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MULTIPLE SCLEROSIS
& OTHER CNS DEMYELINATING DISEASES

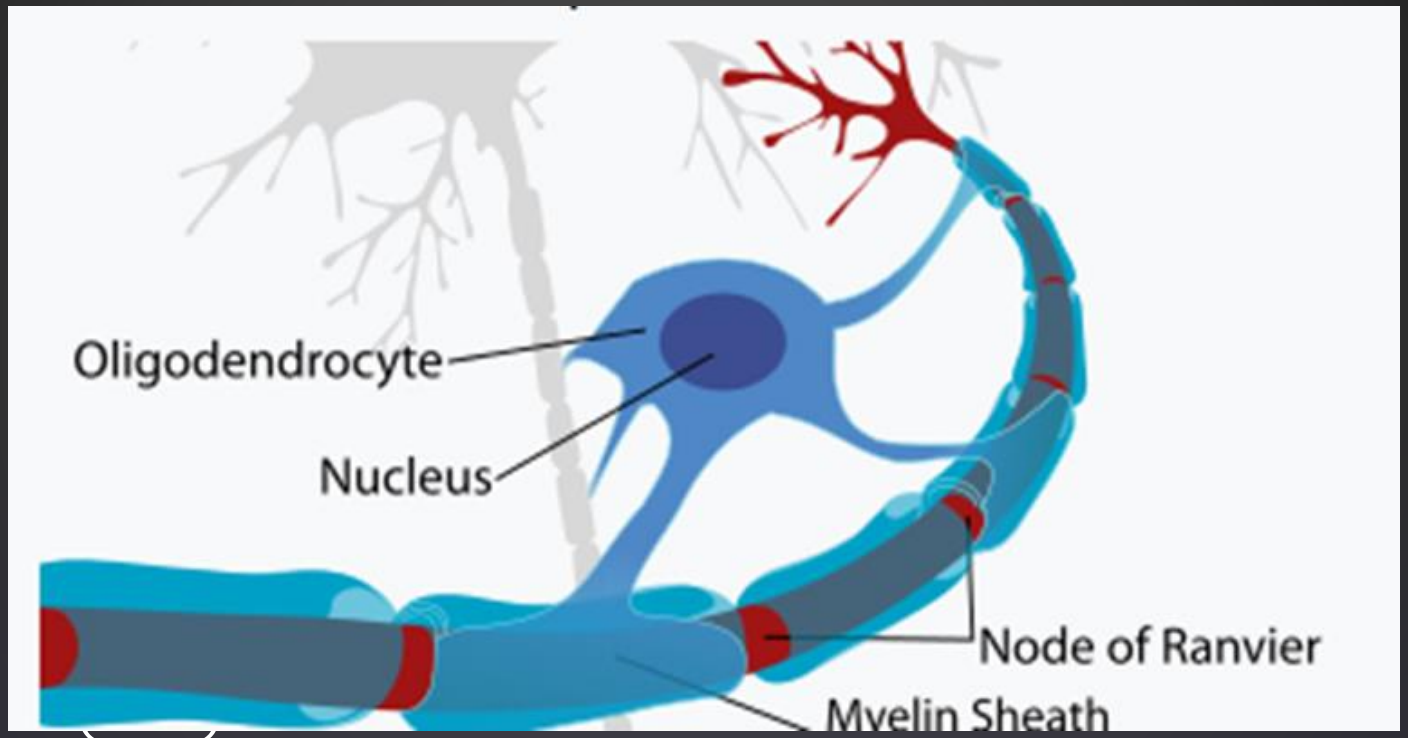
Salman Aljarallah, MBBS, FRCPC, ABNP

Assistant Professor

Consultant Neurologist

Neuroimmunology & Neurological Infections

Modified from slides made by Dr. Nuha Alkhawajah


Oligodendrocyte
Nucleus
Node of Ranvier
Myelin Sheath

DEMYELINATING DISEASES

- Damage of the myelin.
- PNS & CNS.
- Inherited or acquired.
- CNS:
  - Multiple sclerosis (MS)
  - Acute dissaminated encephalomyelitis (ADEM)
  - Neuromyelitis optica spectrum disorder (NMOSD).
- PNS:
  - Guillain Barre syndrome (Acute inflammatory demyelinating polyneuropathy)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP).

Multiple Sclerosis

MULTIPLE SCLEROSIS

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

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1. Filippi et al. NATURE REVIEWS DISEASE PRIMERS; NOV 8 2018; 4
2 . Murray. BMJ 2006 Mar 4; 332(7540): 525–527.

MULTIPLE SCLEROSIS

- MS subtypes :
  - Relapsing remitting (RRMS): the most common
  - Primary progressive (PPMS)
  - Secondary progressive (SPMS)

