Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Multiple Sclerosis

Objectives :

- Not given.

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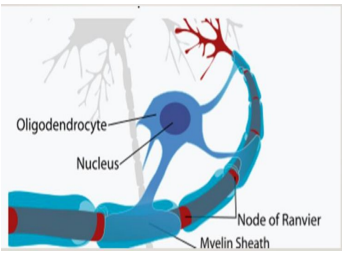
Resources :

- 437 slides | Same 436's slides
- Teamwork 436
- Doctor notes | Dr.Nuha AlKhawajah

Myelin

- A lipid dense layer that surrounds the axons of the neurons.
- Insulates the axon and allows continuous propagation of the electrical impulse.
- Schwann cells peripheral nervous system (PNS).
- Oligodendrocytes central nervous system (CNS). It allows faster propagation of electrical impulses.



Demyelinating Disease

ACQUIRED DEMYELINATING DISEASES

- Damage of the myelin.
- PNS & CNS. It can affect both.
- CNS: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD).
- PNS: acute inflammatory demyelinating polyneuropathy (Guillain Barre syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP).
- MS exclusively affect the **brain**, the **brain stem**, the **cerebellum** and the **spinal cord**, sparing the roots the plexuses the nerves and the neuromuscular junction.

❖ Multiple Sclerosis

Introduction:

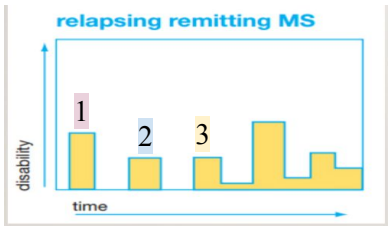
- MS is the most common chronic inflammatory, demyelinating and neurodegenerative disease of the CNS in young adults.
- The most common disorder causing disability in the young. WORLDWIDE after **trauma**.
- It is a heterogeneous, multifactorial, immune-mediated disease that is caused by complex gene–environment interactions.

Disease course:

CLINICALLY ISOLATED SYNDROME

- CIS is the first clinical episode that is suggestive of MS
- characterized by:
- Monophasic episode with symptoms and objective findings that reflect inflammatory demyelinating event in the CNS.
- Acute or subacute, lasting for at least 24 hrs.
- Occurs in the absence of fever or infection.
- Resembles a typical MS relapse (attack) but occurs in a patient not known to have MS.

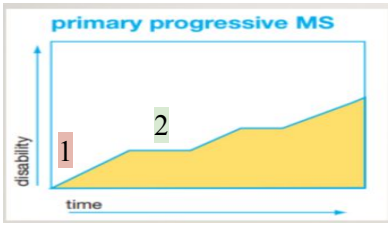
RR MS (The most common course)



85%

A purely RRMS is characterized by the absence of worsening neurological function outside of individual relapses. What does it mean? When a patient first develop a symptom in a timeline zero, for example **optic neuritis** they will have blurring of vision, that will worsen over days and then it will start improving, the patient might go back to his baseline completely normal (without any disability). After some time that could be months or years, he will develop a second attack. In between these 2 relapses the patient is not progressing. After some time the patient may develop a third and forth relapse. At the third relapse the patient accumulated some disability, for example he developed **weakness of the right upper limb,** the power was 2 then with time the power improve to 4, but it never went back to five, so he has some disability here. This disability will remain stable, he will not worsen in between two relapses, so because of that it's called relapsing remitting (IN BETWEEN RELAPSES THE PATIENT IS NOT PROGRESSING).

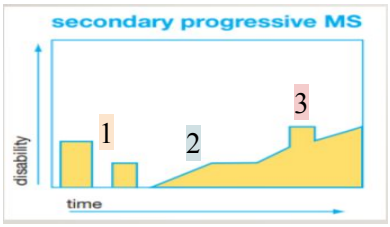
PPMS



15%

Irreversibly worsening neurological function, without preceding relapses. From the BEGINNING at time zero, the patient is having WORSENING of disability, his symptoms are worsening SLOWLY and GRADUALLY. He might have some area of plateau (which will not worsen), but the patient will **never improve!** (they will never regress), So because of that it's not remitting (IT'S PROGRESSIVE). It's **very difficult to treat** in comparison to RRMS.

