Team Medicine

#20

CNS Demyelinating Disease

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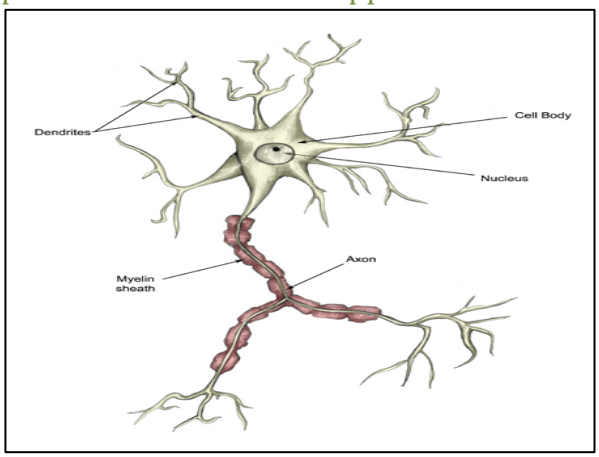
431 Teams

1. MYELIN

* Definition:
  A lipid dense layer that surrounds the axon of the neuron.
  Lipid-rich membrane that surrounds the axon of the nerve.
* Function:
  Insulates the axon to protect it from external damage and allows continuous propagation of the electrical impulse facilitates the propagation of action potentials throughout the nerve.
* Types:
  - Schwann cells → Peripheral nervous system (PNS)
  - Oligodendrocytes → Central nervous system (CNS)
  Schwann cells and Oligodendrocytes are types of neuroglia cells. Their main function is to provide insulation and support for the axons. They do this by creating the myelin sheath.



"A figure showing the body of a neuron"

2. DEMYELINATING DISEASAES

* Damage of the myelin They are diseases that cause damage to the myelin sheath.
* They can involve: PNS or CNS Why? Because myelin is present in the CNS and the PNS.
* They could be: Inherited or acquired. An example of an acquired demyelinating disease is Multiple Sclerosis. An example of an inherited demyelinating disease is Leukodystrophy.
* **CNS:** Multiple Sclerosis (MS), Acute Disseminated Encephalomyelitis (ADEM) and Neuromyelitis Optica.
* **PNS:** Acute Inflammatory Demyelinating Polyneuropathy (Guillain Barre Syndrome) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

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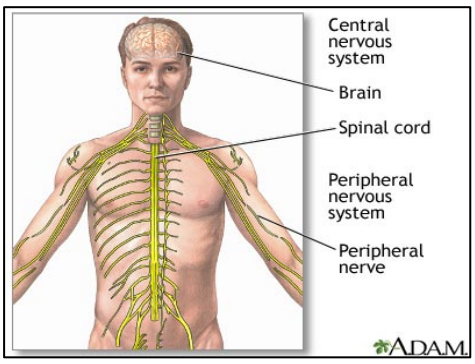
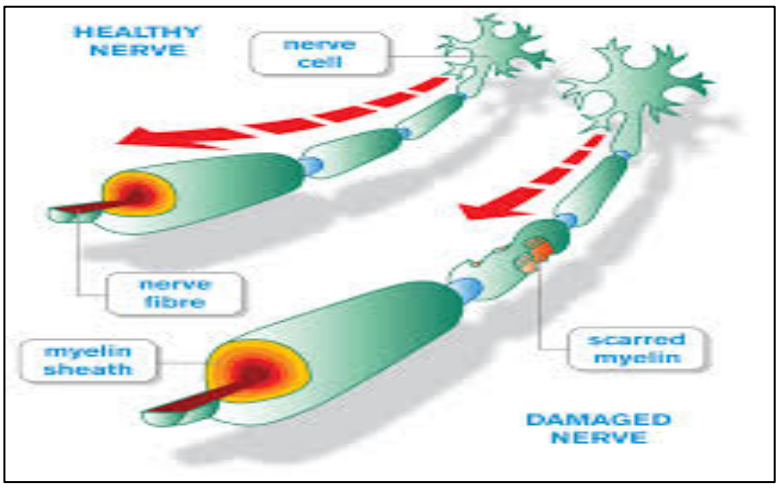
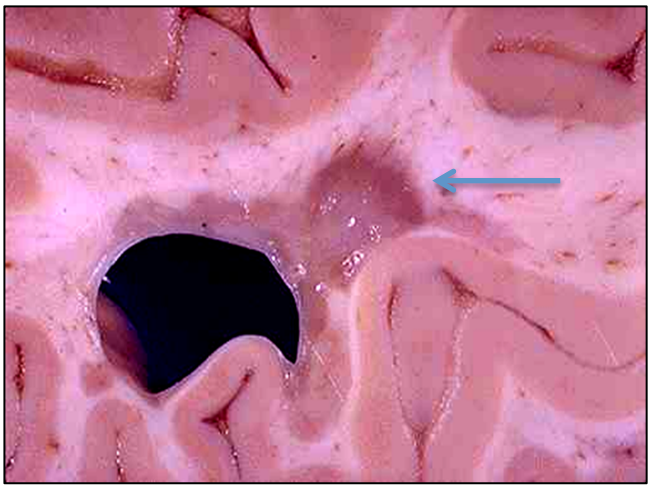