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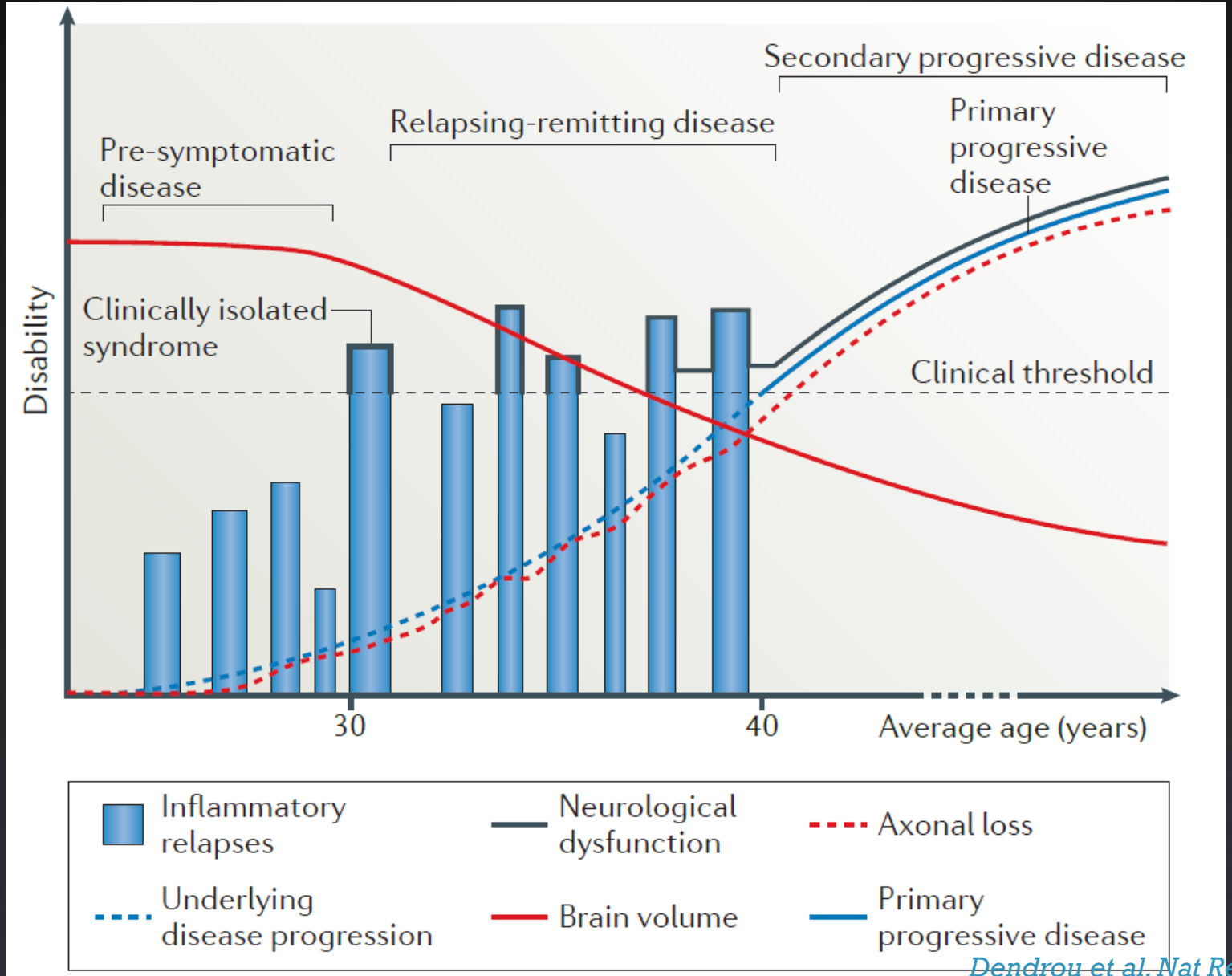
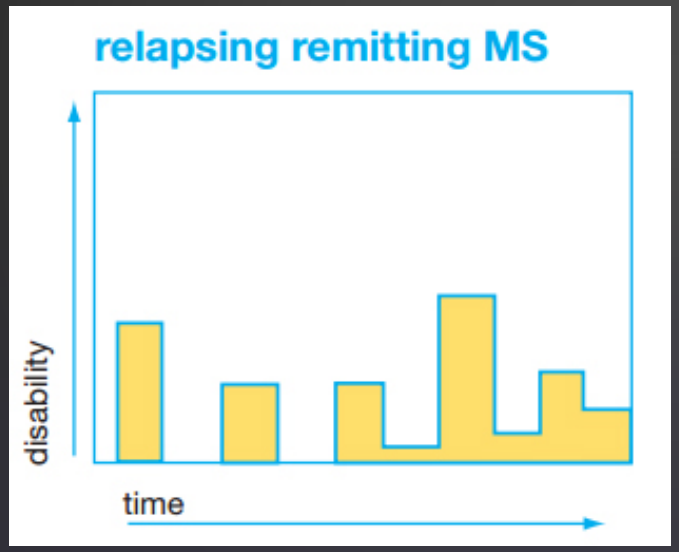
1. Filippi et al. NATURE REVIEWS DISEASE PRIMERS; NOV 8 2018; 4
2 . Murray. BMJ 2006 Mar 4; 332(7540): 525–527.



Dendrou et al. Nat Rev Imm.2015

RRMS

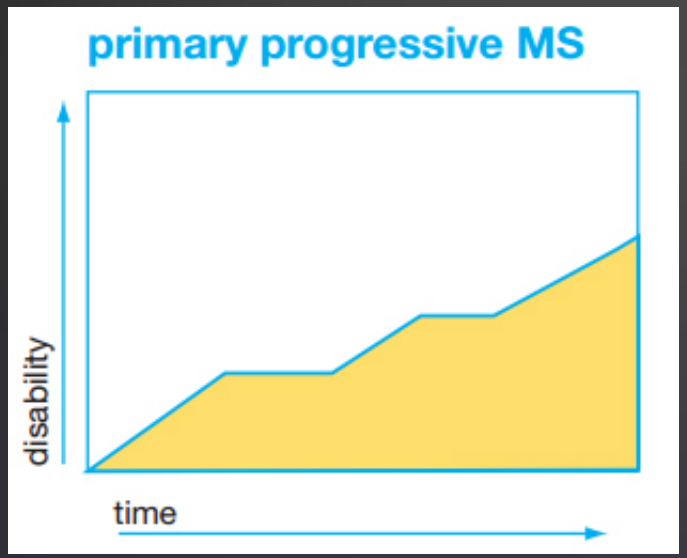


A purely RRMS is characterized by the ***absence*** of worsening neurological function outside of individual relapses

85%

https://www.mstrust.org.uk/about-ms/what-ms/types-ms
Tutuncu et al. Mult Scler. 2013 February ; 19(2): 188–198

PPMS

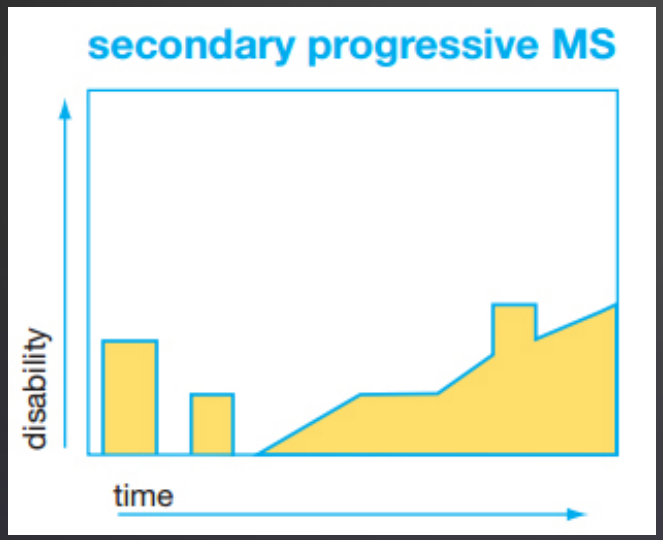


Irreversibly worsening neurological function, ***without*** preceding relapses

15%

https://www.mstrust.org.uk/about-ms/what-ms/types-ms
Tutuncu et al. Mult Scler. 2013 February ; 19(2): 188–198

SPMS



Worsening irreversible neurological function***, preceded*** by RRMS that cannot be explained purely by worsening associated with ongoing relapses

https://www.mstrust.org.uk/about-ms/what-ms/types-
Tutuncu et al. Mult Scler. 2013 February ; 19(2): 188–19

MS DISEASE COURSE

- The median time to conversion to SPMS is 21 years and median age at onset of 54 years. [1]

1.Koch et al. J. Neurol. Neurosurg. Psychiatry 81(9), 1039–1043 (2
2

EPIDEMIOLOGY

- RRMS has an onset between 20-35 years.[1]
- PPMS begins at 40 years of age.[1]
- The median time to SPMS is 21 years and median age at onset is 54.[2]
- About one third of RRMS patients may never develop a progressive disease course[3].
- Up to 10% of patients experience their initial demyelinating event during childhood or adolescence.[1]

1.Filippi et al. NATURE REVIEWS DISEASE PRIMERS; NOV 8 2018; 4
2. Koch et al. J. Neurol. Neurosurg. Psychiatry 81(9), 1039–1043 (2010).
3.Tutuncu et al. Mult. Scler. 19(2), 188–198 (2013).

