PATHOLOGY

SHEET NO.

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Myelin Diseases of CNS

In the previous lecture , we talked about **Multiple Sclerosis (MS)** - the most common **de**myelinating disease of the CNS - an autoimmune demyelinating disease that is characterized by episodes of disease activity that produce white matter lesions .

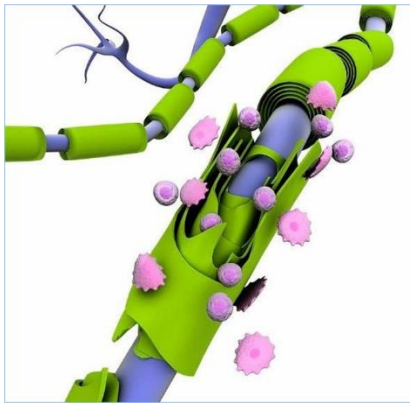
Today , we will continue our talk about other demyelinating disease , and will have a brief discussion on **dys**myelinating diseases of the CNS.

Other Acquired Demyelinating Diseases

Other acquired demyelinating diseases include :

1. Post infectious demyelination.
2. Neuromyelitis Optica.
3. Central pontine myelinolysis.

Post Infectious Demyelination



Definition : Immune-mediated demyelination that follows a number of systemic infectious illnesses, including relatively *mild viral infections* and *some types of vaccinations*.

Viral agents : Measles ,Mumps ,and Rubella have been shown to play a role in the disease process.

Important :

- **The disease is NOT related to direct spread of infectious agents to CNS.**
- The immune process is either cell mediated or humoral.
- Very few cases were reported following bacterial infection.

Mechanism : Immune cells response to pathogen-associated antigens cross-react against myelin antigens, causing myelin damage.

There are two general patterns of post-infectious autoimmune reactions to myelin:

1. Acute disseminating encephalitis
2. Acute necrotizing hemorrhagic encephalomyelitis

1. Acute disseminating encephalitis

Definition : Acute demyelinating disease characterized by non-localizing symptoms that appear 1-2 weeks following infection.

Symptoms : appear 1-2 weeks after infection.

Non-localizing symptoms : headache, deterioration in the level of consciousness , lethargy, coma.

Notes:

- Non-localizing symptoms are symptoms that cannot be attributed to a specific site in the brain (so they are non-specific symptoms).
- This is one area of discrimination between MS and Acute disseminating encephalitis , in which MS symptoms depend on the plaque's location.

Course of the disease : Acute , rapid progression , fatal in 20% of cases.

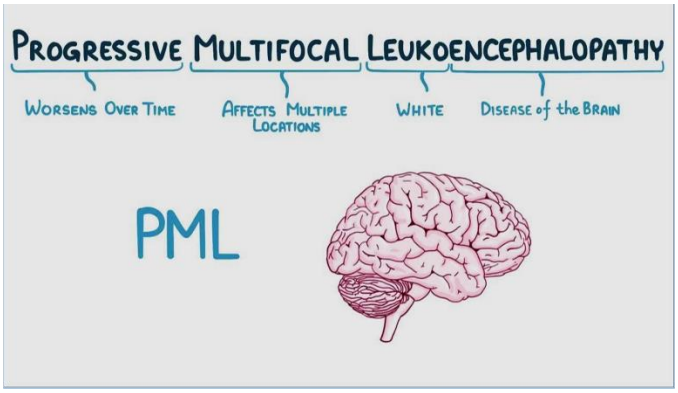
Survivals : patients who survive the acute attack have complete recovery.

2. Acute necrotizing hemorrhagic encephalomyelitis

This is more dangerous and fatal.

Progressive Multifocal Leukoencephalopathy

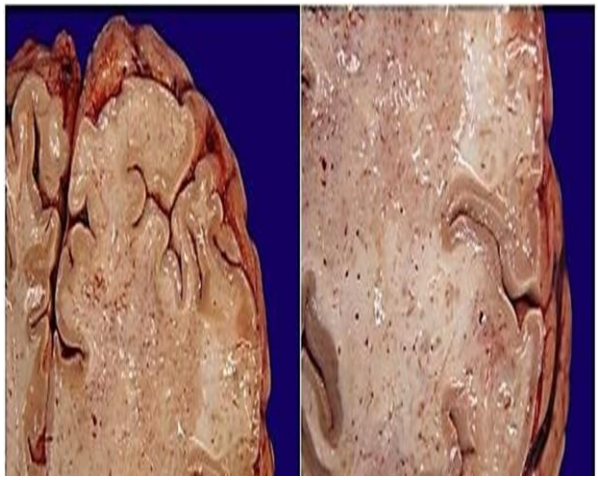
This is something different , PML is NOT a post-infectious demyelinating disease rather , the disease is caused by DIRECT action of the virus.