SPMS

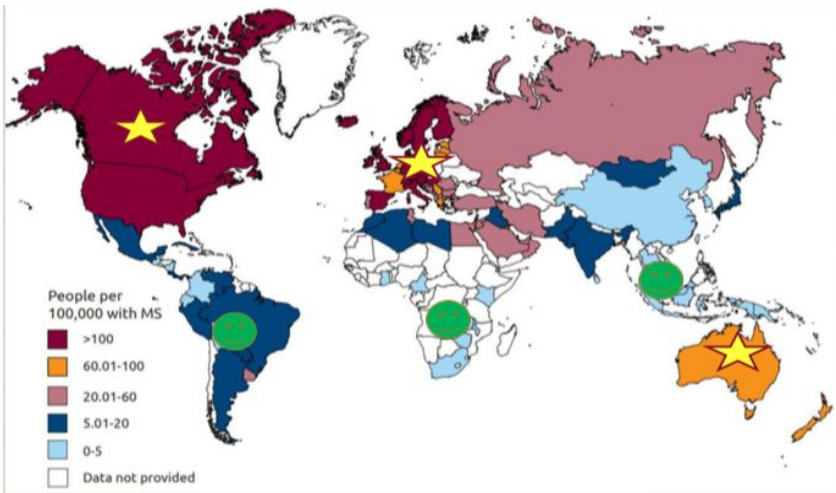


Worsening irreversible neurological function, preceded by RRMS that cannot be explained purely by worsening associated with ongoing relapses. Almost 60-70% of all RRMS patients will develop a SPMS course, and by giving them disease modifying treatment we are trying to delay this stage, because the patient will have relentless disability progression. It starts as RRMS course, then after a median time of 15/19/20 years the patient will start progressing irrespective of these relapses, so this curve resembles PPMS figure patient might still have some relapses, however the PROGRESSION IS CONTINUOUS REGARDLESS OF THE RELAPSES AND IT'S NOT DEPENDENT ON THE RELAPSE ITSELF.

MS Epidemiology

- RRMS has an onset between 20-35 years.
- PPMS begins at 40 years of age.
- The median time to SPMS is 21 years and median age at onset is 54.
- About one third of RRMS patients may never develop a progressive disease course This is a good news! since progressive disease is much more difficult to treat, because the patient already have **brain atrophy** and a lot of **cortical lesions** which are less inflammatory, so don't respond to the anti-inflammatory medications giving in RRMS treatment.
- Up to 10% of patients experience their initial demyelinating event during childhood or adolescence.
- The risk is 0.1% in the general population.
- The risk in people with an affected first-degree relative is 2-4%. It's more than like **20 times** increase from the risk of the general population.
- Concordance in monozygotic twins is 30-50%. This means not only genes that determine the risk of developing MS, but there other environmental risk factors.
- 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 lowest in Sub-Saharan Africa and East Asia.
- The most striking epidemiological characteristic is the apparent uneven distribution of the disease across the world