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MS EPIDEMIOLOGY

- The risk is **0.1%** in the general population.
- The risk in people with an affected first-degree relative is **2-4%.**
- Concordance in monozygotic twins is **30-50%.**

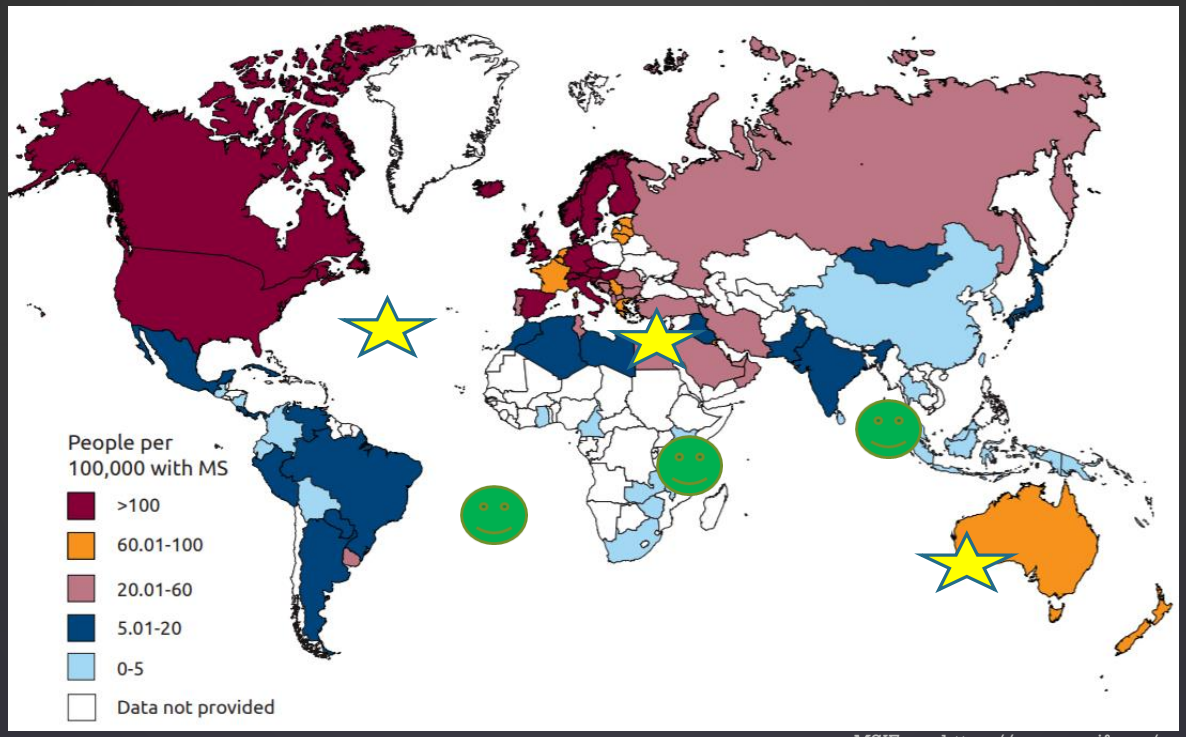
Reich et al. N Engl J Med 2018;378:169-80.

MS EPIDEMIOLOGY

- MS is mainly found in individuals of European descent and is rare in Asian, black, Native Americans and Māori individuals.[1]
- Prevalence varies greatly, being highest in North America and Europe and lowest in Sub-Saharan Africa and East Asia.[2]
- The most striking epidemiological characteristic is the apparent uneven distribution of the disease across the world.[3]

1. Rosati, G. The prevalence of multiple sclerosis in the world: an update. *Neurol. Sci.* **22,** 117–139 (200).
2.MSIF.org HTTP://WW.MSIF.ORG/WP-CONTENT/UPLOADS/2014/09/ATLAS-OF-MS.PDF (2013)
3. Koch-Henriksen et al. ***Lancet Neurol* 2010; 9: 520–32**

PREVALENCE BY COUNTRY



MSIF.org https://www.msif.org/wp- content/uploads/2014/09/Atlas-of-MS.pdf (2013)
Koch-Henriksen et al. ***Lancet Neurol* 2010; 9: 520–32**

LOCAL DATA

- 2516 patients from 20 hospitals
- Projected prevalence 40.40 per 100,000 total population
- Projected prevalence 61.95 per 100,000 Saudi nationals.

Table 1 MS prevalence for Saudi Arabia

Regions	Total hospital (MS)	Hospitals Included in Registry	MS patients from 20 hospital	Prevalence/100000 population	Projected prevalence/100000 population
Western Region	30	7	990	9.3	39.9
Central Region	36	7	866	9.0	46.3
Eastern Region	22	4	378	7.7	42.4
Southern Region	9	2	173	3.6	16.2
Northern Region[a]	8	0	109	4.4	35.2
Total "2017"	105	20	2516	7.7	40.4

[a]Patients referred to other regions. For calculating projected prevalence for northern region we assumed 109 patients were referred from a single hospital of northern region to hospitals in other regions

Aljumah et al. BMC Neurology.20:49(2020).

MS EPIDEMIOLOGY

- 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.
  - Increased cigarette smoking.
  - Obesity.
  - Birth control and childbirth.

Filippi et al. NATURE REVIEWS DISEASE PRIMERS; NOV 8 2018;

MS EPIDEMIOLOGY

- The life expectancy of patients is reduced by **7–14 years.**[1]
- Patients older at onset or with PPMS have shorter survival.[2]
- MS is the main cause of death in more than 50% of patients.[2]
- Suicide is particularly substantially increased.[2]

1.Filippi et al. NATURE REVIEWS DISEASE PRIMERS; NOV 8 201
2-Scalfari et al. Neurology 2013;81:184–192

MS RISK FACTORS

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Risk factor	Odds ratio	*HLA* gene interaction	Combined odds ratio[a]	Effect during adolescence	Immune system implied	Level of evidence
Smoking	~1.6	Yes	14	No	Yes	+++
EBV infection (seropositivity)	~3.6	Yes	~15	Yes	Yes	+++
Vitamin D level <50 mM	~1.4	No	NA	Probable	Yes	+++
Adolescent obesity[b]	~2.0	Yes	~15	Yes	Yes	+++
CMV infection (seropositivity)	0.7	No	NA	Unknown	Yes	++
Night work	~1.7	No	NA	Yes	Yes	++
Low sun exposure	~2.0	No	NA	Probable	Yes	++
Infectious mononucleosis	~2.0	Yes	7	Yes	Yes	++
Passive smoking	~1.3	Yes	6	No	Yes	+
Organic solvent exposure	~1.5	Unknown	Unknown	Unknown	Unknown	+
Oral tobacco or nicotine consumption	0.5	No	NA	Unknown	Yes	+
Alcohol	~0.6	No	NA	Unknown	Yes	+
Coffee	~0.7	No	NA	Unknown	Yes	+

filippi et al. Nature Reviews. 2018

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.

CONT.