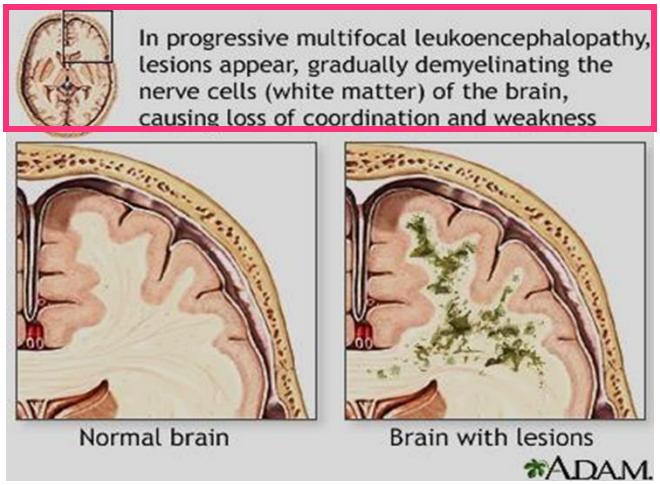


Definition : PML is a disease of the white matter of the brain, caused by a virus infection, it affects multiple locations in the brain and worsens over time.

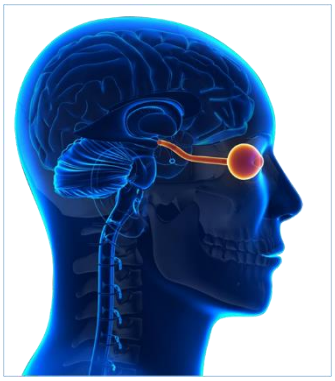
This demyelinating disease occurs after reactivation of the **JC virus (John Cunningham virus)** in **immunosuppressed patients**.

The virus directly infects and destroys oligodendrocytes that synthesize myelin.





Neuromyelitis Optica.



An antibody-mediated (autoimmune) inflammatory demyelinating disease that affects mainly the **optic nerve** ± **spinal cord (may or may not be involved).**

Myelin destruction is caused by antibodies secreted by B cells (antibodies to aquaporin-4).

Aquaporin-4 : a water channel protein that conducts water through the cell membrane.

Antibodies to aquaporin-4 are **diagnostic**.

Symptoms :

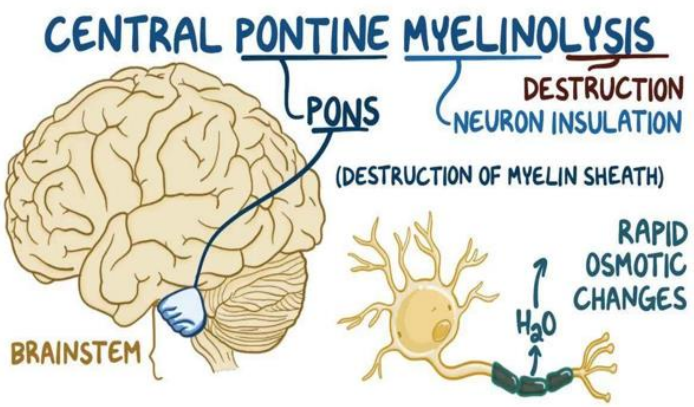
- Optic nerve : diplopia , vision impairment , vision loss.
- **If** spinal cord affected: weakness, bladder dysfunction, etc.

Case study : A patient presents to the clinic with vision impairment and bladder dysfunction (neurogenic bladder). Upon evaluation the clinician has made a set of diagnoses , one of which is Neuromyelitis Optica.

To confirm the diagnoses , what should be done next ?

Answer : A blood test confirming the presence of Antibodies to aquaporin-4

Central pontine myelinolysis.



