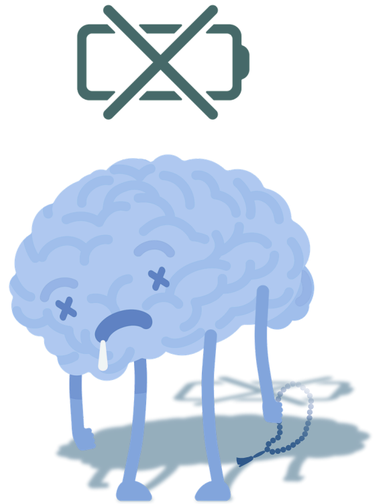
MID

Lecture 2

Pathology Mind Maps

Diseases of Myelin



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This file contains the lecture material presented through mind maps to make the information clearer, more organized, and easier to follow. It is designed to simplify studying and make revision more effective.

We truly hope you find it beneficial.
If it helps you in any way, please remember us in your prayers.

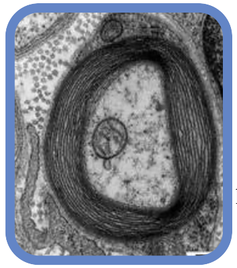
Best of luck in your studies💙!

Myelin overview

رَبِّ اشْرَحْ لِي صَدْرِي وَيَسِّرْ لِي أَمْرِي وَاحْلُلْ عُقْدَةً مِّن لِّسَانِي يَفْقَهُوا قَوْلِي

Definition: protein-lipid complex that is wrapped around the axons

Function: insulate axons and allows quick transmission of neural signals

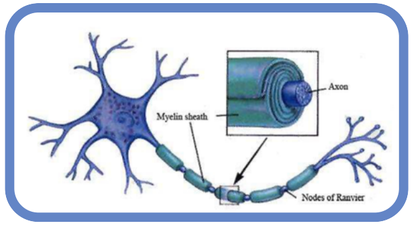


Myelin in this electron microscopic picture appears as layers of plasma membrane wrapped around the axon

Composition: layers of plasma membranes assembled by **oligodendrocytes in the CNS** and **Schwann cells in the PNS**

**Myelinated axons are the predominant component of white matter

Diseases:



CNS Myelin Diseases

CNS <u>De</u>myelinating Diseases (Acquired):

1. Multiple sclerosis (MS):the most common type
2. Neuromeylitis optica
3. Post infectious demyelination
4. Central pontine myelinolysis

CNS <u>Dys</u>myelinating Diseases (Inherited)

PNS Myelin Diseases

1. Guillian Barre Syndrome
2. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
3. Diabetic Neuropathy

Multiple Sclerosis

لَا تَدرِي لَعَلَّ اللهَ يُحدِثُ بَعدَ ذَلِكَ أَمرًا

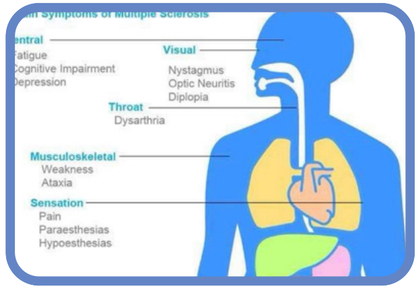
Definition: Episodes of neurologic deficits separated in time which are attributed to white matter lesions that are separated in space(autoimmune destruction of myelin)

Epidemiology: 1 per 1000 persons in USA and Europe

Incidence is believed to be increasing.

Female : male ratio is 2:1

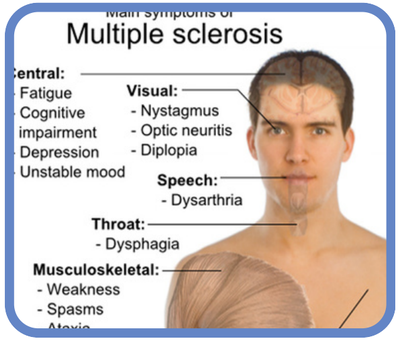
Manifests at any age (usually 20-40), but onset in childhood or after 50 is rare.



Clinical presentation: -Signs and symptoms depend on the **location** of the lesion.

-The clinical presentation is variable.

-Patients might have any of the symptoms. the symptoms are **reversible** but the disease can recur. When it recurs the symptoms might differ from the initial ones.

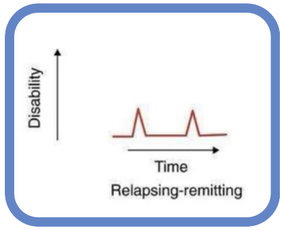


Clinical course:

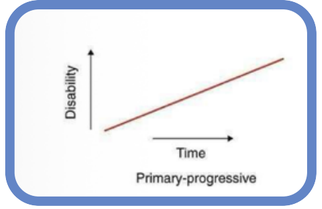
-The course of the diseases is variable

-You **cannot** predict the course of the diseases in different patients. only time will tell!