This is just a reminder of the CNS and the PNS. When we say the CNS, we mean: brain, spinal cord, cerebellum and brain stem. When we say PNS, we mean spinal nerves and cranial nerves except the optic nerve. Why? Because the optic nerve has the same embryonic origin as the brain and even it's myelin sheath is produced by oligodendrocytes NOT schwann cells.

3. Multiple Sclerosis (MS): The main bulk of the lecture.



This is a figure showing:
- Normal Neuron with the myelin sheath surrounding the axon and you can see the conduction of the action potential is fast and efficient from the start until the end of the axon.
- Damaged Neuron affected my MS. You can see part of the myelin is damaged/ scarred, so the action potential will stop at the damaged area. This may cause blocking or slowing of the action potential. (i.e. at times the damaged nerve can conduct but it will do so slowly).



This is a post mortem autopsy of a brain of an MS patient.
- The grey matter (cortex) is normal and healthy.
- The white matter shows a demyelinated plaque. As you can see, there is loss of the white material (lipid-rich myelin sheath).
- The lateral ventricle is normal. (MS commonly affects area around the ventricle.)
- It was thought that MS only affects the white matter, however it is proven now that it can affect both.

❖ Epidemiology:

- Among the most common neurological diseases in young adults
- More common in females (1.5-2.5:1)
- Mean age of presentation is 30 years usually affects people between 20 and 40 , but can rarely affect patients in extreme of ages.
- More people with MS were born in May and fewer people were born in November Why? They say it is because of vitamin D. There is a theory that the level of vitamin D in the mother will affect the risk of MS in a fetus. When a baby is born in May, it means that its conception was in winter, which means there is less sun and therefore less vitamin D for the mother and fetus.
- Of course it is not inherited but they found that first-degree relatives are at 15-33 times greater risk of developing MS when compared to the general population.
- More common in North America and Europe and rare in the tropics again this can be explained by the Vitamin D theory.

❖ Environmental Risk Factors:

- ***Infections:***
  - History of infectious mononucleosis (EBV) is associated with higher susceptibility to MS. They study a group of patients with MS and compared them to healthy normal controls. They found that almost 100% of these MS patients have a history of EBV infection, and most of them had the infection above the age of 15 (not as children). In comparison with the normal group, 90% of the healthy controls had a history of an EBV infection. The theory is that infection triggers the immune attack on the myelin sheath. The proposed explanation for this was that there is antigenic similarity between the virus and the myelin sheath.
- ***Vitamin D:***
  There have been lost of papers on many diseases, including schizophrenia, stroke and they also implicated low levels of vitamin D in cancer.
  - Sunlight may be protective (ultraviolet radiation or vitamin D) A study found that people taking 400 iu (international units)of vitamin D per day were less likely to develop MS in comparison to people who were not taking vitamin D.
  - Sun exposure & serum vitamin D are inversely related to risk/prevalence of MS The degree of sun exposure was also found to affect the incidence of MS.
  - Vitamin D levels are inversely related to MS disease activity For people already diagnosed with MS they found that people with more exposure to sun is tend to have a less severe disease and a slower disease progression.
- ***Smoking:***
  - A higher risk of MS in ever-smokers than in never-smokers. They found that MS tends to be more common in smokers, whether they are currently smoking or they quit years ago.
  - Smoking may also be a risk factor for disease progression. MS patients who are smokers tend to have a more severe disease.
- ***Genitics:***
  - Twins studies showed that genetics has a role but it is not everything.
  - HLA-DR2 (DRB1*1501) (antigen presentation)
  - IL-2Ra & IL-7Ra

❖ Pathology:

As previously shown in the autopsy photo, the hallmark is the demyelinating plaque with inflammatory cells (B-cells, T-cells, macrophages), glial cells with secondary neurodegeneration. Recent studies concentrate on studying how B-cells and T-cells cause this destruction; it might be an autoimmune process.