3. ***Smoking:***
   - a higher risk of MS in ever-smokers than in never-smokers
   - smoking may also be a risk factor for disease progression.

leptin increases the proliferation of auto-aggressive cells responsible for myelin damage.

4. ***Obesity:***
   - in adolescence or early adulthood is associated with increased risk for MS.

MS PATHOLOGY

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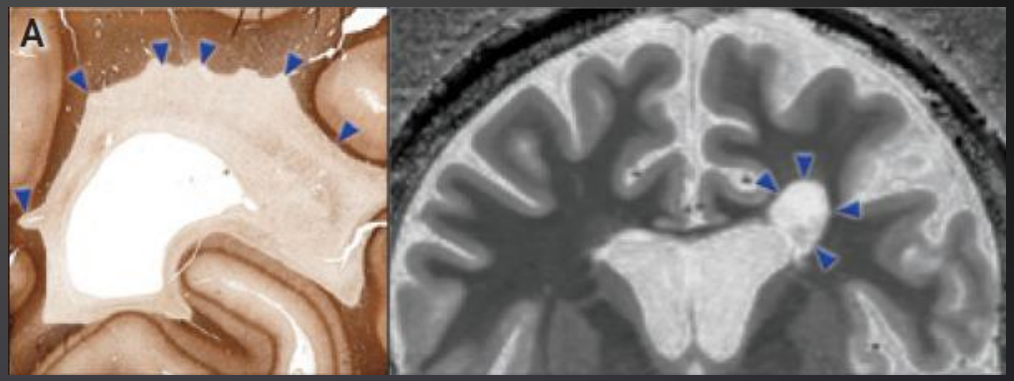
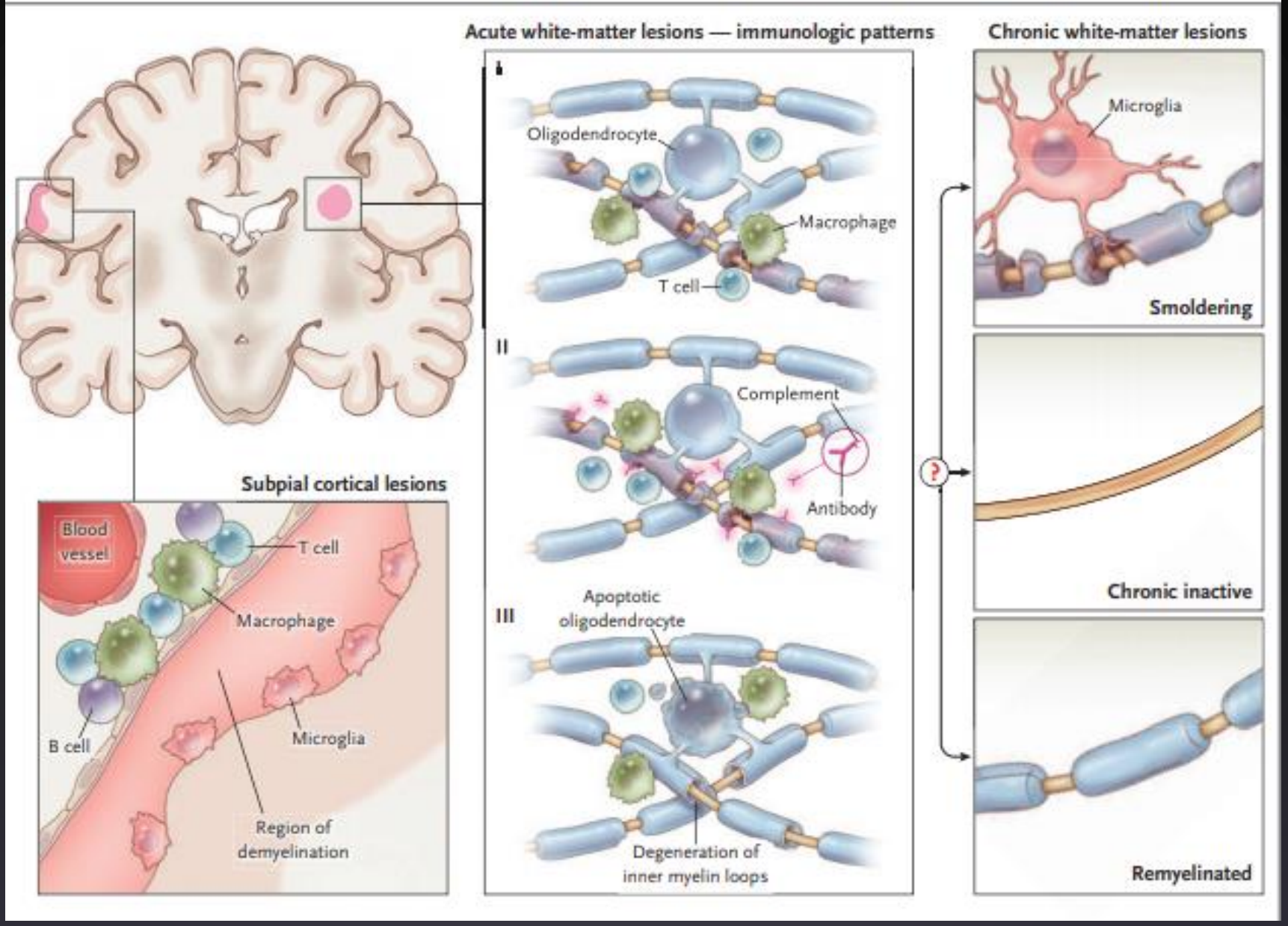
PATHOLOGY & PATHOGENESIS

- Most easily recognized in the white matter as focal areas of demyelination, inflammation, and glial reaction ***plaques.***
- 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.



Reich et al. N Engl J Med 2018;378:169-80.
PICs from very well mind and WIKIPEDIA



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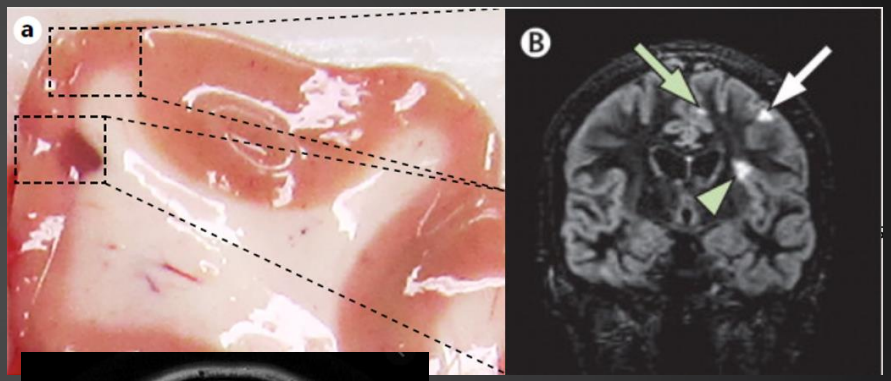
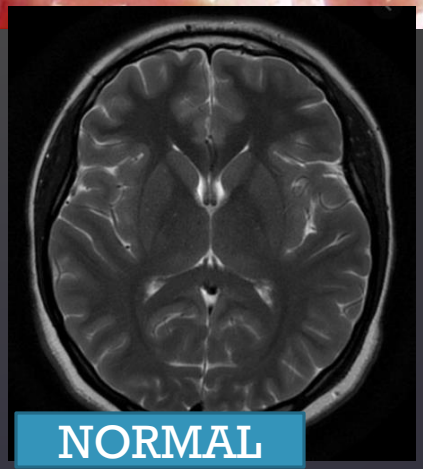
Reich et al. NEngl J Med 2018;378:169-80.

