Pathophysiology Two.

< CNS Pathophysiology Summary >

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*Pathophysiology II :-

- lec (16) :
- Chapter (5) : CNS Disorders

↳ Neurodegenerative disorders ✓✓

↳ inflammatory disorders

↳ infectious disorders

↳ Vascular disorders

↳ Autoimmune Diseases

↳ Tumors

*Neurodegenerative diseases :-

Diseases Result from the Damage of Neurons → "Basic, functional unit of CNC"

these diseases characterized by progressive loss

of Neurones ⇒ So it's not sudden

• general causes of Neurodegenerative diseases :-

↳ Accumulation of specific proteins in the effected areas

. the problem is that the proteins aggregates can spread, move their area to another CNS ⇒ Disease effected area

• the proteins accumulated may cause Activation of the innate immune system & unwanted immune response

• different areas that can be effected in Neurodegenerative diseases :-

↳ Hippocampus : it's an area in CNS that can control the memory, behaviour, language.

So if there is problem related to Neurodegenerative diseases in that area can cause different diseases like Alzheimer's

- **Basal ganglia**: also an area in the Brain, it controles movement. if effected
  - Substantia Negra
  - Neostriatum
  - Hyperkinatic ⇒ Huntington Disease
  - Hypokinatic ⇒ parkinson Disease

- **cerebellum**: part of CNS "Brain", it controles, Regulates Nerve Muscle Movements, if effected
  - Ataxia ⇒ uncontrolled Movements of the Body

- **Myelin Sheet**: the layer that cover, caught Neurons wether in CNS, PNS. there is difference B/w sheets ~~formings~~ in CNS & PNS. in PNS, proteins, & lipids, also cells forming that sheet

- in CNS ⇒ the sheets are called Oligodendrocytes
- in PNS ⇒ Schwann cells

Same sheets the role is to control the speed of signals

So in Neurodegenerative diseases that effect the Myelin sheet in the CNS don't effect those in PNS

Myelinated faster than Non myelinated

- Multiple Sclerosis disease

1. Multiple Sclerosis (MS) :-

Different References Consider it as
- Neurodegenerative disease , other
- Myelin Sheet disease

that's cause the general cause of it is the aggregation, accumulation of proteins.

the cause is Autoimmune Response

So it's considered as Autoimmune Disease

Damage ⇒ N.D. Neurodegenerative

Most Neurons in CNS are Myelinated, located in area called the white Matter.
Some are unmyelinated in the gray matter.

progressive

It's a Neurodegenerative disorder that characterized by demyelination of CNS

↳ Myelenated Neurons in White Matter

↳ Disruption in Brain, Optic nerves, Spinal cord

Diseases effecting the Myelin Sheet are two types

↳ Demyelenating Diseases

↳ Dismyelenating Diseases

Abnormal formation of the Myelen Sheets in the Normally Myelenated Neurons. of the Central Nervous System

Destruction, Degradation or demyelenation of the Normal Myelene Sheets

So it effects the Sensory, Motor function, emotion, Behaviour

my Myelinated Neurons is specific Lesion, its function will be effected

Neuron الخلية العصبية

- Women have more chance of MS 2:1 Ratio

* Causes :-

Autoimmune Response is the main cause.

There are Risk factors increase the possibilities

- Infections ⇒ Mostly Viral → effect BBB permeability
- Chemicals ⇒ in Cosmetics & BBB
- Drugs ⇒ (Toxins, chemical substances)

(Increase permeability)

* Pathogenesis :-

Autoimmune disease ⇒ So Autoimmune Response,

So main cells in the Autoimmune Response are : Th1, Th17

BBB in general prevents the passage of immune cells to the CNS.
The cells responsible for immunity in the CNS are cells called
Microglia.
↳ already exist in CNS, responsible for first immune response in CNS.
immune cells might present in very low amounts "inactive" so don't have any role in CNS
immune cell (Th1, Th17, B-cell)