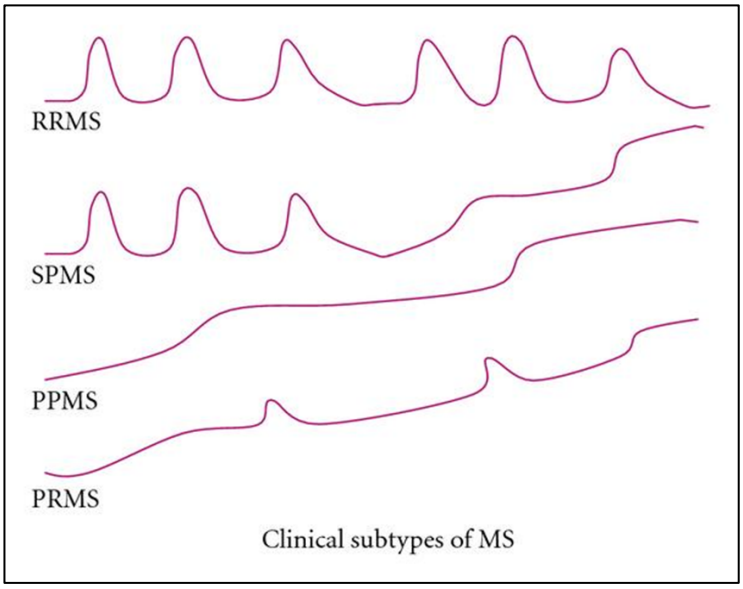
- Pathologic hallmark is focal demyelinated plaques.
- Variable degrees of inflammation, gliosis, and neurodegeneration.
- Recurrent relapses lead to permanent myelin damage and oligodendrocytes loss.

Our aim in treatment is to prevent the relapse. Why? Because we want to prevent the accumulation of disability. How? Each time the myelin is damaged it remyelinates, but with time the patient will lose their oligodendrocytes, so they will lose the ability to remyelinate. Loss of remyelination will lead to axonal damage, neurodegeneration and then a fixed deficit.

After remyelination, the patient sometimes goes back to normal and sometimes they can develop some deficits.

When there is axonal scarring, there is no going back to normal.

The disease can be stopped or maintained in early stages ONLY.



Clinical subtypes of MS

❖ Course:

- Relapsing remitting, secondary progressive, primary progressive or relapsing progressive.
- 80% of the patients will have a relapsing remitting course
- 50% of the RRMS will become secondary progressive
- We have 4 major types of MS:
  - Relapsing-Remitting (RRMS):
    The most common type and the one discussed in our session. 80% of MS patients have a RR course. What does this course mean? It means the patient will have a relapse (an attack) and then the will remit either by medication or without (they will either go back to normal or they will have some mild deficits). The patient will go back to their baseline or near their baseline, BUT they should improve. Otherwise, it is not a RR course. There has to be remission. These patients have EDSS score of 0 in their remission.(skip to page 9 to read about EDSS)

  - Secondary-Progressive (SPMS):
    This is the second most common type. Almost 50% or more of the RRMS patients will go around to develop SPMS. It is called secondary progressive because the patient will begin with a relapsing-remitting course, then after 10-20 years the relapses will stop and they will only have progression. To clarify if a patient has an attack then goes back to remission, then has another attack and goes back to remission , but the next time he develops an attack his remission won't be complete (e.g: power is 4 out of 5). These patients have an EDSS score of 1 or 2 in their remission.

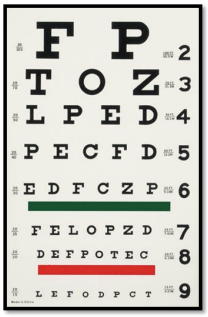
  - Primary-Progressive (PPMS):
    Primary means it is progressive from the beginning. From the onset of the disease, he will never have relapses. If he had a relapse it is secondary progressive. For example, the patient developed lower limb weakness. He will never go back to normal; his power will be 2 and the next time it will be 1 and then 0. Then, he may or may not develop other symptoms. All and any symptoms the patient will develop will only worsen with time. PP is the only type that affects females and males equally. You will see a lot of males with this type of course, and it commonly involves the spinal cord.

  - Progressive-Relapsing (PRMS):
    This type is very rare. The patient is progressive from the beginning, but the patient will have a few relapses in between. However, the relapses happen much less often than they do in RRMS. Why do some patients remit and others are progressive? MS is an inflammatory process. Inflammation heals with time or with steroids given. But, with the progressive courses the patient will have axonal damage. Once the axon is damaged, it cannot regenerate; they will have axonal loss. The remitting courses also have axonal loss, but to a much less degree. Early diagnosis may be helpful in RRMS and SPMS, but for the other 2 there is no cure anyway.