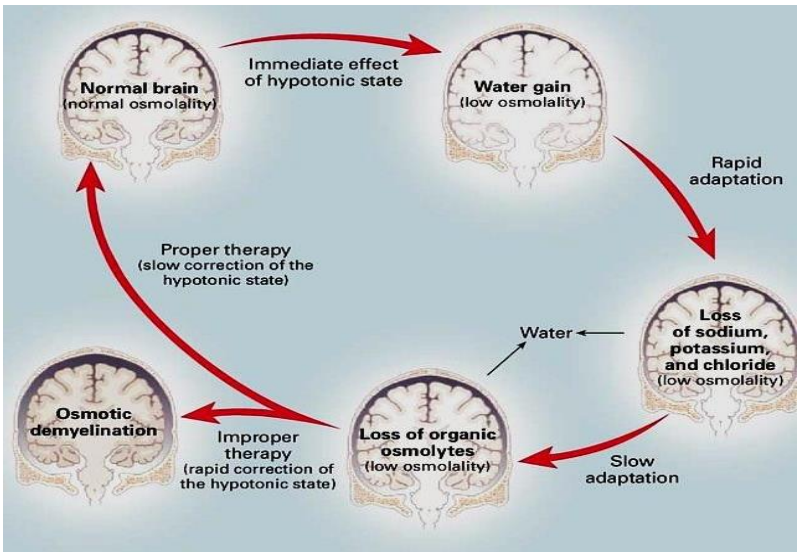
Definition : Central pontine myelinolysis (CPM) is a neurological disorder that most frequently occurs after too rapid medical correction of sodium deficiency (hyponatremia).

Mechanism :

- **Nonimmune** damage to oligodendrocytes typically after **sudden correction** of hyponatremia **(Rapid osmotic changes).**
- **Edema due to sudden change in osmotic pressure** probably is the cause of the damage.
- Damage of oligodendrocytes results in separation of myelin from the axons in the pons mainly
- The rapid rise in sodium concentration is accompanied by the movement of small molecules and pulls water from brain cells. Through a mechanism that is only partly understood, the shift in water leads to the destruction of myelin.
- Certain areas of the brain are **particularly susceptible** to myelinolysis, especially the part of the brain stem **Pons** , hence the name “pontine”.
- Some individuals will also have damage in other areas of the brain, which is called extrapontine myelinolysis (EPM).

Susceptible people (risk factors) are people with chronic electrolyte abnormalities including :

- Alcohol abuse.
- Malnutrition.
- Severe burns.
- Liver transplantation.
- Anorexia nervosa.
- Hyperemesis gravidarum.
- Hyperglycemic states.



Outcomes :

- The Pons contains many vital centers and acts as a motor relay center, this explains why the disease is life threatening.
- Many descending nerve fibers of various tracts synapse in pons. That's why diseases of pons affect motor function and can result in paralysis
- CPM causes rapid quadriplegia (widespread paralysis) and can cause 'locked-in' syndrome (complete paralysis of voluntary muscles, except for those that control the eyes) and might even lead to death.

Prevention :

To avoid Central Pontine Myelinolysis, Hyponatremia should be corrected at a rate of no more than 8-12 mmol/L of sodium per day to prevent central pontine myelinolysis.

Dysmyelinating Diseases of CNS (Leukodystrophies)

Leukodystrophies are inherited dysmyelinating diseases caused by abnormal myelin synthesis or turnover.

Causes : They are caused by mutations of genes whose products are involved in the generation, turnover, or maintenance of myelin.

Some of these mutations affect :

- Lysosomal enzymes.
- Others involve peroxisomal enzymes.
- A few are associated with mutations in myelin proteins.

Inheritance : Most are of autosomal recessive inheritance, although X-linked diseases also occur.

There are so many types of **Leukodystrophies named according to the specific mutation the patient has.**

