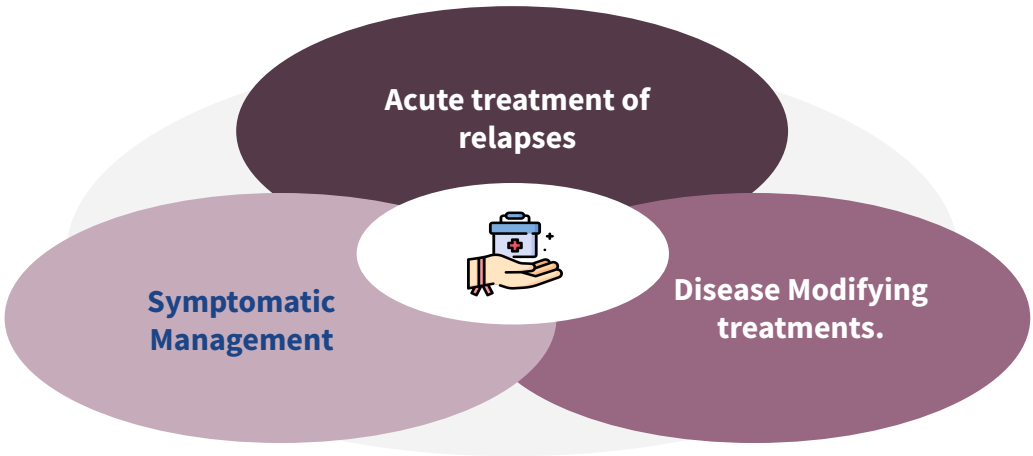
04 Evoked responses

- is a measurement of the electrical signal recorded at the scalp over the occipital cortex in response to light stimulus. can be used to confirm damage to visual pathway
- e.g. visual-evoked responses in optic nerve lesions, may demonstrate clinically silent lesions. However, since the advent of MRI, they are less used in diagnosis
- The limitations of this test for the diagnosis of MS is that many other neurologic diseases can give an abnormal result.

05 Blood tests

- are used to exclude other inflammatory disorders such as sarcoidosis or SLE, or other causes of paraparesis, e.g. adrenoleukodystrophy, HIV, human T-cell lymphotropic virus 1 (HTLV-1) and vitamin B12 deficiency.

Management of MS



◄ Acute treatment of relapses

1

- **Steroids (IV or orally Methylprednisone 1g/day)** for 3 -5 days. very high dose, They speed recovery but **do not influence long-term outcome.**
- **Most of the time relapses resolve on their own but steroids shorten the relapse episode.**
- Only given when relapse is significant or affecting their life (e.g. a pilot comes with blurred vision = needs immediate attention = use steroids)
- Prophylaxis to prevent glucocorticoid-induced osteoporosis should be considered in patients requiring multiple courses of glucocorticoids.

