Multiple sclerosis

435 medicine teamwork

[Important | Notes | Extra | Editing file]

lecture objectives:

- Not given.

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References: Slides, Step up & Davidson

Multiple sclerosis (MS)

Prelude:

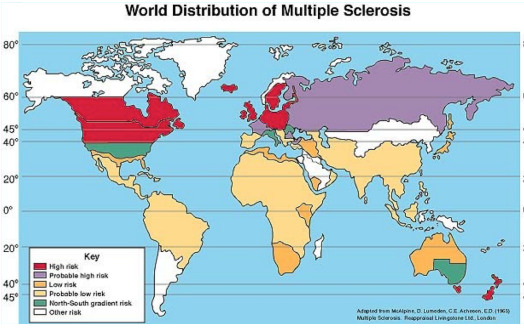
Review of basics:

- **What is myelin?** it's a lipid dense layer that wraps around the axon of some nerve cells.
- **What is the function of myelin?** Insulates the axon and allows continuous propagation of the electrical impulse.
- **What are schwann (neurilemma) cells?** They are cells in the *peripheral nervous system (PNS)* that produce the myelin sheath around neuronal axons.
- **What are oligodendrocytes[1]?** They are cells in the *central nervous system (CNS)* that produce the myelin sheath around neuronal axons.

Characteristics:

Definition:

- Multiple sclerosis is an inflammatory demyelinating disease of the CNS where we have clinical evidence of dissemination in space, dissemination in time. And provided that there is no other alternative neurologic disease explaining the presentation. This will be explained further on.
- **Multiple sclerosis a clinical diagnosis!** No lab test alone will be able to **confirm** the diagnosis.



Epidemiology:

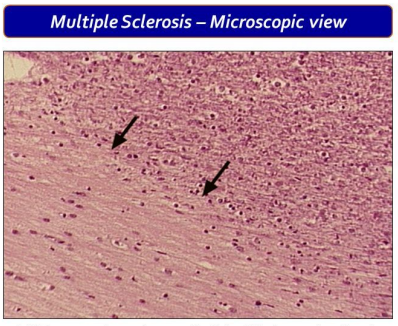
- Worldwide occurrence of 1.1-2.5 million cases.
- Most common neurological disease of young adults.
- Mean age of presentation is 30 years, range of onset is 15-45 years.
- Common in north America and Europe, rare in the tropics. There are multiple theories behind this; is it because of the geographical distribution? the hygiene theory? or the ethnicity
- A brief story from the doc: a sudanese female migrated long time ago to SA, recently she got MS, which is very rare in african heritage…. umm

Immunopathology:

Check this diagram out after reading what we've wrote (highly recommended).

'Direct proof of an autoimmune response is lacking
No specific autoantibody or autoreactive T cells'

- The pathologic **hallmark** of multiple sclerosis is **multiple focal areas of myelin loss within the CNS (plaques or lesions)**.
- **Selective demyelination of the white matter of CNS**. (dosen't affect PNS nor the grey matter in CNS)
- **Classical location** of plaques are at the **periventricular** regions of the brain, **optic nerves**, and the **subpial** regions of the spinal cord.
- Several basic processes drive the formation of these plaques: **Inflammation → myelin breakdown → astrogliosis and oligodendrocyte injury → neurodegeneration and axonal loss → remyelination**



A high power photomicrograph of the MS plaque showing the pallor of the plaque almost devoid of myelin. There is a decrease in oligodendroglial nuclei and an increase of astrocyte nuclei characteristic of an older MS plaque.

[1] Remember; **satellite** oligodendrocytes are **NOT** involved in myelination.