❖ SYMPTOMS: They depend on the site of the CNS involved (Ex: pain, ataxia, weakness, memory deficits, visual disturbance…)

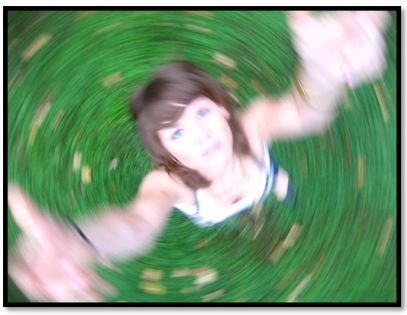


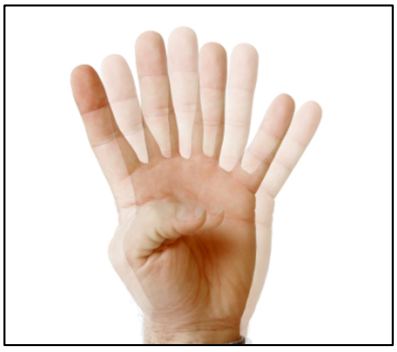




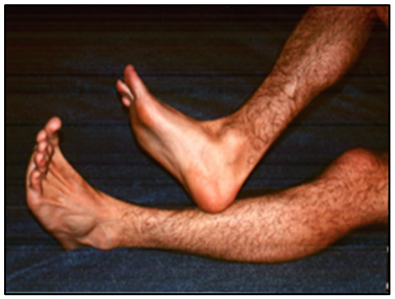
- **OPTIC NEURITIS:** One of the most common isolated syndromes. It is the inflammation of the optic nerve. (Isolated means MS only in one area)
  - Blurred vision. Decreased visual acuity.
  - Pain exacerbated by eyes movement. Eye-pain, which is worse with movement. This is very specific for optic neuritis.
  - Reduced perception of colors. Decreased sensitivity to contrast, especially red.
  - Flashes of light on moving the eyes
  - Enlarged blind spot. The blind spot is normal physiologically; it is there because the head of the optic nerve does not have photoreceptors. It is usually really tiny and cannot be seen unless enlarged.

- **BRAIN STEM RELATED SYMPTOMS:**
  It either involves a nucleus of a cranial nerve or it involves the actual cranial nerve while it is exiting the brain stem. Once the cranial nerve exits the brain stem, it is no longer considered a part of the CNS. **Vertigo** is a very common symptom. **Trigeminal neuralgia** is a very sharp electric-like pain that lasts for a fraction of a second and always along the distribution of the trigeminal nerve. Touching the face, chewing, talking or brushing the teeth induces it. **Diplopia** is also a very common symptom. Facial weakness is one of the common signs.





- **CEREBELLUM RELATED SYMPTOMS:**
  - Oscillopsia is the illusion of an unstable visual field; it is not true. It is a symptom that is seen in a person with nystagmus. The patient will complain that they see the room moving.
  - Dysarthria is slurred speech.
  - Ataxia. A patient can have an ataxic gait or difficulty coordinating hand movements.

- **BRAIN AND SPINAL CORD SYMPTOMS:**
  - Cognitive dysfunction: memory impairment, reduced concentration, and depression, processing speed.
  - Weakness (monoparesis, paraparesis, quadriparesis). Weakness can present in any pattern. Monoparesis is the involvement of one arm or one leg due to involvement of the brain or the spinal cord. It could also be paraparesis, which is usually due to a lesion in the spinal cord. If the patient is unlucky, it could be Quadriparesis due to a lesion in the cervical spinal cord.
  - Sensory loss/numbness/pain/burning sensation.
  - Sphincteric dysfunction. Ask about patient about frequency, urgency, and incontinence. Also, ask about stool incontinence and retention.
  - Lhermitte's Phenomenon. It is an electric-like sensation (or sometimes numbness and tingling) that runs from the neck and down along the back on flexing the head. It is indicative of a lesion in the cervical spinal cord. It is not specific for MS, but it is commonly seen. It could be due to any lesion. For example, a tumor or a disk compressing the spinal cord. When a patient flexes their head, the lesions become irritated and emit impulses.

- **TRANSVERSE MYELITITS:** It is not a diagnosis, confirmed by MRI for the spinal cord.
  - A general term that indicates inflammation of the spinal cord.
  - Could be caused by MS, NMO, infections, connective tissue diseases, vasculitis (ex: Lupus or Sjogren's) or paraneoplastic.
  - Spinal cord related motor, sensory &/or autonomic dysfunction. Patients will present with symptoms suggestive of spinal cord involvement. For example, weakness. It depends on the level. Cervical spinal cord will give quadriparesis, and lumbar or thoracic will give paraparesis.
  - Sensory level. The patient will tell you feel like they have a band or a belt around their abdomen or around their chest. It is detected during examination.
  - Unilateral or bilateral. Usually it involves both sides of the body, but sometimes it involves both sides.
  - A lumbar puncture for CSF examination will show increased WBC count and proteins. Why? It is inflammation. It will show what any simple inflammation would show.