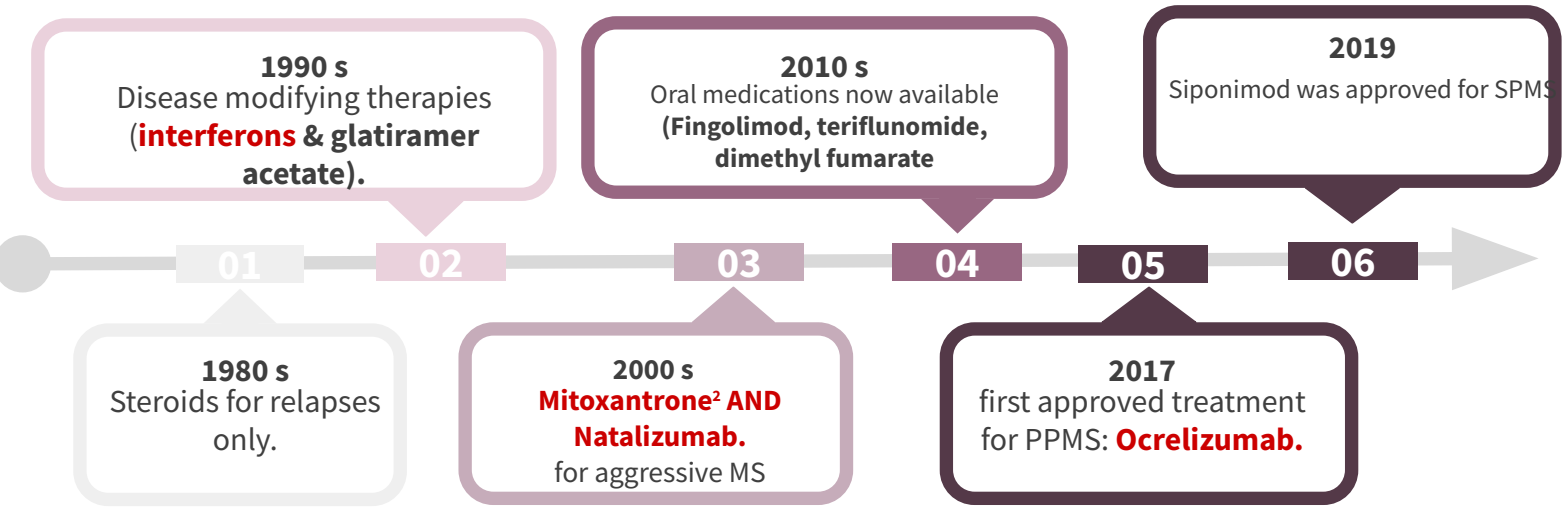
2

- **Plasma exchange** is used for those who don't respond to steroids

Management of MS *cont.*

◀ Disease modifying treatments[1]

1. **Reduction of number of relapses per year.**
2. **Reduction of number of new MRI lesions.**
3. **Prolongation of time to development of secondary progressive disease**
4. **Reduction of long term disability.**



Males Dr: You only need to know Natalizumab and interferon beta, no need to get into the details

Drug	Route	Side effect
Interferon beta	S/C, IM Alternate-day or weekly	In widespread use for reducing relapse rate
Glatiramer acetate	Alternate-day S/C	Similar efficacy to interferon-beta
Teriflunomide	Daily oral	May cause diarrhoea, alopecia, hepatotoxicity Highly teratogenic
Fingolimod	oral	Superior efficacy to interferon-beta in randomised trials Cardiac conduction defects, especially with first dose
Dimethyl fumarate	oral	May cause flushing and gastrointestinal disturbance Risk of Progressive multifocal leukoencephalopathy (PML)
Natalizumab[3]	i.v. monthly	Rarely, Progressive multifocal leukoencephalopathy **PML (fatal)** Hypersensitivity reactions
Alemtuzumab	i.v. once and repeat at 1 year	May precipitate autoimmune reactions, e.g. thyroid disease, ITP
Ocrelizumab	IV	

1- **Why do we even give lifelong disease modifying agents and make patients endure their side effects if patients stay healthy for long time?** Because after multiple episodes the oligodendrocytes will no longer be able to replace the myelin → exposed axon → future episodes will lead to loss of axons which is irreversible → SPMS (which we are trying to prevent)

2- Not used anymore because it causes leukemia

3-MCA blocks α-4 integrin vascular adhesion molecule. Prevents T cells entering CNS

Management of MS cont.

◀ Disease modifying treatments cont.

Management Depends on the patient: Age, comorbidities, severity of MS

- **Old management:**
  - First line: interferon . Second line: fingolimod 3rd line: ocrelizumab, rituximab
- **Now:**
  - Low efficacy DMT (eg: interferon, teriflunomide) vs high efficacy DMT (eg: natalizumab)

Examples:

- **Patient with depression:** do not give interferon as it worsens depression
- **Patient with cardiac condition:** do not give fingolimod - causes heart block and seriously arrhythmias
- **Patient came with only tingling, no residual disabilities after the attack, few lesions on MRI→** give low efficacy DMT (interferon or teriflunomide)
- **Patient with only numbness, but had a previous relapse in which she described ataxia and difficulty walking, do we give her low efficacy DMT?** No (if u check MRI, you might find extensive lesions, multiple on spinal cord (very bad prognostic sign)) → start on fingo (medium efficacy DMT) or Natalizumab (high efficacy DMT)

◀ Symptomatic treatment

Symptoms	Treatment
Spasticity	• Self-management, including stretching, physiotherapy, splinting • Skeletal muscle relaxants: **baclofen**, tizanidine, clonazepam • Gabapentin • Botulinum toxin type A for focal spasticity • Cannabis: oromucosal spray • Intrathecal baclofen pump • Intrathecal phenol – destructive procedure in advanced disease with paraplegia
Pain	• Trigeminal neuralgia – carbamazepine, lamotrigine • **Lhermitte's – carbamazepine**
Fatigue	• Fatigue management programme • treat depression with antidepressants and CBT • Amantadine (often ineffective)
Erectile dysfunction	• **sildenafil**, tadalafil or vardenafil
Tremor	• Beta-adrenoceptor- blocking drugs • Botulinum toxin type A injections (head or arms) • Deep brain stimulation for severe Holmes tremor
Urinary symptoms	• Antimuscarinics, e.g. oxybutynin, tolterodine, solifenacin, trospium • Desmopressin spray ± antimuscarinic • Intermittent self-catheterization (ISC) • Botulinum toxin type A intravesical injections (usually also require ISC) • Bladder training exercises • Indwelling catheter
Impaired mobility	• Physiotherapy ± walking aids • Treat spasticity • Fampridine – selected patients