Prevalence by Country

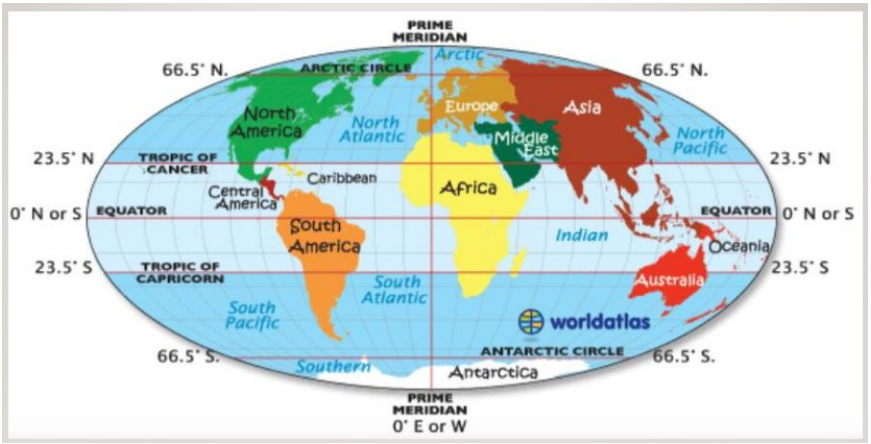


- In Saudi Arabia and the Gulf area, it's considered a **moderate** prevalence area.
- A recent study in Saudi showed a prevalence of 40 per 100000 population (Saudi + Non-Saudi), 60 per 100000 population (Saudi only).

Three factors are in effect

Population genetics	Interplay between genes and geographically determined physical environment this could be **infections** that are more prevalent in some areas and less in others. Some studies shows that certain infections (helminthic infections) are **protective**.	socioeconomic structure

A HIGHER LATITUDE CORRELATES WITH INCREASED PREVALENCE AND INCIDENCE OF MS



- Latitude: is the point at earth that determines the distance between the equator and this country.
- High latitude continent, it's **further away** from the **equator**, it's in a **temperate** zone for example, **United State of America**. Compare this to areas of low latitude such as, **Africa**, **South America** and **South East Asia**, all of these continents are **lying on** the **equator** and all of these have LOWER prevalence of MS than the areas which are further away from the equator.
- One theory is the sun exposure, the **further away** from the **equator** the LESS sun exposure you get per day. The sun is protective.
- There's a vitamin D theory and the **ultra violet rays** itself has a protective factor.

- The prevalence of MS has increased since the 1950s, especially in women.
- The female to male ratio of MS, has increased to ~**3:1**.
- This suggests a possible role of environmental risk factors:
  - Occupation Shift work like, working at night and sleeping in the morning, does ↑ the risk of MS.
  - Increased cigarette smoking.
  - Obesity
  - Birth control and childbirth Having more children is protective but the evidence is weak. Some studies shows that birth control pills are protective and some incriminated them as the cause for MS.
- The life expectancy of patients is reduced by 7–14 years.
- Patients older at onset or with PPMS have shorter survival.
- MS is the main cause of death in more than 50% of patients. Patient may develop **sepsis**/**PE**.
- Suicide is particularly substantially increased.

MS Risk factors

Environmental Risk Factors

1. **EBV Infection:**
   - 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.
2. **Vitamin D:**
   - Sunlight may be protective (ultraviolet radiation or vitamin D).
   - Sun exposure & serum vitamin D are inversely related to risk/prevalence of MS.
   - Vitamin D levels are inversely related to MS disease activity.
3. **Smoking:**

- a higher risk of MS in ever-smokers than in never-smokers Also, **passive** smoking ↑ the risk of MS.
- smoking may also be a risk factor for disease progression. More disease burden, higher lesion count and more **rapidly** progression.
- It's thought that smoking has risk of developing MS by two ways: 1- The **toxins** that can affect the function of neurons and can be damaging to the myelin. 2- **Inflammatory** effect on the body.

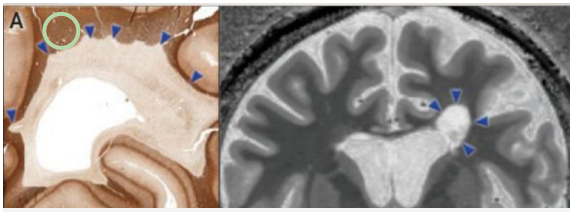
4. **Obesity:**

- in adolescence or early adulthood is associated with increased risk for MS. If you have been of **average normal weight as a child or adolescent** and you became obese later in your adult life you will not have ↑ risk of MS vs. if you were **obese since you were a child or teenager or in your early adulthood**. WHY? Obesity as a child is associated with ↑ in the **number** of **adipocytes** vs. obesity as an adult which is increase in the **size** rather than number of adipocytes.
- leptin increases the proliferation of auto-aggressive cells responsible for myelin damage. Released by **adipocytes**.