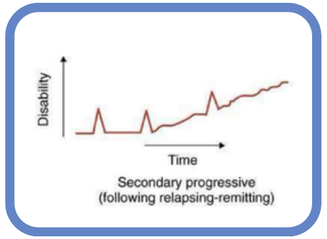
1.**Relapsing remitting** means the patient will have symptoms (relapses) separated by periods of complete remission (completely normal)



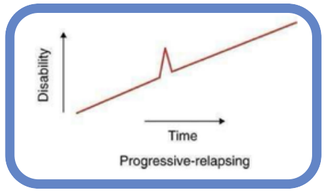
2.**Primary progressive**: when symptoms start, the patient will have symptoms continuously without periods of remission, and the symptoms get worse with time.



3.**Secondary progressive**: disease starts as 1 above, but after sometime changes to pattern 2.



4.**Progressive relapsing**: like in 2, but at times symptoms get even worse.



Outcome: Natural history of MS is determined by:

1.The **limited capacity of the CNS to regenerate normal myelin**(although myelin can be restored in the CNS, this is less efficient than in the PNS)

2.The **secondary damage to axons** that might occur after repeated relapses.

NOTE: usually diseases of myelin do not affect axons, but with repeated attacks of autoimmune destruction to myelin, the autoimmune response and associated inflammatory reaction can cause secondary axonal damage, this occurs late in the course of the disease. note that it is the inflammation that causes the axonal damage, not the myelin destruction per se.

Pathogenesis

Overview: Genetic susceptibility + environmental trigger

Loss of tolerance of self-proteins in myelin sheath → Genetic + environmental factors contribute in it

Environmental: probably viral infection (**not certain**)

Genetic Predisposition: 15-fold higher in first-degree relatives

Monozygotic twin concordance **~25%.** Association with **HLA DR2**

Polymorphisms in genes encoding cytokine receptors (IL2 & IL7), these in genes encoding cytokine receptors (IL 2 & IL7), these two cytokines control the activation and regulation of T cell mediated immune response

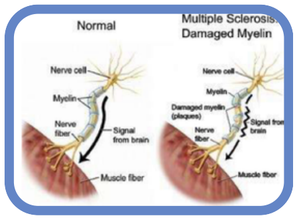
Note: Genetic variations do not fully explain the variation in the clinical course

T Cells: $CD4^+$ T helper cells play a major role → Th1 & Th17: react against myelin antiges and secrete cytokines

Th1 → secrete interferon-gamma → activates macrophages

Th17 → recruit white blood cells

Activated leukocytes produce chemicals that destroy myelin



Other Cells & Axons: $CD8^+$ T lymphocytes + B lymphocytes may also contribute to myelin destruction

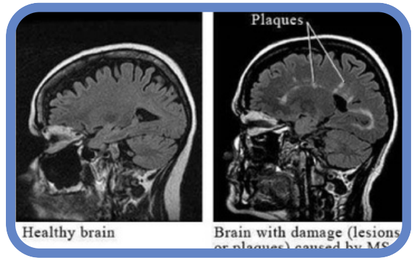
Secondary axonal damage from toxic effects of lymphocytes, macrophages, and their secreted chemicals

Morphology: **White matter disorder**

• Multiple well circumscribed slightly depressed grey tan irregularly shaped lesions= plaques

• These plaques appear grossly firmer than normal white matter

(SCLEROTIC, hence the name: multiple sclerosis) . Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum and spinal cord



2 types of plaques can be seen:

-**Active plaques**: ongoing myelin breakdown, macrophages containing myelin debris.

-**Quiescent(inactive plaques)**: inflammation disappears leaving behind little or no myelin. Instead there is astrocytic proliferation and prominent gliosis

اللهم أعني علي ذكرك، وشكرك وحسن عبادتك

Neuromyelitis optica

Definition: Inflammatory demyelinating disease affecting mainly the optic nerve and spinal cord(autoimmune)

*This disease was Previously thought to be a subtype of MS, but not any more! it is a distinct entity

Diagnosis: **Antibodies to aquaporin-4**

(AQP4)belongs to the aquaporin family of integral membrane proteins that conduct water through the cell membrane

Important notes:

- In **neuromyelitis optic**a, myelin destruction is caused by antibodies secreted from B cells.
- In **multiple sclerosis (MS)**, myelin destruction is mainly due to cellular immunity (T helper cells and cytotoxic T cells).
- The role of **B-cell immunity in MS** is not well understood, but B cells definitely play a role.
- The evidence includes:
  a. Immunoglobulins are found in the CSF of patients with MS (oligoclonal bands).
  b. B-cell depletion therapies dramatically improve symptoms in MS.