- Demyelination is accompanied by variable gliosis and inflammation with **relative axonal preservation**. Relative axonal preservation helps us to differentiate MS lesions from necrosis (e.g. trauma). In necrosis; axons and myelin are depleted to the same extent!
- Yet despite relative axonal sparing, axonal injury still does occur. This is evident by the presence of axonal swellings (irregularly swollen axons with a beaded appearance), accumulation of amyloid precursor protein (a marker of focal accumulations of proteins that are typically moved along axons by fast axonal transport) and mild axonal loss.مؤخرًا وجدوا إن حتى الاكسونز تتأثر إلى حد ما.
- **Acute** *axonal* injury occurring in early MS lesions contribute to the relapse related disability observed predominantly during the disease's inflammatory phase. While **chronic** *axonal* injury will cause axonal loss or sclerosis resulting in **permanent** deficits.يقولك أن في الحقيقة تأثُر الاكسونز هو السبب وراء الأعراض الشديدة اللي تؤدي إلى العجز أثناء الهجمة. أيضًا هو السبب وراء الأعراض التي لا تزول بعد زوال الهجمة
- In the long term; accumulating myelin loss reduces the efficiency of impulse propagation or cause complete conduction block leading to **permanent** impairment of CNS functions.
- Lymphocytic inflammatory infiltrate is mainly **CD8 (+) cytotoxic T-lymphocytes and humoral.**
- The extent of axonal damage in *active* lesions correlates **significantly** with the **number of lymphocytes and activated microglia.**
- Extensive remyelination is apparent by the presence of newly formed myelin sheaths and oligodendrocyte precursor cells. This process is frequently encountered within active plaques of early multiple sclerosis.
- Why don't we classify it as an autoimmune disease? **Direct proof of an autoimmune response is lacking, no specific autoantibody or autoreactive T cells**

Risk factors:

Genetic Factors	
Gender	More common in females than males (3:1)
Family history	First degree relatives are 15-33 times at greater risk Concordance rate in dizygotic twins: 3-5%, and in monozygotic twins: 20%.
Race	MS is more commonly seen in caucasians
Polymorphism	Polymorphism of HLA proteins is estimated to account for 17%-60% of the genetic susceptibility to MS. HLA-DR2 on chromosome 6 Single nucleotide polymorphisms in the chains of **IL2 and IL7 receptors**.
Environmental Factors	
Infections	- History of infectious **mononucleosis** (**EBV**[2]) is associated with a higher susceptibility for MS. - Antibodies to EBV were higher in people who developed MS than in control samples. - HHV-6[3]: antibodies were three times higher in women with progressive MS.
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
Smoking	- A higher risk of MS in ever-smokers than in never-smokers.

[2] Epstein-Barr Virus
[3] Human herpesvirus 6

	- Smoking can also be a risk factor for increased disease progression.
Obesity	- Obesity in adolescence/early adulthood is associated with an increased risk for MS. - Leptin increases the proliferation of auto-aggressive cells responsible for myelin damage.

Signs and symptoms:

Deficit	Symptom **MS can be SILENT! no signs or symptoms.**
Transient sensory deficit	- **Most common initial presentation.** - Decreased sensation or paresthesia in upper or lower limbs. - **Lhermitte phenomenon (electric like sensation induced by neck flexion) Very classic symptom; caused by cervical demyelination.** - **Uhthoff phenomenon. (heat intolerance)**
Fatigue	- One of the most common complaints. Not related to exercise!
Motor symptoms	- Weakness. (can progress to paralysis) - Spasticity. - Caused by pyramidal tract involvement. (upper motor neuron)
Visual disturbances	- Optic neuritis ○ **Subacute onset (1-10) days.** ○ **Mononuclear** visual loss. ○ **Pain on movement of eyes.** ○ Central scotoma (black spot in center of vision). ○ Reduced perception of colors) ○ Afferent pupillary defect. It's a medical sign observed during the swinging-flashlight test whereupon the patient's pupils constrict less (therefore appearing to dilate) when a bright light is swung from the unaffected eye to the affected eye. ○ Median visual acuity 20/60 vision is not severely affected as in neuromyelitis optica - Internuclear ophthalmoplegia—strongly suggests the diagnosis ○ A lesion in the **medial longitudinal fasciculus** results in **ipsilateral medial rectus palsy** on attempted lateral gaze (adduction defect) and horizontal nystagmus of abducting eye (**contralateral** to side of lesion). ○ Diplopia can occur.
Cerebellar involvement	- Can cause ataxia, intention tremor, dysarthria. - Classical patients: 1. A patient came complaining of weakness, this is related to what? Pyramidal tract lesion 2. A patient came complaining of sensory symptoms, this is related to what? Spinothalamic lesion 3. He came with ataxia --> cerebellar lesion
Autonomic involvement	- May present as impotence, constipation &/or urinary incontinence. Sexual dysfunction, you'll not know about it until you ask the pt.
Cerebral involvement	- Cortical demyelination → late onset dementia. - May occur in advanced illness and manifests as memory loss, personality change, and emotional lability; anxiety and depression are common.