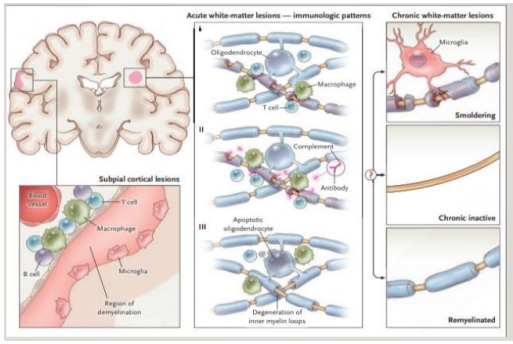
MS Pathology

- Most easily recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction → plaques. **(This is the hallmark of the disease)**
- Characterized by breakdown of the blood–brain barrier (BBB).
- 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.

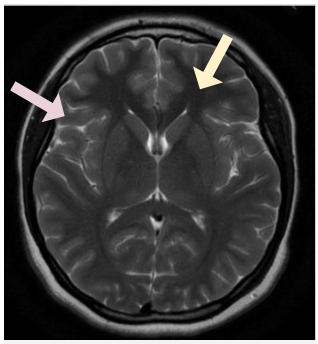
Pathology & Pathogenesis



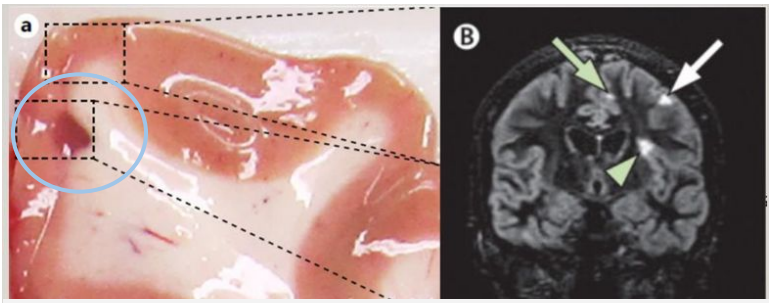
- An MRI showing a (focal **plaque**) the arrowheads
- In the postmortem autopsy, the area in brown is normal white matter (normal staining dark brown) compare it to the areas of arrowheads (**very light brown**) because it's devoid of myelin.



- Lesions are most easily recognized in the white matter.
- Demyelination also involves gray matter.
- Cortical lesions are less inflammatory than their white- matter counterparts and have substantially less permeability of BBB.



Normal MRI brain, (light gray) area is the gray matter and the area inside is the white matter (dark gray), so most of the lesion will affect the white matter however still the cortex will be involved.



- In the MRI image, the white arrow shows you a **cortical lesion**.
- The autopsy specimen showing you a lesion (loss of a white glossy color), this lesion involves both the gray and the white matter.
- The problem in progressive MS, they have LARGE number of these **cortical lesions**, and these lesions are usually very difficult to treat, because they tend to be less inflammatory and the **BBB is not that impaired**!, so a lot of medications don't penetrate to treat these lesion and clean the inflammation. It's more of a **local inflammation** rather than a peripheral and central inflammation like in the RRMS.

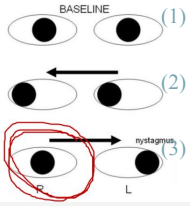
Optic Neuritis

Due to inflammation of the optic nerve (one of the most common symptom)

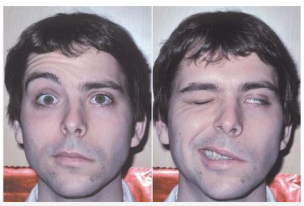
- Blurred vision.
- Pain exacerbated by eyes movement.
- Reduced perception of colors. If you test them with ishihara plates. They will also have decrease in red saturation less intense (less dark or bright).
- Flashes of light on moving the eyes.
- Enlarged blind spot.
- Reduction in the visual accuracy.