Post infectious demyelination

Definition: Demyelination occurring after viral infection.
The demyelination is **not** due to direct effect of the virus

Mechanism: Pathogen-associated antigens → Cross-react with myelin antigens (molecular mimicry)→Trigger autoimmune response against myelin → Demyelination

Onset: acute, monophasic, and usually more severe than MS

اللهم اعتق رقابنا من النار

Types:

- **Acute Disseminating Encephalitis:**
  - Symptoms 1-2 weeks after infection
  - Non-localizing symptoms: headache, lethargy, coma
  - Rapid progression , fatal in 20% of cases
  - Survivals: complete recovery
- **Acute necrotizing haemorrhagic encephalomyelitis :** more dangerous and fatal

Central pontine myelinolysis

- **Definition:** Non-immune process causing edema of oligodendrocytes resulting in separation of myelin from the axons in the pons mainly
  -**Occurs after rapid correction of hyponatremia**
  -Edema due to **sudden change in osmotic pressure** probably is the cause of the damage
- **Prevention:** Hyponatremia should be corrected at a rate of no more than 8–12 mmol/L of sodium per day to prevent central pontine myelinolysis
- **Clinical Outcome:** Causes rapid quadriplegia and can cause **Locked-In Syndrome (LIS)**

اللهم إنك عفوٌّ كريم تحب العفو فاعف عنّا

Locked-In Syndrome (LIS)

Definition: a condition in which a patient is aware but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles in the body except for vertical eye movements and blinking

Etiology: damage in the ventral part of the pons due to pontine infarction, pontine hemorrhage, trauma, central pontine myelinolysis, tumor, or encephalitis

Clinical State: -Patient is conscious and cognitively intact.
-Nearly complete paralysis of voluntary muscles except vertical eye movements and blinking.
-Eye movements preserved because supranuclear ocular motor pathways run dorsally and are not affected.
-Patient can communicate using eyelid movement; otherwise completely immobile.

Dysmyelinating diseases

Definition: -Inherited dysmyelinating diseases = leukodystrophies
-Most are autosomal recessive, some X-linked

Genetic Basis: Mutations in : Lysosomal enzymes, perixosomal enzymes, or myelin protein

Clinical Course: -Several types of dysmyelinating diseases exist.
-Affected children are normal at birth but start loosing developmental milestones during infancy and childhood.
-They might have deterioration in motor skills, spasticity, ataxia... these diseases are progressive and fatal.

Table 1. Different Types of Leukodystrophies and with Clinical Features

Disorder	Inheritance	Enzymatic defect	Clinical manifestations
Pelizaeus-Merzbacher	X-linked recessive and autosomal dominant	Not identified	Onset in infancy, progressive CNS deterioration
Metachromatic leukodystrophy	Autosomal recessive	Aryl sulfatase A	Most common type of leukodystrophy, onset at one to two years, associated with bouts of fever and abdominal pain, gall bladder dysfunction
Krabbe's disease	Autosomal recessive	Galactocerebrosidase	Also known as globoid cell leukodystrophy, onset at four to six months of age
Adrenoleukodystrophy	X-linked recessive	Defective metabolism of long chain fatty acids	Also known as sudanophilic cerebral sclerosis, onset at 5 to 10 years of age, accompanied by hypoadrenalism
Canavan's disease	Autosomal recessive	Not identified	Onset at two to four months of age, increased water content of brain, questionable defect in mitochondrial function leading to increased plasma membrane permeability to water and cations; children have macrocephaly without evidence of hydrocephalus
Alexander's disease	Autosomal recessive	Mitochondrial defect	Onset within first year of life

just to give you an idea of the diversity of leukodystrophies.. don't attempt to memorise!

Guillian Barre syndrome

﴿قُل عَسَى أَن يَكُونَ قَرِيبًا﴾
يا ربّ اجعل بيننا وبين أحلامنا مُلتقى

Definition&cause: **Autoimmune neuropathy**
Often follows: bacterial, viral, or mycoplasma infection
Can also follow immunisation or surgery
Most commonly after **Campylobacter jejuni, CMV, EBV**

CSF Findings: Increased protein and few WBC

Types:
- **Demyelinating**: predominant in USA & Europe
- **Immune-mediated axonal neuropathy**: more common in Asia

Clinical Features: Acute symmetric neuromuscular paralysis → Often **begins distally, ascends proximally**
Sensory and autonomic disturbances may occur
5% present with ophthalmoplegia, ataxia, and areflexia → called **Fisher syndrome**
Muscle paralysis may cause respiratory difficulty → possible death
Autonomic involvement: cardiac arrhythmia, hypo-or hypertension
Recovery: neuropathy resolves 2–4 weeks after onset; most patients recover