PATHOLOGY & PATHOGENESIS

- 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.





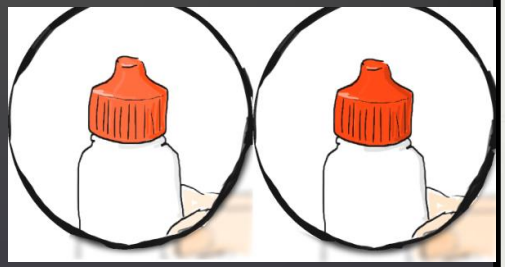
Fillipi et al . Nature rev dis primers. 2018 Nov 8;4(1):4
First Pic from Wikipedia

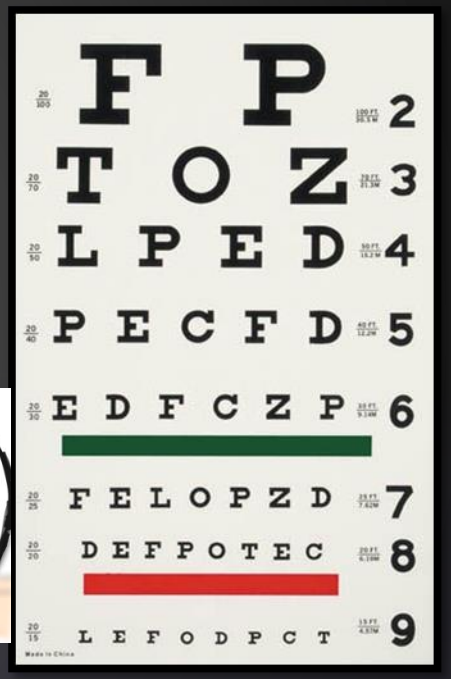
CLINICAL PRESENTATION OF MS

- Relapses:
  - 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.
  - Caused by inflammation and new demyelination
  - Treatment is with steroids
- Pseudorelapses "Pseudoexacebations":
  - Recurrence of symptoms of previous relapses in the context of infection or fever
  - Caused by slowing of conduction across previously demyelinated axon
  - Treatment is of the infection

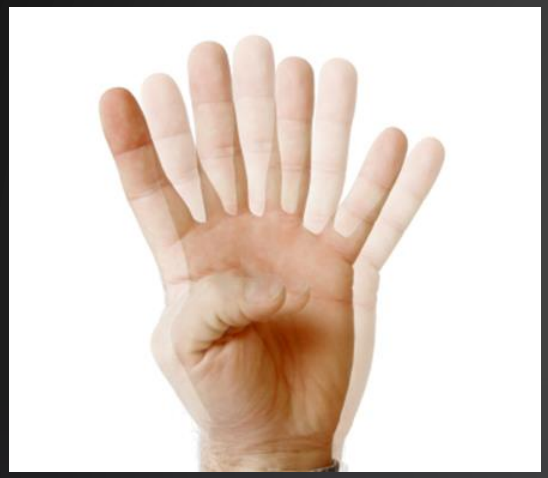
OPTIC NEURITIS

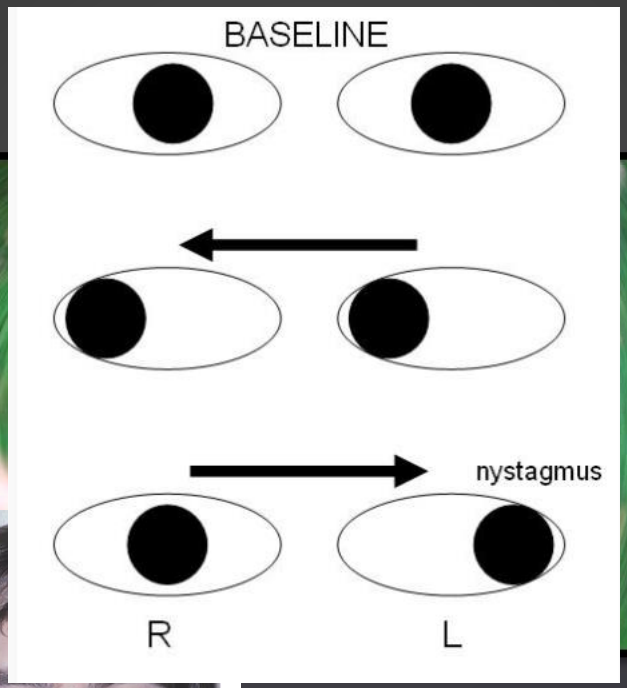
- Blurred vision.
- Pain exacerbated by eyes movement.
- Reduced perception of colors.
- Flashes of light on moving the eyes.
- Enlarged blind spot.

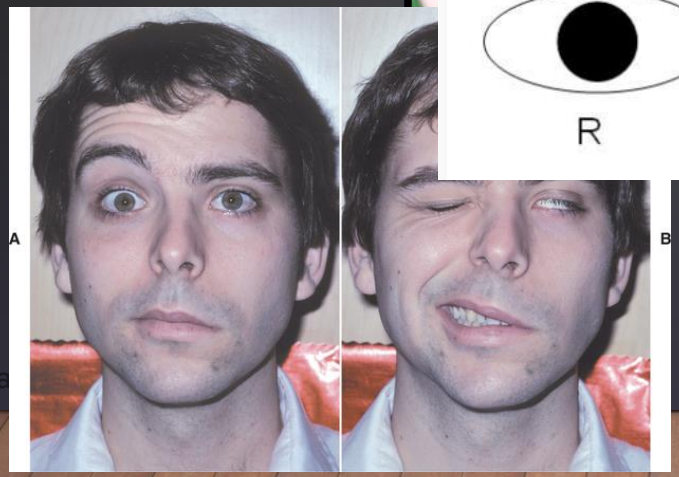




BRAIN STEM RELATED MS SYMPTOMS







CEREBELLUM RELATED MS SYMPTOMS

- Oscillopsia.
- Dysarthria.
- Imbalance.