- **Relapse or Attack:** When an MS patient comes in with a neurological complaint, we need to know if it is a true relapse. Because, if it is, we have to give them steroids. The neurological complaint may not be related to their MS; it could be a stroke or peripheral neuropathy, for example. What is the definition of a relapse? It has to meet certain conditions so it can be diagnosed as a relapse…
  - Patient-reported symptoms or objectively observed signs. They have to be CNS signs and symptoms, and not a symptom of peripheral nerves. For example, MS will not present as numbness on the distribution of the median nerve.
  - Typical symptoms of CNS acute inflammatory demyelinating lesions. A good history and CT scan will help establish that it is not a stroke.
  - It should last at least 24 hrs. Less than that is not a relapse, even if it's related to MS.
  - No fever or infection.

  - **Uhthoff's Phenomenon:** It is also due to inflammation and demyelination, but with 2 differences; it lasts less than 24 hours. It accompanies an increase in body temperature for any reason like exercise, an infection or a hot bath.
  - Neurological dysfunction same as a relapse. The presentation is CNS symptoms.
  - Stereotyped
  - Less than 24 hours. This is very important.

- Reversible. It will be transient and reversible spontaneously. The patient will not need medication to reverse the symptoms. It will FULLY reverse on its own.
- Related to fluctuations in axonal conduction properties due to increasing body temperature. The explanation is that the injured axons are very sensitive to changes in body temperature. Even if it is half a degree only. With increase in body temperature, the demyelinated axons will not conduct impulses, because the usual slow conduction will be blocked. Most of the time, the presenting symptom will be blurring of vision.

❖ Diagnosis:

It is a deceiving disease and it can present with anything (ex: Cerebellar syndrome, spinal cord syndrome, optic nerve, brain… etc.). How do we know it is MS and not something else? The patient has to have 2 attacks separated by at least 30 days. If it is less than 30 days, it will be considered the same attack. This is what we call dissemination in time. Dissemination is space has two means of detection; either by history or by MRI. The patient has to have two separate lesions in 2 separate places (Involves 2 different sites in the CNS). So the patient will either need to give a history of symptoms in 2 different sites, or an MRI can show us 2 lesions without a history of symptoms. For example, a patient will present with ataxia only. When we did an MRI, we found one lesion in the cerebellum and another in the frontal cortex. This is MS.

- **McDonald diagnostic criteria:** You don't really have to focus on this.
  - Dissemination in time: history of at least two attacks. For example, patient had optic neuritis in 2012 and ataxia 2014.
  - Dissemination in space: clinical evidence of involvement of two CNS sites OR of one lesion with reasonable historical evidence of another site being affected. For example, a history of optic neuritis and a history of ataxia.
    If the patient is a typical MS patient (female, young, you excluded other things), you don't even need an MRI. The history will be good enough.

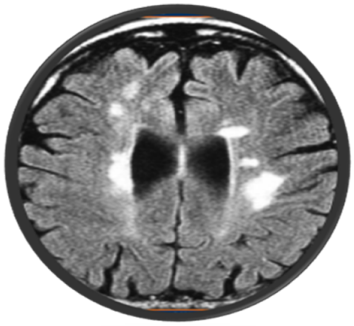
Mc Donald criteria for MS

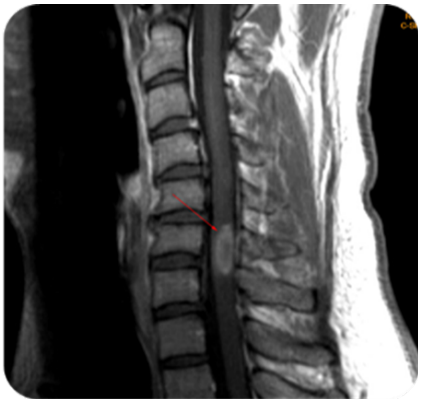
Dissemination in space	Dissemination in time
1 T2 lesion or more in at least two MS typical CNS regions: • Periventricular • Juxtacortical • Infratentorial • Spinal cord	• Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time **OR** • A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing **OR** • Await a second clinical attack

For example, if a patient only has optic neuritis symptoms and the rest of the exam is completely normal (it may be her first neurological attack). You do an MRI and Follow the rule of dissemination in space and time with MRI instead of the history. Dissemination in space on MRI would be one or more lesions in 2 of these 4 areas:
-Periventricular (around the ventricle)
-Juxtacortical (between the cortex and the sub-cortex, just below the cortex)
-Infratentorial (below tentorium cerebelli, between cerebellum and brain stem)
-Spinal Cord
Dissemination in time on MRI is the presence of contrast-enhancing lesion and non-contrast-enhancing lesions at the same time. Why? Contrast enhancement indicates an acute lesion (an ongoing inflammation). The non-enhancing lesion would indicate and older lesion. Another form of dissemination in time is the presence of a new lesion when compared to a baseline MRI.