Other Demyelinating Diseases

01 Neuromyelitis Optica Spectrum Disorder , Also known as Devic's disease.

This is a distinct inflammatory relapsing demyelinating disorder, previously thought to be a variant of MS. It is characterized by longitudinally **extensive transverse myelitis (>3 segments)** and bilateral or recurrent optic neuritis. NMOSD causes necrosis from the first attack.

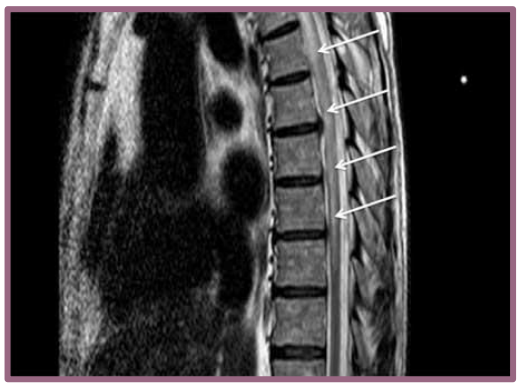
1. **More common in females (9:1**
2. **Mean age is 10 years later than MS.**
3. **More common in Asian and African populations.**
4. **Affects mainly the optic nerves and the spinal cord[1].**
5. **More severe attacks than in MS.** Presenting with nausea, vomiting and hiccups are important red flags in NMO
6. **Usually negative OCB in the CSF. While 90% of MS has positive OCB**
7. **More likely to have pleocytosis in the CSF.**
8. **Serum antibodies to aquaporin-4 water channels on astrocytes are diagnostic**
9. **Spinal MRI scans show lesions that are typically longer than three spinal segments**

◀ Pathology

Astrocytopathy

Targets aquaporin 4 (a water channel) rich areas (aquaporin 4 abd in 70%). Target aquaporin 4 **confirms the diagnosis of NMO** and should be done for every suspected case

Vasculocentric and rosette pattern deposition of immunoglobulin and complement.



Lesions are longer compared to MS

MANAGEMENT

Acute treatment of relapses
steroids or plasma exchange.
more severe than MS most of them need plasma exchange

Disease Modifying treatments
chronic immunosuppression with azathioprine, Rituximab,mycophenolate mofetil….
- **MS treatments may worsen NMO[2]**

1- unlike MS. However, NMOSD can still affect any area of the CNS
2- except rituximab (works for both MS and NMO) so if you have a patient whose presentation is confusing (not sure is it MS or NMO) give rituximab. However, rituximab may worsen MOG disease (subtype of NMO)

Other Demyelinating Diseases

02

Acute Disseminated Encephalomyelitis

This is an **acute monophasic demyelinating condition** in which areas of perivenous demyelination are widely disseminated throughout the brain and spinal cord. The illness may arise spontaneously but **often occurs a week or so after a viral infection**, especially measles or chickenpox, or following vaccination, suggesting that it is immunologically mediated.

1. **CNS inflammatory demyelinating disease.**
2. **Frequently preceded by vaccination or infection.**
3. **More common in children.**
4. **Equal males to females ratio**
5. **Affects all ethnicities.**
6. **Usually a monophasic illness (no relapses).**

◀ Pathology

Wide spread white and gray matter peri venous ‘‘sleeves’’ of inflammation and

Axons are relatively spared
unlike MS and NMO.

◀ Symptoms

Encephalopathy[1] (lethargy, stupor, coma, seizure). Headache, vomiting, pyrexia, delirium and meningism

Multifocal neurological deficit (visual symptoms, ataxia, TM..).

May fluctuates over a 3 months period for one single attack (If more than 3 months, it’s not ADEM)

MANAGEMENT

Acute treatment of relapses
Steroids, plasma exchange and intravenous immunoglobulins using the same regimen as for a relapse of MS, is recommended.