Neuropathic pain	- A frustrating but common complaint that manifests as hyperesthesias (excessive physical sensitivity) and trigeminal neuralgia.
Dysphagia	The prevalence of dysphagia increases with increasing disability putting the patient at risk for **aspiration pneumonia**, **and the congested cough is an indication that aspiration has already occurred.** Very serious complication. Dysphagia reflects the involvement of cortico-bulbar, cerebellar or brainstem regions.

Types of MS:

Type	Course
Relapsing remitting (RR-MS) 	**Most common → 80% of MS patients.** **Clinical exacerbation** of neurological symptoms (**relapse** نكسة) If it's the first time, we call it an attackهجمة. followed by complete or incomplete remission during which the person fully or partially recovers from the acquired neurological deficits. Note that not every relapse resolves 100% completely. This is especially true if the patient came late on presentation. But if he comes within 1-2 weeks of onset and you treat them; they'll most likely resolve completely. But if it's months late, it won't resolve completely. Case from the doctor: A female patient complained of unsteady movement for a month. In her history; A year ago, she had sensory symptoms on her left side, was treated and subsequently, her symptoms improved. 5 years ago she had optic neuritis. This history is very suggestive for MS. Is her symptoms progressive or relapsing and remitting? relapsing and remitting
Primary progressive (PP-MS) 	Gradual progression of the disease from onset, no overlapping relapse or remission. 10-20% of cases. A patient came because of weakness in her lower limb since 2 years. She denied that it affected her daily activity but complains that it's now getting worse day by day and she can't even walk 10 meters anymore. Very suggestive of progression **later on will discuss the :حطوا له كرايتيريا لحاله relapses & remissions ولأنه مافيه** **general criteria of MS diagnosis** **Primary Progressive MS** 1 year of disability progression (retrospectively or prospectively determined) independent of clinical relapse. **Plus two of the following criteria:** ● One or more T2-hyperintense lesions characteristic of multiple sclerosis in **one** or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial. ● Two or more T2-hyperintense lesions in the spinal cord. ● Presence of CSF-specific oligoclonal bands.
Relapsing progressive (RP-MS) 	Initially presents as PP-MS, but, during the course of the disease; individuals develop true neurologic deficit exacerbations. In other words, steady progression of clinical neurological damage with **superimposed relapses and remissions**.

Secondary progressive (SP-MS) 	Steady progression of neurological damage with or without superimposed relapses and minor remissions. Patients will have experienced a period of RR-MS before which may have lasted 2-40 years. Relapses and remissions fade over time. **50% of RR-MS will develop eventually SP-MS.**

Clinically Isolated Syndrome

اللفظ الطبي اللي نقوله لمّا يجي شخص لأول مرة مع أعراض تتناسب مع التصلب اللويحي لكن لسى ما بعد تأكدنا

A monophasic clinical episode with patient-reported symptoms and objective findings developing acutely or subacutely, with a duration of **at least 24 h**, with or without recovery, and in the absence of fever or infection; similar to a typical multiple sclerosis relapse (attack and exacerbation) but in a patient not known to have multiple sclerosis.

- can be monofocal (reflecting pathology in a single location) or multifocal; the specific manifestations of a clinically isolated syndrome depend on the anatomical location (or locations) of the pathology.
- Typical presentations include unilateral optic neuritis, focal supratentorial syndrome, focal brainstem or cerebellar syndrome, or partial myelopathy.

Atypical for CIS (لو المريض جا فيها نفكر بشيء غير التصلب اللويحي)			
Bilateral optic neuritis	Complete ophthalmoplegia	Complete myelopathy	Encephalopathy
Headache	Alteration of consciousness	Meningismus	Isolated fatigue

Clinical attack (relapse or exacerbation):

- A **clinical attack** is considered if the symptoms are present for **at least 24 hours** and is preceded by more than 30 days of clinical stability. There has to be no better explanation (other than MS) for the attack and we must rule out **psuedorelapse**. Examples of psuedorelapse: metabolic stress, infections that worsens the symptoms. or if the symptoms last for LESS than 24 hours. (in a relapse the symptoms have to occur for MORE than 24 hours.)
- Patient-reported symptoms or objectively observed signs.
- Typical of CNS acute inflammatory demyelinating lesion.
- No fever or infection.