Myelene sheet contains proteins, lipids ... maybe one of these constituents are considered to be antigen, so immune system treat it as foreign substances or maybe treat oligodendrocytes that forms the sheet in CNS as foreign substance

*We mentioned that immune cells don't cross the Blood Brain Barrier, how does T cells

the responsible for the pathogenesis?!
that constitutes that is being treated as foreign substance "protein" it can cross BBB from Brain to Blood.
It detected by Dendritic cells, Macrophage ⟹ stimulation of innate immune system, Adaptive
Being differentiated ⇐ Th0
to
Major
↳ Th1 ⟹ Activation through IL-2 to CD-2, and through the Mitogen pathway secretion of the IF-γ
Activates Macrophage, B-cell
Secret Anti-Body ⇐ Turns into Plasma B-cell
Ig G Mainly
that's all in the Blood outside the BBB

All the Risk factors Mentioned collectively the permeability of BBB so immune cells that are Activated against Antigen cross BBB Attacking the (APC) Antigen through Antigen-presenting cell, Macrophage, Dendritic cell Anti-Body CD-2 ... all the attacks the Anti-gen in Myelin sheath or oligodendrocyte so damage of them so Demyelination of Neurons so MS.

*Symptoms:-

Depends on which Area the Demyelination occurs.
it May happen in Any area of Myelinated Neuron

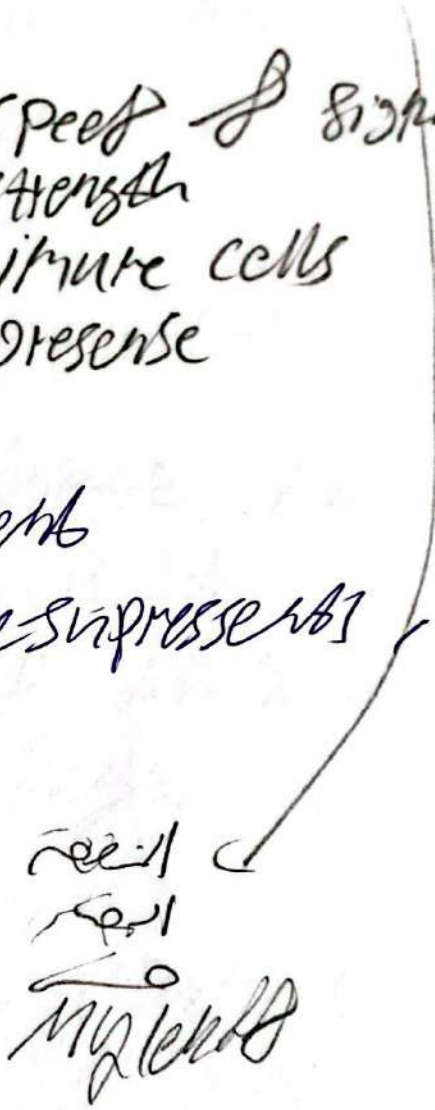
Double vision

- Cerebellum ⇒ Ataxia, Tremor
- Cranial Nerve ⇒ Diplopia, loss vession
- Motor Neurons ⇒ paralysis
- Sensory Neurons ⇒ Numbness, burning

maybe there is damage in ~~cerebellum~~ more than one area, or maybe all of them.

- Diagnosis
  - through symptoms
  - imaging (plaques) → area of demyelination
  - Evoked potential → speed & strength
  - CSF → detect cytokines, immune cells presense

- Treatment:-
  generally no treatment but we can use immunosuppressants drugs to symptoms.



Parkinson disease (PD) :-

it's a progressive Neurodegenerative disorder characterizes by hypokinetic movement disorder that caused by loss of dopaminergic Neurons, in Basal ganglia ① Substantia Nigra, ② Neostriatum, ③ cerebellum

↳ part of Brain controles movement through Balance B/W Two Neurotransmitter Ach \ Dopamin.