Pic from protokinetics.com

BRAIN AND SPINAL CORD MS SYMPTOMS

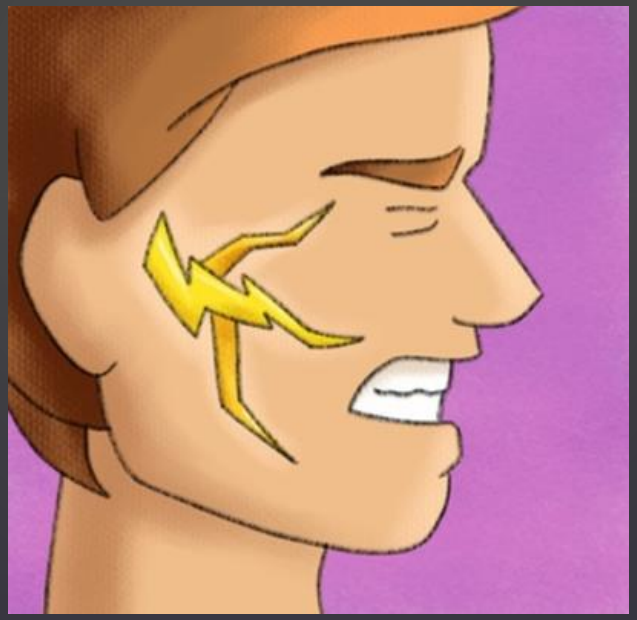
- Weakness (monoparesis, paraparesis, quadriparesis).
- Sensory loss/numbness/pain.
- Sphicteric dysfunction.
- Lhermitte's sign??
- Cognitive dysfunction: memory, concentration, processing speed.

TRANSVERSE MYELITIS

- A general term that indicates inflammation of the spinal cord.
- Could be caused by MS, infections, connective tissue diseases…..
- Spinal cord related motor, sensory &/or autonomic dysfunction.
- Sensory level.
- Unilateral or bilateral.

PAROXYSMAL SYMPTOMS

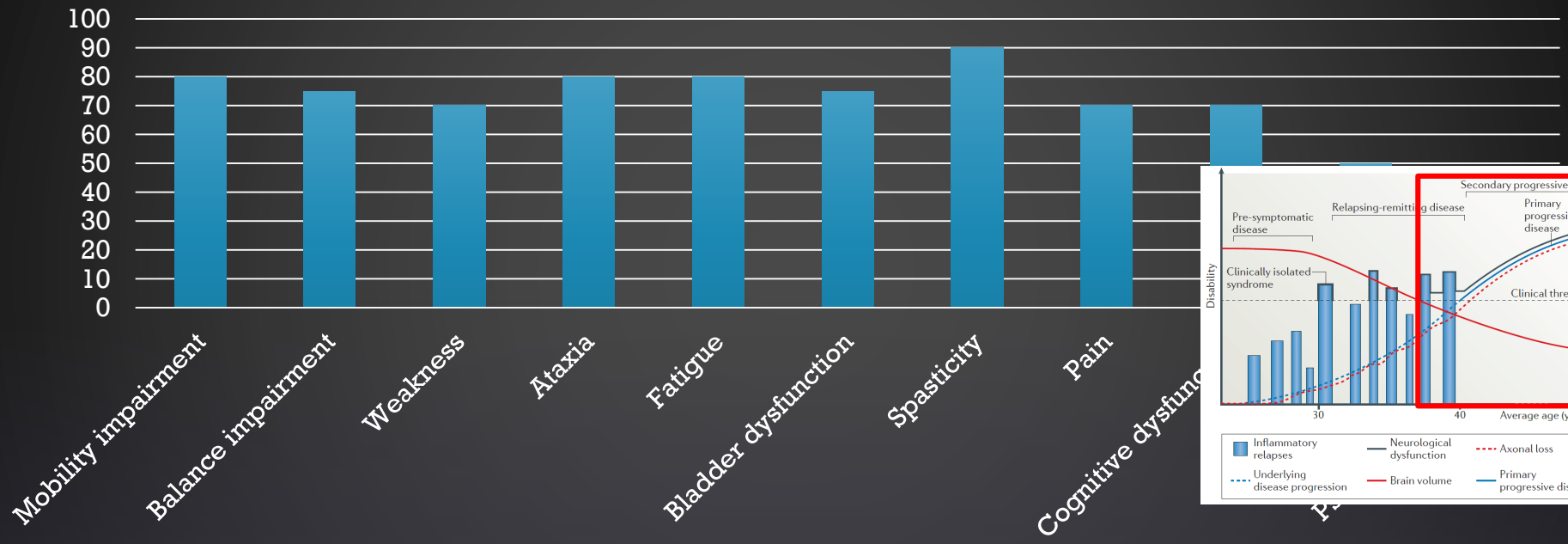
- Symptoms of short duration "seconds" "minutes"



UHTHOFF'S PHENOMENA

- Neurological dysfunction.
- Stereotyped.
- Less than 24 h.
- Reversible.
- Related to fluctuations in axonal conduction properties due to increasing body temperature.

PREVELANCE OF SYMPTOMS IN PROGRESSIVE MS



Lancet Neurology, ISSN: 1474-4422, Vol: 14, Issue: 2, Page: 194-207

DIAGNOSING MS

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DIAGNOSING MS

History & Exam

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2017 MCDONALD CRITERIA

	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¶

Lancet Neurol 2018; 17: 162–73

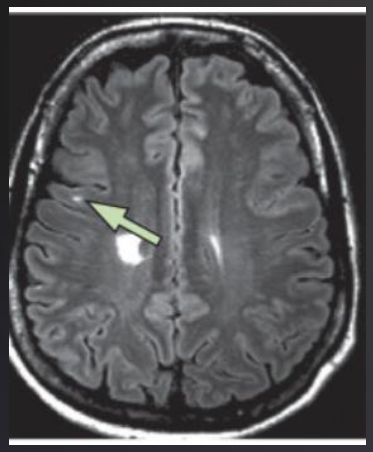
CLINICALLY ISOLATED SYNDROME (CIS)

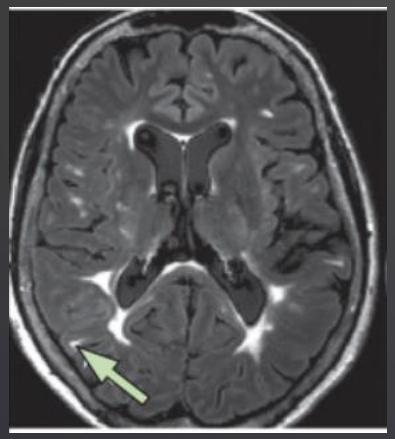
- CIS is a term that describes the first clinical relapse that is suggestive of MS but does not fulfil the criteria

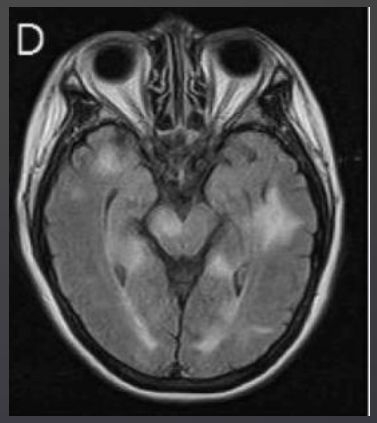
Thompson et al. Lancet Neurol 2018; 17: 162–73