Diagnosis

★ History & Exam

MS is mainly a clinical diagnosis. Suspect MS if the patient is for example a **young adult** with **relapsing and remitting neurologic signs** and symptoms that are difficult to explain. *Try to exclude other differentials.*

WE CAN BRING IT AS AN OSCE → ex: young 20-30, several episodes of neuro symptoms, multiple signs on examination. Top ddx HAS to be MS. no excuses!

MS mimicker

Always look at the age; if you have a 60 year old w/HTN, DM. complaining of loss of memory. Your MRI showed multiple **NON enhancing lesions.**

= It's obviously not MS, you're looking at a small vessel disease

- Sarcoidosis.
- Behcet Disease. Here you'll find extra-neurological symptoms such as; **mouth ulcers.**
- B12 Deficiency.
- Lyme/brucellosis. Lyme is the equivalent of brucellosis in the west.

★ MRI

The **most sensitive** test and is considered **diagnostic** in the majority of the cases. However, the number of lesions on the MRI is not necessarily proportional to disease severity or speed of the progression. MRI is abnormal in 90% of MS patients.

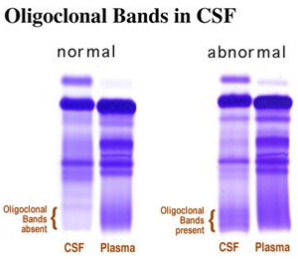
IMPORTANT!

Doctors notes: If I have a patient with weakness and on MRI we have multiple lesions affecting the pyramidal tract explaining the weakness then great.

But if I have a patient with loss of vision and on MRI there is a lesion on the optic nerve and another lesion in the brain without corresponding symptoms. Why is that? We don't know!

The lesion that takes up the contrast aka enhanced lesions are ACTIVE lesions while if there are other lesions but they don't take up the contrast then we call them NON ACTIVE

★ Lumbar puncture and CSF analysis



Although no laboratory tests are specific for MS, high levels of CSF-restricted **oligoclonal bands** and **IgG index** are present in 90% of MS patients & can be regarded as additional confirmatory test. We don't see oligoclonal bands in normal individuals. You can find them in MS pts and in CNS infections, the difference between the two is that in infections the bands will disappear after you treat the pts, on the other hand, bands will persist in MS pts. **But it's not specific (can be seen in sarcoidosis & in many infections e.g. Syphilis)**! Also note that in MS IgG oligoclonal bands are restricted to the CSF (intrathecal immunoglobulins not found in the serum). So elevated SERUM oligoclonal is NOT characteristic of MS.

Mc Donald's MS diagnostic criteria:

- The McDonald criteria, first developed in 2001 and revised in 2005,and in 2010.
- Final revisions of McDonald criteria was in 2017.
- Diagnosis of **"Clinically definite MS"** needs demonstration of **dissemination of space and time.**
- Dissemination in space and time both have clinical and imaging aspects, for example (in space):
  1- Clinically: if the pt tells you that he\she has optic neuritis and ataxia (which are two symptoms from two different places). If he\she tells you only one symptom, you have to do an MRI to see if there is more than one lesion.
- In time:
  1- Clinically: more than one attack per one year.
  2- Imaging: by comparing the image you took now with last year's image. or at the same image we'll see the non-enhancing and enhancing lesions.

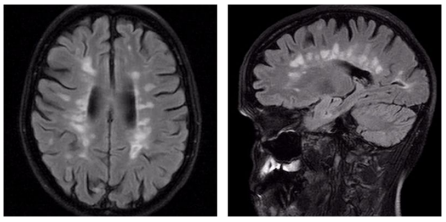
The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset		
Attacks	**Number of lesions with objective clinical evidence**	**Additional data needed for a diagnosis of multiple sclerosis**
≥2 clinical attacks	≥2	none
≥2 clinical attacks	1 (as well as clear-cut 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.**

الزبدة: لازم يكون فيه هستوري لهجمتين + two white matter lesion سواء اكتشفناها بالفيزكل اقزام أو بالـMRI
أو هستوري لهجمتين +one white matter lesion on MRI + abnormal CSF (oligocolonal bands)