Brain stem related MS symptoms

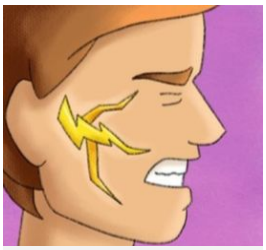
Double vision



Internuclear ophthalmoplegia (INO). (1) the patient is looking straight (normal). (2) then they ask the patient to look to the right side (normal). (3) then they ask the patient to look to left side, there is failure of adduction of the right eye + nystagmus in the abducting left eye, we call this right INO.



Facial weakness. He has left facial weakness. He can't raise his eyebrows. He has deviation of the mouth when he tries to smile to the right side. He can't close his eyes.



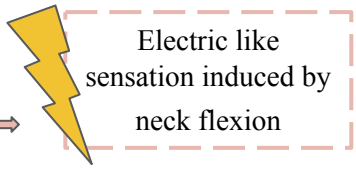
Trigeminal neuralgia, Which is severe electric like shooting pain. Involving the divisions of trigeminal nerve. It's not specific for MS, but can occur **frequently**.

Cerebellum Related MS symptoms

- Oscillopsia: A visual disturbance in which the object in the visual field appears to oscillate
- Dysarthria.
- Imbalance.

Brain and spinal cord MS symptoms

- Weakness (monoparesis involving one limb, paraparesis involving both lower limbs (always think of **spinal cord** lesion), quadriparesis).
- Sensory loss/numbness/pain.
- Sphincter dysfunction.
- **Lhermitte's sign** It's not specific for MS, can cause by any lesion in cervical cord.
- Cognitive dysfunction:memory,concentration,processing speed.



Transverse Myelitis

- A general term that indicates inflammation of the spinal cord. It's not a disease! It's a **clinical syndrome**.
- Could be caused by MS,infections,connective tissue diseases. SLE and Sjogren's syndrome.
- Spinal cord related motor, sensory &/or autonomic dysfunction.
- Sensory level.
- Unilateral or bilateral.

UHTHOFF'S PHENOMENON

- Neurological dysfunction.
- Stereotyped. Which means it will always comes the same.
- Less than 24 h. Lasts for minutes to hours.
- Reversible.
- Related to fluctuations in axonal conduction properties due to increasing body temperature. The patient will say "when I **exercise** I have some blurring of vision or when I take a **hot shower** I have some numbness in my hand". This is due to the increase in body temperature → will delay the conduction of electrical impulses in the axons (this is like in everybody), but because you're a healthy person (has normal myelin) you won't have any symptoms.

Diagnosis of MS

▪ Dissemination in time: history of at least two attacks separated by at least one month. Any symptom that occur in one month is considered as one relapse.

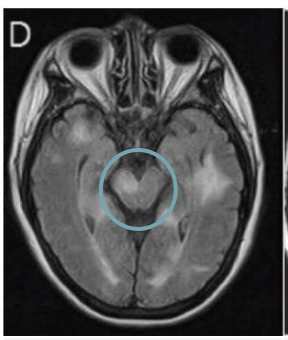
▪ Dissemination in space: clinical evidence of involvement of two CNS sites OR of one lesion with historical evidence of another site being affected It means that on MRI, we will see **2 different areas of the brain** are involved or **the brain + the spinal cord** (2 different sites) or the patient will have only 1 site involved, he's presenting now with (optic neuritis), but 1 year ago he gave history of (transverse Myelitis).

History & Exam

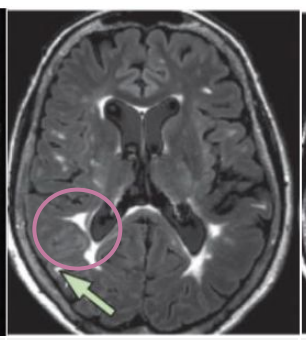
Don't memorize the table

	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¶

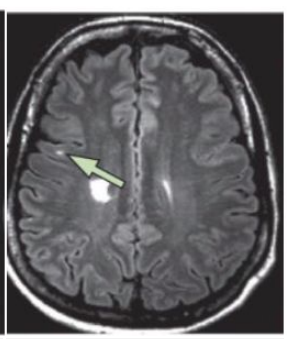
Imaging : MRI of the brain and spinal cord THE MOST IMPORTANT INVESTIGATION