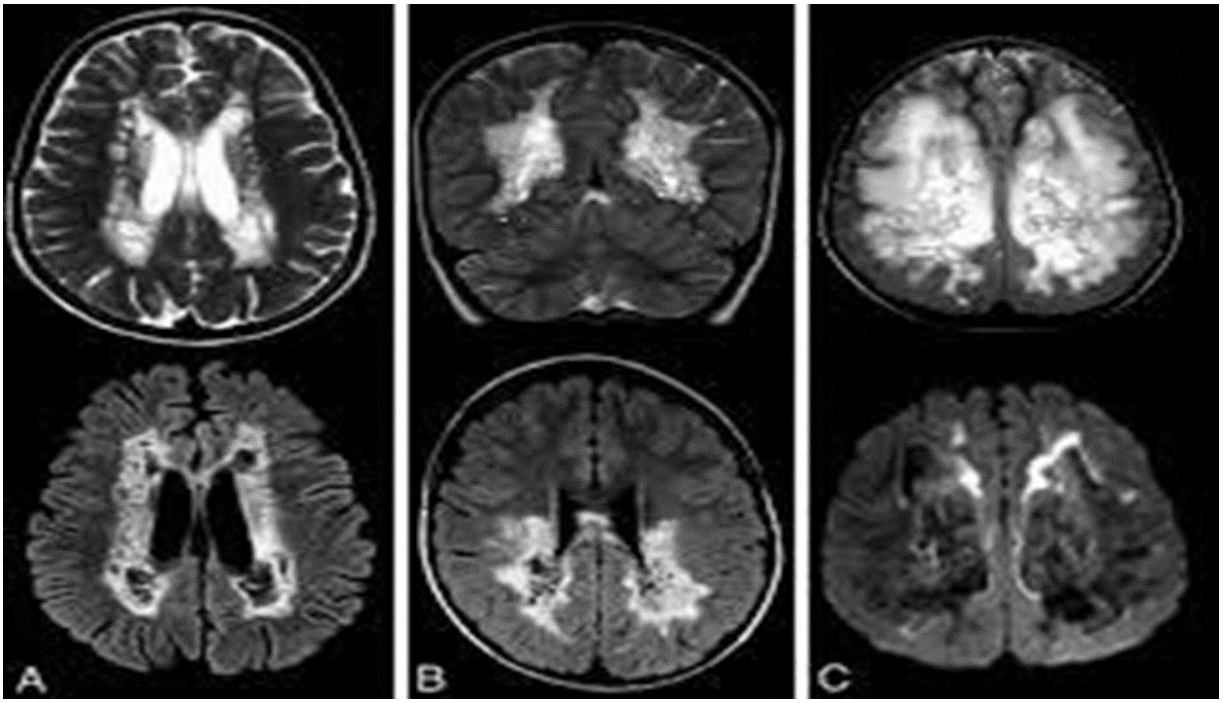
Leukodystrophies versus demyelinating disorders

Leukodystrophies differ from demyelinating diseases in that Leukodystrophies present as :

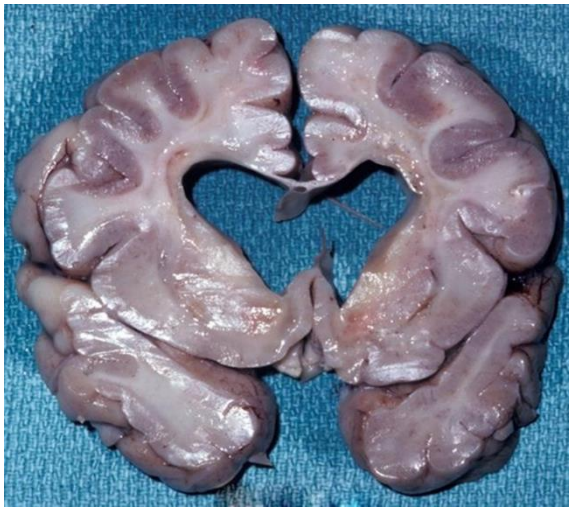
1. **Insidious** and **progressive** loss of function.
2. Often begin at **younger** ages (childhood).
3. Associated with **diffuse** and **symmetric** changes in white matter on imaging studies **(In contrary to MS).**

Symptoms : Deterioration in motor skills, spasticity, hypotonia, or ataxia.

Morphology (Imaging) : diffuse ***symmetric*** involvement of white matter.



Morphology (Gross) :



White matter is abnormal in **color** (gray and translucent) and **volume** (decreased).

Early : patchy involvement, or a predilection for certain site of involvement.

Late : all of white matter affected.

With loss of white matter :

- Brain becomes atrophic.
- Ventricles enlarge (compensatory change).
- Secondary changes in gray matter can be found.

Histology may differ according to the specific type of leukodystrophy :

- Myelin loss associated with infiltration of macrophages.
- Macrophages often become stuffed with lipid.
- Some diseases show specific **inclusions** created by the accumulation of particular substances in affected cells.

Summary

- Because of critical role of myelin in nerve conduction, diseases of myelin can lead to widespread and severe neurologic deficits.
- Multiple sclerosis, an autoimmune demyelinating disease, is the most common disorder of myelin, affecting young adults. It often pursues a relapsing-remitting course, with eventual progressive accumulation of neurologic deficits.
- Other, less common forms of immune-mediated demyelination often follow infections and are more acute illnesses.
- Leukodystrophies are genetic disorders in which myelin production or turnover is abnormal.