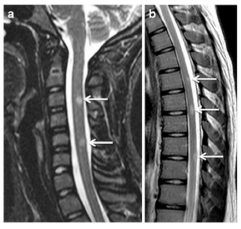
MRI T2

Perivenricular (Dawson finger)

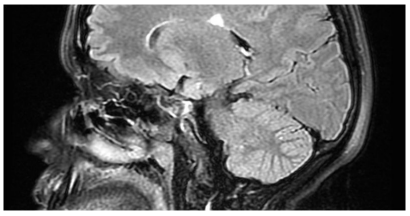


Radiographic feature depicting demyelinating plaques through the corpus callosum, arranged at right angles along medullary veins (callososeptal location). They are a relatively specific sign for MS which presents as T2 hyperintensities.

Spinal lesion



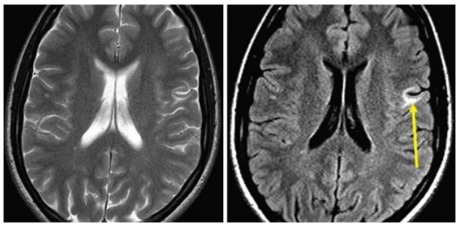
Corpus callosum lesion



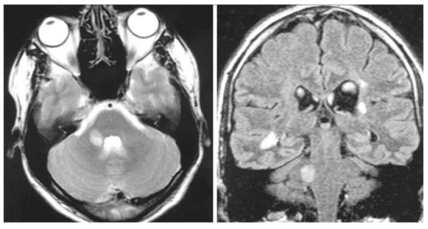
Characteristics of MS lesions on MRI:

- Large ≥ 3 mm
- Ovoid
- Oriented perpendicular to ventricles
- Enhancing:
- Open ring enhancement
- Multifocal homogenous

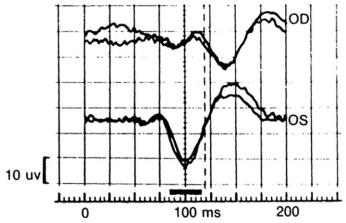
Juxtacortical lesion



Infratentorial lesion



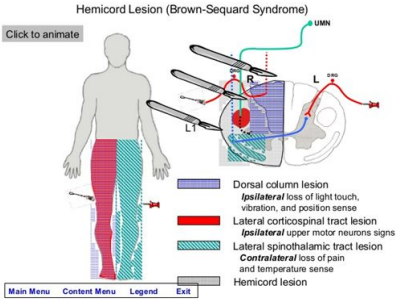
Delayed Visual Evoked Potentials response



This sign is not specific for MS but it helps.

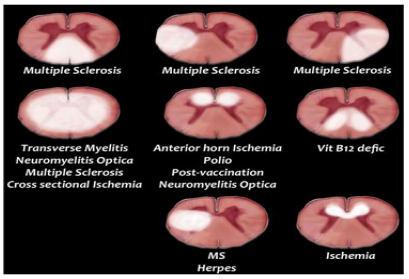
Myelitis in multiple sclerosis

Usually it's partial, mimicking brown squared syndrome



(VEP) A visual evoked potential is an evoked potential caused by a visual stimulus, such as an alternating checkerboard pattern on a computer screen.These responses usually originate from the occipital cortex, the area of the brain involved in receiving and interpreting visual signals.

Visual evoked potential: we stimulate the optic nerve and record the occipital lobe if theres an optic nerve lesion --> delayed potential used when we can't use MRI



Transverse myelitis

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

Management of relapsing-remitting multiple sclerosis:

- Acute attacks (relapses) of MS are typically treated with glucocorticoids (IV methylprednisolone for 5 days).
- Indications for treatment of a relapse include functionally disabling symptoms with objective evidence of neurologic impairment.

	Rout	Mechanism of action	Side effect
Interferon	S/C, IM	Cytokine modulator, decrease expression of matrix metalopproteases	Injection site reaction
Natalizumab very good	IV	Alpha-4 integrin monoclonal antibody	Progressive multifocal leukoencephalopathyPML
Fingolimod	Oral	Inhibit egress of lymphocyte from lymph nodes	Cardiac conduction abnormalities
Dimethyl fumarate	Oral	Anti-oxidative, anti-inflammatory	
Teriflunamide	Oral	Inhibit lymphocytre proliferation (anti-metabolite)	
Alemtuzumab	IV	Anti-CD52 (B, T and NK cells)	Autoimmunity
Ocrelizumab	IV	B cell depletion this drug gives us the proof of b cells involvement!	
Caldribine	Oral	Inhibit lymphocytre proliferation (anti-metabolite)	

Other side effects of MS medications:

- Increase liver enzyme
- Lymphopenia

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.