Disease Modifying treatments
no need for DMT because it’s not relapsing disease, REMEMBER **monophasic illness**

1-Helps you differentiate between MS and ADEM. ADEM patients usually come in a very bad shape and are admitted to ICU

Other Demyelinating Diseases

03

Behçet's disease

- Behçet's principal features are recurrent **oral and/or genitalulceration**, inflammatory ocular disease (uveitis) and neurological syndromes.
- Brainstem and cord lesions, aseptic meningitis, encephalitis and cerebral venous thrombosis occur.
- There is a predilection for ethnic groups along the ancient 'Silk Road' – Turkey, the Middle East and Asia. Behçet's is associated with the **HLA- B51 allele.**

An area for your notes

From Dr slides

Summary

1 Multiple sclerosis

- A demyelinating disease.
- Can affect any part of the CNS.
- A disease of young adults.
- More common in females.
- RR course is the most common initial course.

2 NMOSD

- A demyelinating disease.
- Can affect any part of the CNS but mainly optic nerve and spinal cord.
- Older group in comparison to MS.
- More in females.
- Relapsing course.

3 Acute inflammatory demyelinating disease.

- Monophasic.
- More common in children.
- Follows infection or vaccination.
- Encephalopathy is a prerequisite for the diagnosis in children.

	MS	NMO	ADEM
Age	**30**	**40**	**5-8**
Gender	**females 3:1**	**females 9:1**	**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	**Steroids and PLEX**	**Steroids and PLEX**	**Steroids and PLEX**
Disease Modifying Treatment	**Yes**	**Yes**	**No need**

Lecture Quiz

Q1: A 29-year-old female comes to the office because of intermittent muscle cramps and weakness of her left leg for 3 months. She says these episodes usually last a week, and then completely resolve. Other symptoms she has intermittently experienced are blurred vision, difficulty in maintaining balance, as well as urinary urgency and incontinence. Visual examination is normal. There is decreased muscular power in her left leg, and an up-going left-sided plantar reflex. Which of the following medications would most likely reduce this patient's muscle cramps?

A. Acetaminophen
B. Baclofen
C. Donepezil
D. Propranolol

Q2: A 56 year-old man comes to the office because of abnormal sensations for a week. He says when he flexes his neck, he suddenly feels an electric shock-like sensation run through his back to his legs. Neurological examination shows weakness, lack of coordination and numbness in his left leg. Plantar reflexes are up-going bilaterally. MRI scan shows multifocal zones of demyelination at the angles of the lateral ventricles. Which of the following symptoms is the patient most likely describing?

A. Horner's syndrome
B. Lhermitte's symptom
C. Uhthoff's symptom
D. Kernig's sign

Q3: A 25-year-old woman comes to the office because of recurring double vision. She says that she has experienced episodes lasting several days which self-resolve, and then reoccur several weeks later. This pattern has happened repeatedly over the past year. She says she has also had some loss of bladder control associated with these episodes. She is very nervous about the progression of these symptoms. Visual examination shows a gaze palsy. Which of the following will most likely be found on further examination?

A. Neither eye moves past midline when attempting right gaze
B. Right eye does not move past midline when attempting right gaze
C. Right eye does not move past midline when attempting left gaze
D. Right pupil does not respond to direct light

Q4: A 29-year-old female comes to the emergency department because of sudden visual loss in the right eye and severe pain on eye movement for 2 days. She says she has never experienced this before, but has had intermittent tingling of her face and upper extremities accompanied by increasing fatigue for the past year. Visual examination shows a relative afferent pupillary defect, and decreased color vision. Brain MRI shows increased signal in the right distal optic nerve and a left periventricular plaque. Which of the following is the most appropriate initial treatment?

A. Interferon-a only
B. Mitoxantrone followed by interferon-a
C. Methylprednisolone (IV) followed by oral prednisone.
D. Oral prednisone only F Mitoxantrone only

Q5: A 30-year-old man complains of bilateral leg weakness and clumsiness of fine movements of the right hand. Five years ago he had an episode of transient visual loss. On physical examination, there is hyperreflexia with Babinski sign in the lower extremities and cerebellar dysmetria with poor finger-to-nose movement on the right. 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 contrast
C. Quantitative cerebrospinal fluid (CSF) IgG levels
D. Testing for oligoclonal bands in cerebrospinal fluid
E. CT scan of the head with intravenous-iodinated contrast

Answers: Q1:B | Q2:B | Q3:C | Q4:C | Q5:B

Answers Explanation File!

THANKS!!

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Send us your feedback:
We are all ears!