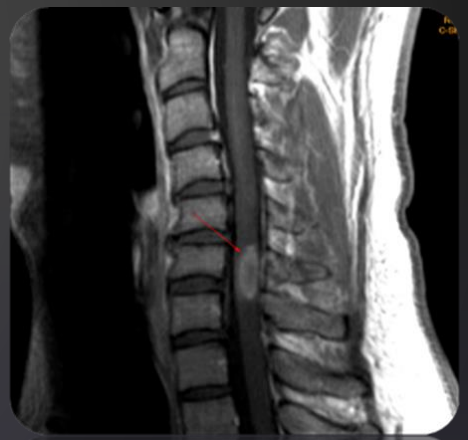
DIAGNOSIS OF MS

- Imaging: MRI of the brain and spinal cord





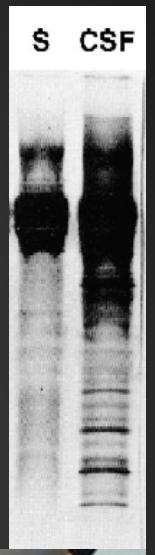


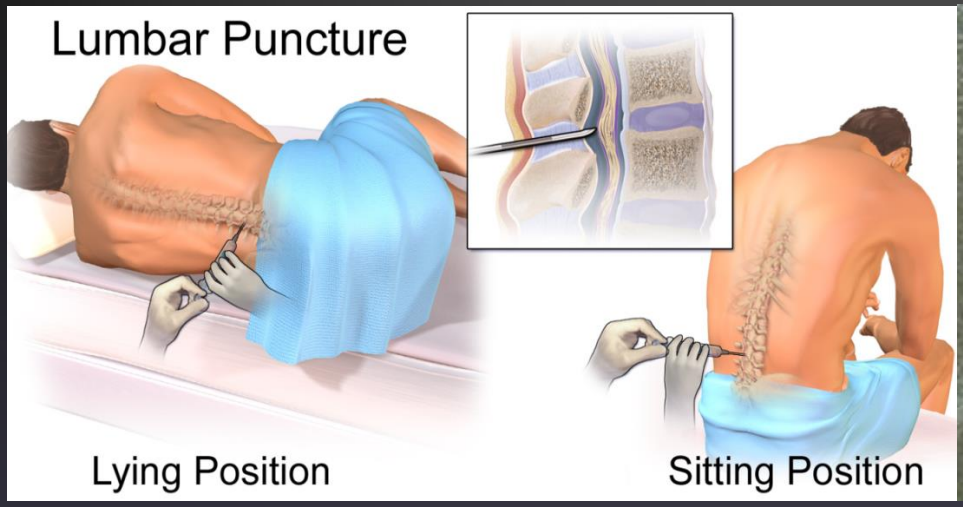


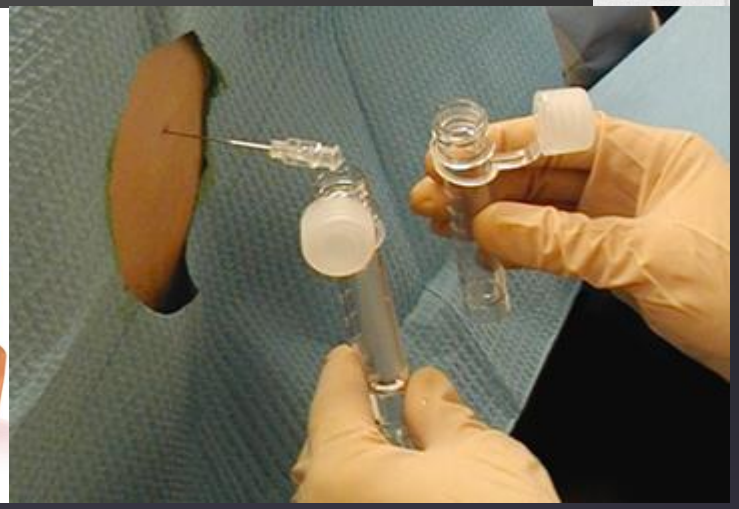
Fillipi et al. Lancet Neurology 2016
Chen et al. Multiple Sclerosis 2010

MS DIAGNOSIS

- Oligoclonal bands confirms diagnosis of MS.







MS TREATMENT

A. Acute treatment of relapses.

B. Disease Modifying treatments (DMTs)

To prevent relapses

C. Treatment of symptoms:

- Neuropathic pain
- Spasticity
- Neurogenic bldder

D. Rehabilitation

E. Remyelination: experimental

MS TREATMENT

A. **Acute treatment of relapses**

- High dose pulse steroids (IV methylprednisone) for 3-5 days
- Plasma exchange:
  - Only for severe relapses

MS TREATMENT

B. Disease Modifying treatments

- Indicated for relapsing remitting MS.
- Not effective in progressive MS
- 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.

Salman Aljarallah

FDA-APPROVED TREATMENT FOR RRMS

1. Interferon Beta
2. Glatiramer acetate
3. Natalizumab
4. Mitoxantrone
5. Fingolimod
6. Siponimod
7. Ozanimod
8. Ponesimod
9. Teriflunomide
10. Dimethyl fumarate
11. Diroximel fumarate
12. Monomethyl fumarate
13. Ocrelizumab
14. Ofatumumab
15. Alemtuzumab
16. Cladribine

Only DMT is PPMS and RRMS

Rituximab is widely used although it does not have an FDA approval for MS but

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NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

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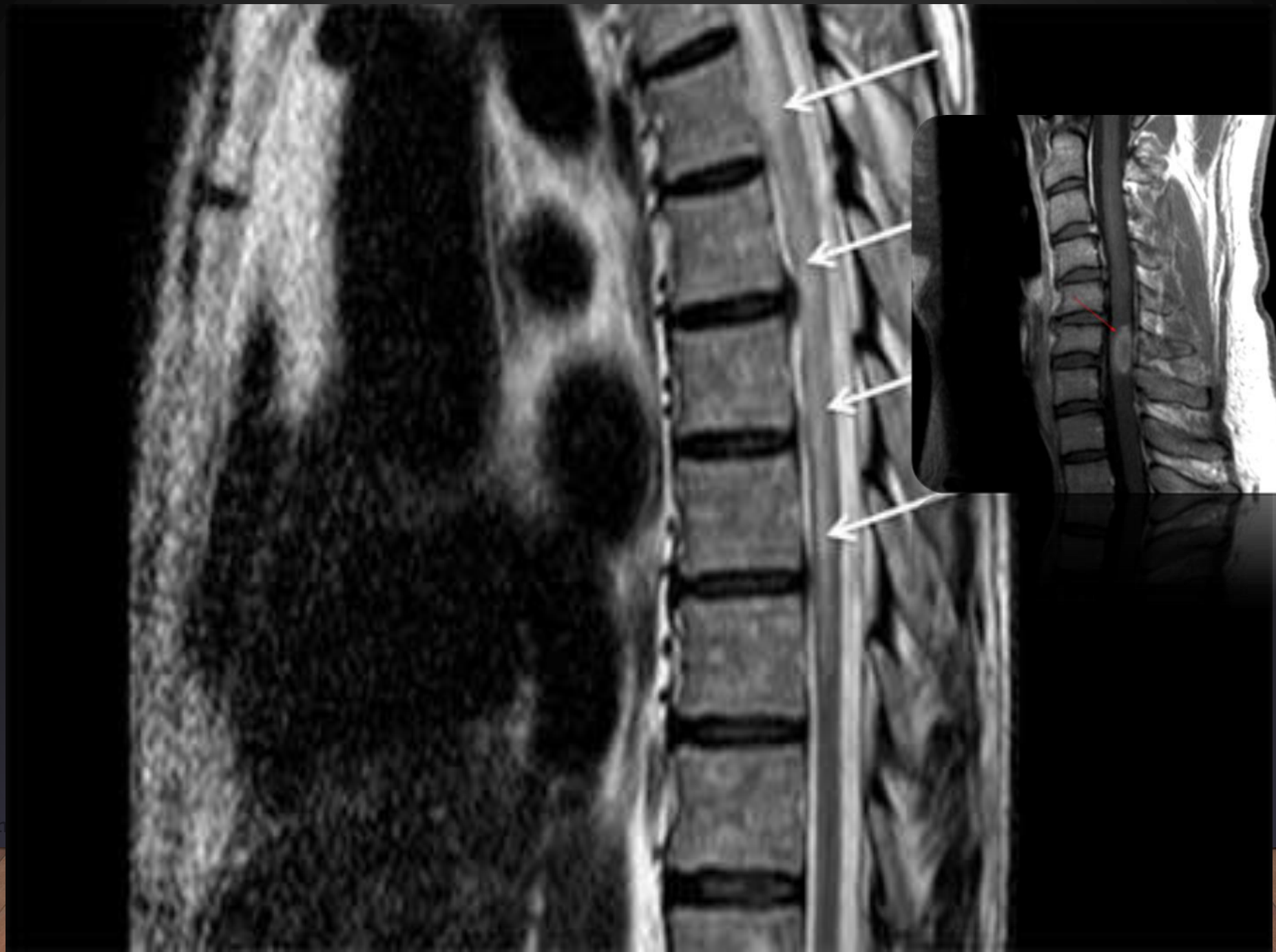
NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD)