Chronic inflammatory demyelinating polyneuropathy CIDP

- **Characterised by:** Chronic acquired inflammatory symmetric, mixed sensorimotor polyneuropathy that persists ≥ 2 months
- It is **immune mediated** but usually there is no previous history of infection.
- Occurs in patients with other autoimmune diseases and in AIDS patients

Diabetic neuropathy

اللهم إنا نسألك الحسنى وزيادة

Overview & Epidemiology:

Most common complication of diabetes

Prevalence: from 7% within 1 year of diagnosis to 50% for those with diabetes for >25 of diagnosis

Risk depends on **duration of diabetes and blood sugar control :**Worse control → higher risk

Cardiovascular autonomic neuropathy → shortens life expectancy

Loss of feeling in lower limbs → high risk of amputation (1–2% of patients)

Clinical Manifestations:

Can be polyneuropathy or mononeuropathy

Forms of neuropathy:

1. Distal symmetric sensorimotor polyneuropathy (most common)

Symptoms: numbness, tingling, weakness, and pain

These symptoms usually start in the longest nerves in the body and so first affects feet, later hands → "**stocking-glove**" pattern

2. Autonomic neuropathy → changes in bowel, bladder, or cardiac function
3. Lumbosacral neuropathy → pain in lower legs

Pathogenesis:

Mechanism: unknown, probably due to nerve ischemia from small vessel disease

Factors contributing to neuropathy:

Microangiopathy

Longstanding **hyperglycemia** → downstream metabolic cascade leads to peripheral nerve injury through an:

↑ Flux of **polyol pathway**, ↑ Formation of advanced **glycation end-products** (AGEs), Excessive **cytokine** release, Activation of **protein kinase C**, **Oxidative stress**

All these mechanisms → damage the nerves

Exam style question

Which of the following combinations is correct?

A. IL 2 receptor polymorphisms and better outcome of MS

B. Central pontine myelinolysis and predominance of sensory symptoms.

C. Acute disseminating encephalomyelitis and viral infection of oligodendrocytes.

D. Neuromyelitis optica and cellular autoimmune myelin destruction affecting optic nerve and spinal cord

E. Quiescent Plaques in MS and astrocyte proliferation.

Explanation of the question

A. **Wrong**. Genetic changes do not predict outcome or course of diseases in MS

B. **Wrong**. the pons is involved mainly in motor function, so in central pontine myelinolysis the symptoms are motor mainly.

C. **Wrong**, in both forms of post infectious demyelination, there is no direct infection to olidodendricytes and the cause of demyelination is autoimmunity due to cross reaction

D. **Wrong**, neurmyelitis optical is caused by auto antibodies.. not cellular immunity

E. **Correct**, quiescent plaques occur during repair phase and contain gloss astrocytes are the main cells responsible for this.

اللهم اجعل أجر هذا العمل صدقة جارية عن روح **عمر عطيه عوده المرابي**

- اللَّهُمَّ اغْفِرْ له وَارْحَمْهُ، وَاعْفُ عنْه وَعَافِهِ، وَأَكْرِمْ نُزُلَهُ، وَوَسِّعْ مُدْخَلَهُ، وَ اغْسِلْهُ بمَاءٍ وَثَلْجٍ وَبَرَدٍ، وَنَقِهِ مِنَ الخَطَايَا كما يُنَقّى الثَّوْبُ الأبْيَضُ مِنَ الدَّنَسِ.
- اللَّهُمَّ أبدله داراً خيراً من داره، وأهلاً خيراً من أهله، وأدخله الجنّة، وأعذه من عذاب القبر ومن عذاب النّار.
- اللهمّ يمّن كتابه، ويسّر حسابه، وثقل بالحسنات ميزانه، وثبّت على الصراط أقدامه، وأسكنه في أعلى الجنات، بجوار حبيبك محمد صلّى الله عليه وسلم.
- اللهم اغفر لحينا وميتنا وشاهدنا وغائبنا وصغيرنا وكبيرنا وذكرِنا وأنثانا اللهم من أحييته منا فأحيِه على الإسلام ومن توفيته منا فتوفه على الإيمان اللهم لا تحرمنا أجره ولا تضلنا بعده.
- اللهم اغفر له وارفع درجته في المهديين، واخلفه في عقبه في الغابرين، واغفر لنا وله يا رب العالمين، وافسح له في قبره، ونوّر له فيه.
- اللَّهُمَّ أنزل على أهله الصّبر والسلوان وارضهم بقضائك.

اللهم لا تفجعنا بأنفسنا ولا أهلنا ولا أحبتنا، اللهم أعوذ بك من فواجع الأقدار ومن مصائب الدنيا وتقلب حوادثها، اللهم إنا نخاف الفقد فلا تحملنا ما لا طاقة لنا به.