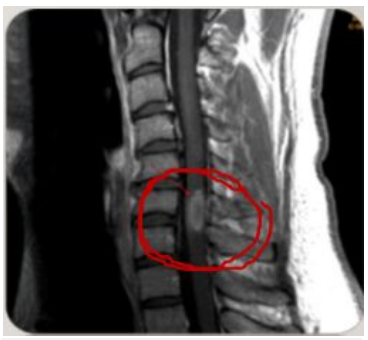
Brain stem lesion



Periventricular lesion



Cortical lesion



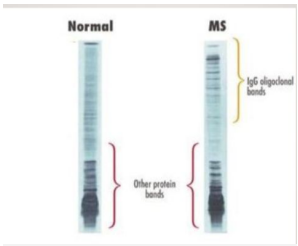
Spinal cord lesion

Lumbar Puncture

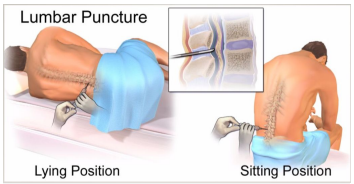
ANOTHER IMPORTANT INVESTIGATION that we don't always need, looking for **oligoclonal bands,** which are immunoglobulin bands that are present in almost 90% or more of MS patients.

We rarely do this test, sometimes we use it to: 1- Determine dissemination in time, because it can replace the presence of another attack.

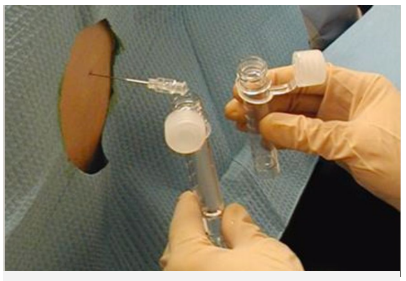
2- differentiate MS from another disease which is called NMOSD.



Oligoclonal bands (right)
Normal CSF (left)



LM will do it after applying some local anesthesia. Patient on his side, will introduce the needle at the level of **iliac crest L4-5**, so it's far below the end of the spinal cord between L1-2.



CSF analysis, in patient with MS will have **zero cells** or **very few cells** and **clear fluid** with usually **normal protein**.

MS treatment

A. Acute treatment of relapses.

- Steroids (IV Methylprednisolone) for 3-5 days To **reduce** the **duration** of the **relapse**,but it does not affect the future risk of having relapses. It has no effect on disease progression.
- plasma exchange We will do it to clear inflammatory cells from the blood, if the patient **didn't respond** to steroid (rare).

B. Disease Modifying treatments.

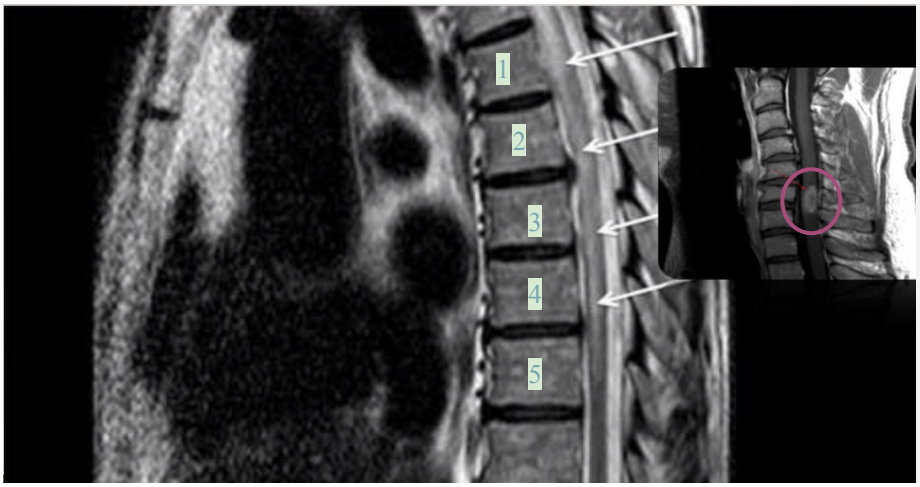
- Reduction of number of relapses per year.
- Reduction of number of new MRI lesions.
- Prolongation of time to development of secondary progressive disease.
- Reduction of long term disability.