- **Imaging:** MRI of the brain and spinal cord. Always order MRI brain for isolated syndromes. You might find lesions in the brain.
  These are examples of MRIs of patients with MS.
  MRI findings showed MS lesions in patients with no signs, indicating a subclinical period

This is an axial cut. This is what we call a high T2 signal intensity lesion. The lesions are juxtacortical and periventricular, which is typical for MS.

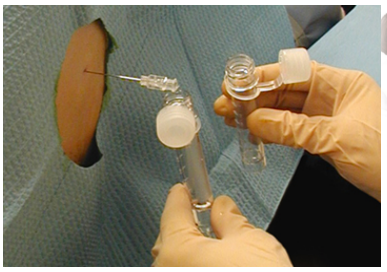


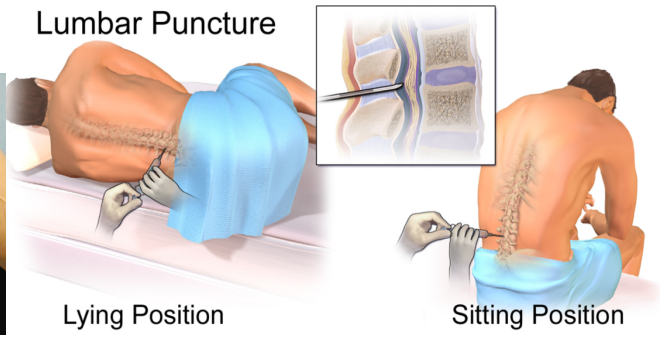


This is a sagittal cut of the spinal cord. It shows a high signal intensity lesion in the thoracic cord. The spinal cord lesions are usually small. On axial cut, the lesion does not occupy the entire transverse section of the SC.

MRI with contrast shows enhancement in lesions (partial ring).
Lesions surrounding the corpus callosum are the most characteristic sign for MS.

- **Lumbar puncture**: oligoclonal bands and IgG index.
  It can be done in a sitting or lying position. The needle is introduced between L1 and L2, then into the subarachnoid space.

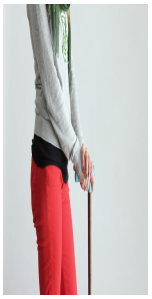


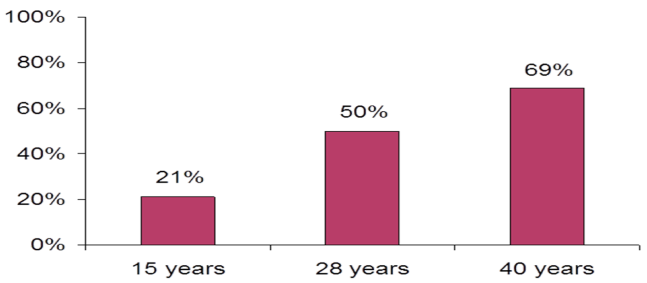


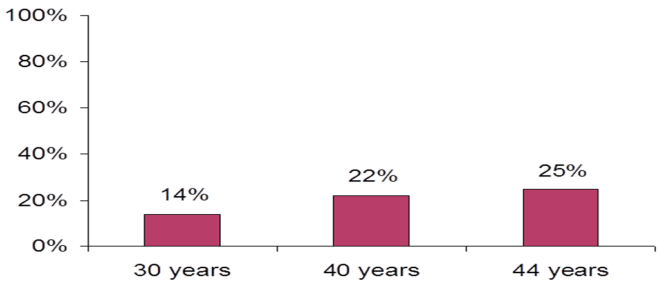
Other tests : Visual evoked potentials is an old test that was used to detect if there is optic neuritis.

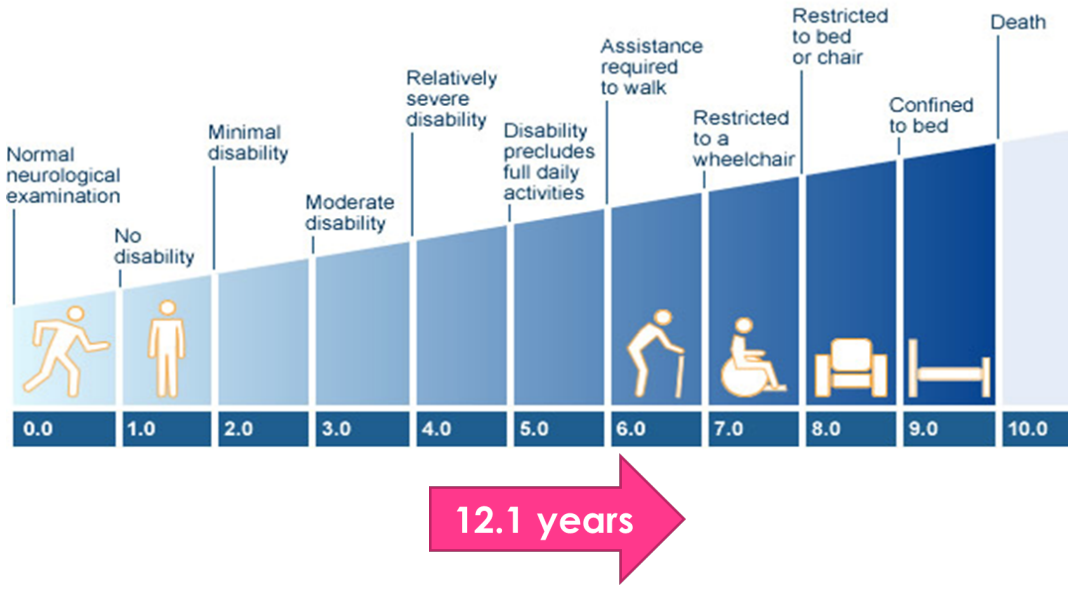
❖ **Prognosis:** This is very important and it is what patients care about the most.