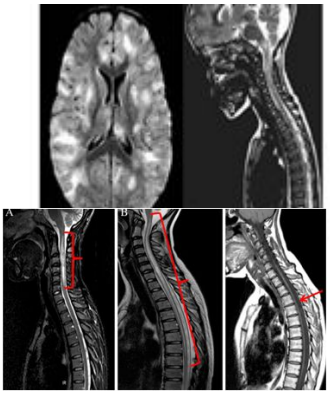
Other demyelinating diseases:

- Damage of the myelin.
- Inherited or acquired.
- PNS & CNS.

Central Nervous System Remember MS belonged here ;-)	Peripheral Nervous System
Acute Disseminated Encephalomyelitis **(ADEM)**	Acute Inflammatory Demyelinating Polyneuropathy (Guillain Barre syndrome - **GBS**)
Neuromyelitis Optica **(NMO)**	Chronic Inflammatory Demyelinating Polyneuropathy **(CIDP)**
Progressive multifocal leukoencephalopathy	

★ Acute Disseminated Encephalomyelitis (ADEM)

Postinfectious encephalomyelitis or ADEM

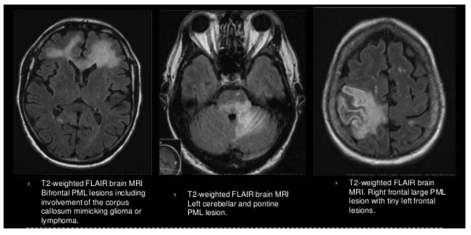


- Monophasic with preceding event common (70%)
- Most common in children
- Altered LOC and seizures common
- **MRI**: bilateral lesions, grey matter involvement

★ Neuromyelitis optica

- Also known as Devic's disease.
- Relapsing (55%), monophasic (35%)
- **MRI**: cord lesions, chiasmal signal changes
- **CSF**: generally >100 wbc, high protein, rare OCB

★ Progressive multifocal leukoencephalopathy



- Rare but serious demyelinating disease of the brain, often resulting in severe disability or death, caused by lytic infection of oligodendrocytes by the JC polyomavirus (JCV).
  Important to know that it comes with **Natalizumab!**
  The drug will prevent lymphocytes from crossing the BBB, and this will cause the JC infection.

MCQs

1) A 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. Which feature below is associated with a milder disease course?

a. Her age of 42
b. Her initial presentation of ataxia
c. Her female gender
d. The interval between the two episodes (Two months)

2) Which of the following clinical findings should a medical student identify in a patient as an early characteristic of multiple sclerosis?

a. Vision loss
b. Dementia
c. Muscle atrophy
d. Clonus

3) A patient with multiple sclerosis presented with facial muscle spasms accompanied by stabbing pain. The patient says that "it gets worse during meals when I'm chewing food" These symptoms are due to a lesion on which cranial nerve?

a. VIII
b. VII
c. VI
d. V

4) When assessing a patient diagnosed with multiple sclerosis, which of the following would require immediate action by the physician?

a. Fatigue and depression
b. Paresthesia and tremor
c. Nystagmus and diplopia
d. Dysphagia and congested cough

5) When analyzing the cerebrospinal fluid of a patient diagnosed with multiple sclerosis (MS), which of the following results would the healthcare provider anticipate?

a. Clear with decreased WBC
b. Clear with increased proteins
c. Cloudy with increased turbidity
d. Pinkish with increased RBC

6) A medical student is teaching a group of patients diagnosed with multiple sclerosis about common bladder problems. Which of the following will the student include?

a. "You should not attempt to urinate until you feel that your bladder is full".
b. "Drinking lots of citrus juices will decrease the amount of bacteria in your urinary tract".
c. "MS may cause the bladder to contract and empty more often than usual".
d. "Drinking caffeinated beverages can help you empty your bladder completely".

Answer key:

1 (C) | 2 (A) | 3 (D) | 4 (D) | 5 (B) | 6 (C)|