MS treatment Cont.

- 1980's: Steroids for relapses only.
- 1990's: Disease modifying therapies (interferons & glatiramer acetate).
- 2000's: Mitoxantrone nowdays rarely use because of very severe side effects for aggressive MS and Natalizumab excellent medication for severe MS.
- 2010's: Oral medications now available (Fingolimod, teriflunomide, dimethyl fumarate..).
- 2017 first approved treatment for PPMS: Ocrelizumab.

❖ Neuromyelitis optica spectrum disorder(NMOSD)

- Also known as **Devic's** disease.
- More common in females (9:1). Very rare in males.
- Mean age is 10 years later than MS.
- More common in Asian and African populations.
- Affects mainly the optic nerves and the spinal cord. Because of that it is called Neuromyelitis **optica**, however it can also affect the brain and the brain stem, but the patient tend to have less lesions there.
- More severe attacks than in MS.
- Usually negative OCB in the CSF.
- More likely to have pleocytosis in the CSF.



An MRI scan showing a **longitudinally extensive lesion** (white arrows), which is one of the characteristic features of NMOSD, extending over three or more vertebral segments. The lesions here extending almost over 5 vertebral segments.
THIS IS VERY RARELY OR NEVER SEEN IN MS.
MS lesion (short), extending over one and a half vertebral segments only.

NMO pathology

- Astrocytopathy.
- Targets aquaporin 4 (a water channel) rich areas (aquaporin 4 abd antibodies in 70%).
- Vasculocentric and rosette pattern deposition of immunoglobulin and complement.
  Seen in pathology section.

Treatment

MS treatments may worsen NMO

A. Acute treatment of relapses
same as MS

- steroids or plasma exchange.

B. Disease Modifying treatments completely different than MS

- Chronic immunosuppression with azathioprine,Rituximab, mycophenolate mofetil....

❖ Acute Disseminated Encephalomyelitis(ADEM)

- CNS inflammatory demyelinating disease.
- Frequently preceded by vaccination or infection
- More common in children.
- Equal males to females ratio.
- Affects all ethnicities.
- Usually a monophasic illness (no relapses).

Pathology:

- Wide spread white and gray matter peri-venous‘‘sleeves’’ of inflammation and demyelination.
- Axons are relatively spared in comparison to MS and NMOSD.

Symptoms:

- Encephalopathy (lethargy,stupor,coma).
- Multi focal neurological deficit (visual symptoms,ataxia, TM..).
- May fluctuates over a 3 months period.

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

Treatment

• Acute treatment:Steroids,plasma exchange and intravenous immunoglobulins. Very similar to MS and NMOSD.

• Disease modifying treatments:??? **No, it’s monophasic!**

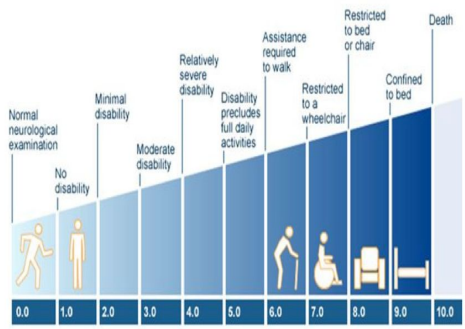
Prognosis

- Fifty percent of patients will require a cane 28 years after disease onset.
- Twenty five percent will require a wheelchair 44 years after disease onset.