- Fifty percent of patients will require a cane 28 years after disease onset. That's half of the patients. This is a massive number. For example, if a 12-year-old girl was diagnosed with MS, she will be using a cane at the age of 30.
- Twenty five percent will require a wheelchair 44 years after disease onset.









The EDSS score: We use this in the clinic to follow up with the patient. 0 means normal exam and 10 is death due to MS. They found that the patient needs 6 years to move from 3 (moderate disability) to 6 (using a cane). They need 12 years only to progress from 3 to using a wheelchair.

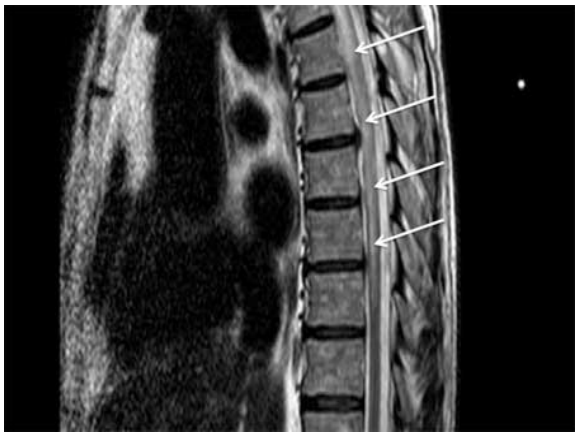
❖ **Treatment:** Two types of treatment: treating a relapse or preventing a relapse.

- Acute treatment of relapses: steroids and plasma-exchange.
- Prevention of relapses: This has advanced a lot in the past 30 years.

- 1980's: Steroids for relapses only.
- 1990's: Disease modifying therapies (interferon given 3 injections per week and copaxone).
- 2000's: Mitoxantrone for aggressive MS and Natalizumab given once a month.
- 2010's: **Oral medications now available (Fingolimod).** They have less efficacy than other types(sub-cutaneous) but have much less side effects.
- Symptomatic treatment is also considered (to treat depression, sexual dysfunction.. etc.)

4. NEUROMYELITIS OPTICA: Very severe disease, which is much worse than MS. The good thing is that it has its own treatment.

- More common in females (9:1). It is very rare to find a male with NMO.
- Mean age is 10 years later than MS. The mean age is older in NMO. For example, if the mean age in MS is 30, it will be 40 in NMO.
- More common in Asian and African populations. Less common in North America and Europe.
- Affects mainly the optic nerves (optic neuritis) and the spinal cord (transverse myelitis). That is why it is frequently confused with MS.
- More severe attacks than in MS.



This is an MRI of a NMO patient. You can see the lesion here is much larger than the MS lesion. This is what we call a longitudinal extensive lesion (involves more that 3 vertebral segments); Characteristic for NMO and rarely seen in MS. So if you see a lesion like this, you have to rule out NMO.
Criteria for the Diagnosis of NMO:
Optic neuritis + transverse myelitis + specific antibodies (aquaporin 4 antibodies) + longitudinal extensive lesion on MRI + The MRI is not typical for MS.

- **Pathology:**
  - Astrocytopathy; it is a demyelinating disease but it mainly affects the astrocytes (type of glial cells).
  - Targets aquaporine 4 (a water channel) rich areas. The channels are located at the foot-processes of the astrocytes.
  - Vasculocentric deposition of immunoglobulin and complement around the vessels as well as inflammatory cells around the main vessel.
- **Treatment:**
  - Acute relapse: steroids or plasma exchange. Same as MS because it is an inflammatory process.
  - Relapse prevention: chronic immunosuppression with azathioprine, mycophenolate mofetil and cyclophosphamide. The prevention is very different from MS because Interferon and Fingolimod worsens NMO patients. That's why it's very important to differentiate between the 2. The most important things to differentiate between the two: Age (they tend to be older but not elderly), Spinal lesion on MRI (longitudinally extensive), Females (Much more commonly involved in NMO) and NMO is a more severe aggressive disease that is unresponsive to Interferon.