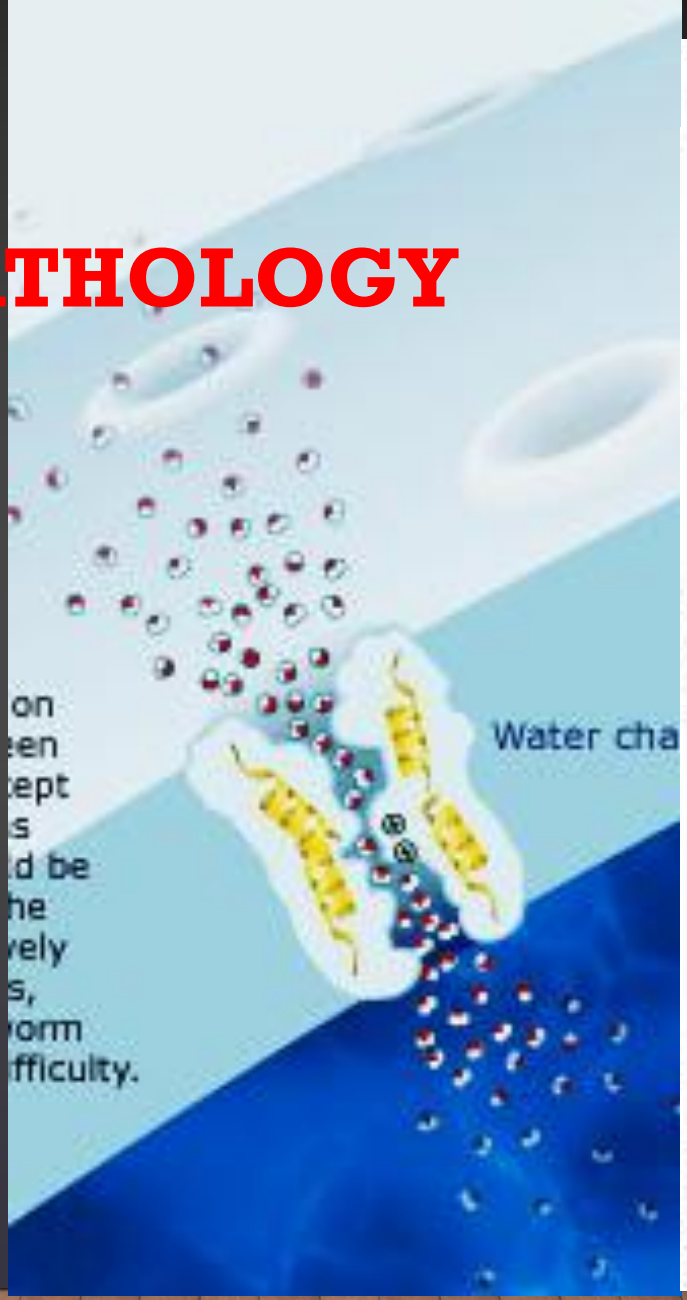
- Also known as Devic's disease.
- More common in females (**9:1**).
- Any ***age***.
- Affects ***mainly*** the optic nerves and the spinal cord.
- More severe attacks than in MS.
- Usually negative OCB in the CSF.
- More likely to have pleocytosis in the CSF.

Eugène Devic
1858 – 1930



NMOSD PATHOLOGY

- It is NOT primary demyelinating disease.
- Astrocytopathy but demyelination is secondary.
- Antibody targets aquaporine 4 (a water channel) on the astrocytes.
- Vasculocentric and rosette pattern deposition of immunoglobulin and complement.
- Confirmation of diagnosis is by testing anti-AQP4 (anti-NMO) antibody in the serum.



NMO TREATMENT

A. Acute treatment of relapses

- Similar to MS relapses

B. Disease Modifying treatments

- Azathioprine
- Mycophenolate mofetil
- Rituximab
- Inebilizumab
- Satralizumab
- Eculizumab

MS treatments may worsen NMO

Acute Disseminated Encephalomyelitis (ADEM)

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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 recurrence).

ADEM

PTHOLOGY:

- Wide spread white and gray matter peri-venous "sleeves" of inflammation and demyelination.
- Axons are relatively spared.

ADEM

- **SYMPTOMS:**
  - Encephalopathy (lethargy, stupor, coma).
  - Multifocal 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

ADEM TREATMENT

- Acute treatment: Steroids, plasma exchange and intravenous immunoglobulins.

- Disease modifying treatments: ???

SUMMARY

- **MS:**
  - 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.

SUMMARY

- **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.

SUMMARY

- **ADEM:**
  - Acute inflammatory demyelinating disease.
  - Monophasic.
  - More common in children.
  - Follows infection or vaccination.
  - Encephalopathy is a pre-requisite for the diagnosis in children.

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

Thank you

MS TREATMENT

- 1980's: Steroids for relapses only.
- 1990's: Disease modifying therapies (interferons & glatiramer acetate).
- 2000's: Mitoxantrone for aggressive MS and Natalizumab.
- 2010's: Oral medications now available (Fingolimod, teriflunomide, dimethylfumarate..).
- 2017 first approved treatment for PPMS: Ocrelizumab.