Features of a better prognosis in MS include:

1. Onset below 25 years of age
2. Optic neuritis or sensory before cerebellar symptoms on first presentation
3. A long interval (over 1 year) between relapses
4. Fewer lesions on MRI
5. Full recovery from relapses
6. Being a female (MS is more severe in males)

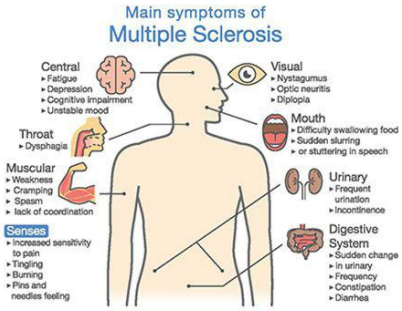
Progressive MS carries a worse prognosis than RR-MS.



Summary (from the Doctor's Slides)

• MS:

this pic. wasn't included in doctor's slides



- ➢ 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.

•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. They don't have progressive course.

• ADEM:

- ➢ Acute inflammatory demyelinating disease.
- ➢ Monophasic.
- ➢ More common in children.
- ➢ Follows infection or vaccination.
- ➢ Encephalopathy is a prerequisite for the diagnosis in children.

Summary (from the Doctor's Slides)

MS vs NMO vs ADEM

	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	Streoids and PLEX	Streoids and PLEX	Streoids and PLEX
Disease Modifying treatment	Yes	Yes	No need

Types of MS:

-Relapsing-Remitting MS (RRMS). (This is the most common form)
-Secondary-Progressive MS (SPMS)
-Primary-Progressive MS (PPMS)

Risk factors for MS:

1- EBV infection. 2- vitamin D deficiency 3- smoking 4- obesity

Diagnosis of MS :

Dissemination in time: history of at least two attacks separated by at least one month.
Dissemination in space: clinical evidence of involvement of two CNS sites OR of one lesion with historical evidence of another site being affected.

signs:

- Lhermitte phenomenon (electric like sensation induced by neck flexion)
- Uhthoff phenomenon. (heat sensitivity/intolerance)

Treatment:

Acute treatment of relapses:
Steroids (IV Methylprednisone) for 3-5 days. • plasma exchange
Disease Modifying treatments.
Reduction of number of relapses per year.
Reduction of number of new MRI lesions.
Prolongation of time to development of secondary progressive disease.
Reduction of long term disability.

Questions

1. What is the pathological landmark for multiple sclerosis?
A. Multiple focal areas of myelin loss within the CNS.
B. Multiple focal areas of myelin loss within the PNS.
C. Single focal area of myelin loss within the PNS.
D. Single focal area of myelin loss within the CNS.

2. Which one of the following is imaging modality of choice for multiple sclerosis?
A. CT scan with contrast
B. CT scan without contrast
C. X-ray
D. MRI with contrast

3. Which one of the following describes the Primary progressive type of multiple sclerosis?
A. Gradual progression of the disease from onset, no overlapping relapse or remission.
B. Steady progression of clinical neurological damage with superimposed relapses and remissions.
C. Steady progression of neurological damage with or without superimposed relapses and minor remissions.
D. Clinical exacerbation of neurological symptoms followed by complete or incomplete remission.

4.42-year-old woman presents with ataxia. Gadolinium-enhanced MRI reveals multiple subcortical white matter lesions as well as enhancing lesions in the cerebellum and spinal cord. She is diagnosed with MS. Two months later she develops optic neuritis. What feature is associated with a milder disease course?
A. Her age of 42
B. Her initial presentation of ataxia
C. Her female gender
D. Her MRI scan appearance

5.How many attacks and lesions are required to diagnose MS clinically ?
A. Tow attacks & one lesion
B. Two attacks & two lesions
C. One attack & two lesion
D. Three attacks & two lesions

6.which of the following is correct regarding the dissemination in time for the diagnosis of Multiple sclerosis ?
A-history of at least two attacks separated by at least two months.
B-history of at least two attacks separated by at least one month.
C-history of at least two attacks separated by at least three months.
D-history of at least attacks separated by at least one month.

answers: 1-A ,2-D ,3-A ,4-C ,5-B ,6-B