5. ADEM:

- Acute disseminated encephalomyelitis.
- CNS inflammatory demyelinating disease.
- Frequently proceeded by vaccination or infection. Meaning it is an autoimmune process brought on by an infection of vaccination, which are both common in children. Because of antigenic similarity.
- More common in children. It is much more common in children than MS. Think of ADEM if a child has an MS-like clinical presentation.
- Usually a monophasic illness (no relapses). It hits once most of the time. The damage happens once and they usually have a good prognosis. The biggest and the most important difference between ADEM and MS.
- **Pathology:** Perivenous "sleeves" of inflammation and demyelination. Not Important.
- **Treatment:** Steroids, Plasma Exchange and IV Immunoglobulins (Ig).

Summary:

Multiples Sclerosis	**Neuromyelitis Optica**	**ADEM**
Onset typically occurs in the 20- to 50-year-old age group. (Young) Ms affects females much more frequently than males.	Occurs in an older age group than in MS. The disease affects mostly females.	Occurs commonly among children.
Has a relapsing remitting course that could progress.	Only a relapsing course with no progression.	A monophasic disease with no relapse and remission pattern.
The symptoms depend on the involved site but common symptoms are: Diplopia and optic neuritis Unusual sensations "pins and needles" Bladder problems Trouble walking "Ataxia" Dizziness Fatigue Muscle spasm Speech problems or swallowing difficulties,	Presents commonly with optic neuritis and transverse myelitis. Optic neuritis: - Decreased visual acuity with "blurred vision" - Pain on movement of the affected eye. - Patients may loose some of their color vision in the affected eye (especially red) - Enlarged blind spot.	Symptoms usually begin 1–3 weeks after infection or vaccination. Major symptoms include fever, headache, drowsiness, seizures and coma.
* Pathological mark: Focal inflammatory demyelinated plaques. On MRI: Abnormal areas with hidden damage appear in the brain and spine.	* Longitudinal extensive transverse myelitis (LETM) is a characteristic feature of neuromyelitis optica. (LETM) is defined as a spinal cord lesion that extends over three or more vertebrae, as seen on MRI of the spine.	* Characterized by the presence of perivenous sleeves of demyelination and inflammation.
Treatment: Explained above.		

Questions:

Q1: Ms. C is a 35-year-old white female. She came to Neurology Clinic for evaluation of her long-term neurologic complaints. The patient relates that for many years she had noticed some significant changes in neurologic functions, particularly heat intolerance precipitating a stumbling gait and a tendency to fall. Her visual acuity also seemed to change periodically during several years. Two months ago the patient was working very hard and was under a lot of stress. She got sick with a flu and her neurologic condition worsened. At that time, she could not hold objects in her hands, had significant tremors and severe exhaustion. She also had several bad falls. Since that time she had noticed arthralgia on the right and subsequently on the left side of her body. Then, the patient abruptly developed a right hemisensory deficit after several days of work.

The most appropriate next step to do is?

A. Preform a LP to analyze her CSF.
B. Preform an electrophysiological test.
C. Do a brain CT scan.
D. Do an MRI scan.
E. Lab analysis of blood sample.

Q2: A 35- year old female patient complains of numbness and weakness involving the left leg. The patient reports the signs and symptoms have progressed over the past two days. History reveals that the patient had a gastrointestinal illness two weeks before the consult. A year ago, the patient had a transient absence of vision in one eye, but the symptom resolved without treatment. On physical examination, the patient is unable to stand or walk despite reasonable strength in lower extremities. The patient is also noted for nystagmus, scanning speech and decrease reflexes in the right leg.

The following are included in the differentials in this case: Select all that apply.

I. Multiple Sclerosis.
II. Huntington disease.
III. Guillain-Barre Syndrome.
IV. Amyotrophic Sclerotic disease.

A. I,II
B. I,III
C. I,II,III
D. I,II,III,Iv

Answers:	**Q1: D** **Q2: B**

Explanations:

Q1

By themselves, there are no specific tests that can determine if a person has MS or is likely to have it in the future. Current diagnosis of definite MS involves both clinical (history and neurological exam) and paraclinical (MRI, Spinal Tap, Evoked potentials) evidence. *The initial test after taking a history from the patient and preforming a through neurological examination is MRI.*

Q2

Multiple sclerosis and Guillain-Barre syndrome are included in differentials. Multiple sclerosis is manifested by the Charcot's triad, which includes nystagmus, scanning speech and intentional tremor. A transient absence of vision in one eye is a common finding in Ms. Guillain-Barre syndrome is manifested by weakness in the lower extremities and associated with a recent gastrointestinal illness.