↳ Cholenergic pathway

↳ Dopaminergic pathway

In case of parkinson's disease there is No Balance B/W them due to Destruction, degeneration of dopaminergic Neurons in Substantia Nigra

- Since it's effect is on the Movement the problem is in Motor Neurons.

In Sever cases the ↓
Sensory cell Recep Sensory

Causes :-

Depends on the Type :-

Primary PD

idiopathic ⇒ unknown cause, in general the cause is known "it's Neurodegenerative Disease" & the general cause is degeneration of some proteins,

in case of PD the protein is α-synuclein which is protein is substantia Nigra of in Neurons, it ① controls the Movement of vesicles containing Neurotransmitter and controls the secretion of Neurotransmitters,

② have role in DNA Repair

as any protein, after period of time the Body gets rid of it through phagocytosis "Autophagocytosis" "Normally"

If there is aggregation in α-synuclein that causes damage in Neurones.

in PD there is aggregation in α-synuclein forming large molecules causing damage of Neurones ⇒ "Dopaminergic Neurons"

"it's unknown what causes the aggregation"

- the problem increases in elderly

↳ Secondary PD :-

Damage in dopaminergic Neurones due to encephalopathy like encephalitis, Vascular disease, Dopaminergic Antagonist.

The Result is ↓ Dopamine as Neurotransmitter so imbalance B/W Dopamine/Ach so PD

كلطقة في الامتحان انتبه !!

Basal gang
↳ stre..
↳ subset.. Neg

Pathogenesis -

PD is Degenerative Disease against Dopaminergic Neurons in Substantia Nigra ①

البازل (annotation)

other Part of Basal ganglia have Rule in PD which is Neostriatum ② to Control the Motor function.

Striatum can Be Supplied to different Neurones like cholenergic Neurons, glutamenergic Neurones and the Substantia Negra ① supplies it by dopamenergic Neurones

inhebatory Neures — Activating Neurons

in Normal cases Balance should be B/W Ach / Dopamin mainly and glutamate

also Striatum supplies Substantia Nigra through GABA Neurones

There Must Be Balance Btw these Neurotransmitters to get the Normal Motor Movements.

Lewy Bodies

aggregate ("α-syn")

Due to X-Lacty ("Genetic Problem...") there will be degeneration in the pathways. X-Segment in Substantia Nigra "Dopaminergic Neurons", so Damage in Dopaminergic Neurons so Imbalance.

Now the inhibitory pathway that causes Balance to the Activatory Neurons

So over Activation of Symptoms of parkinsons disease

*Symptoms:-

- Tremor
- Rigidity
- Bradykinesia
- Postural instability

Motor

Also:- GIT Problems, Speaking Problems CNS problems

Tremor

↳ occurs at Rest

↳ disappears at Movement, sleeping

↳ mainly in hands Moves to lips, Jaw, legs

↳ Bell-Rolling shape of hand

Rigidity

↳ Stiffness, harness in skeletal Muscles
Due to over-stimulation in Muscle
Due to ACh "imbalance"

Bradykinesia "Slow Movements"

↳ due to problems in Joints "imbalance"

postural instability

↳ Not able to stand straight
due to impairment in postural Reflux

* Treatment -

Recovery of Balance BTW Ach, Dopamin.

↳ Dopaminergic Agents

↳ Dopaminergic Replacement therapy

↳ Stimulation of Dopamin synthesis

↳ Cholinergic Antagonists

*Pathophysiology II :-

- lec (17) :

3 Alzheimer's Disease (AD) :-

it's also a Neurodegenerative disease, Result from damage in Neurones in hippocampus

- Some References consider Alzheimer's Disease as "Dementia". التعريف

↳ CNS Disorder that is chronic, progressive, occurs in an area called cerebral cortex that is responsible for cognitive skills such as: thinking, judgment, Memory

also one of subtypes of Alzheimers is Alzheimer Dementia.

- Causes of dementia :-

Vascular diseases
Cerebral
infection ---

But Major cause is Alzheimer's Disease 70% of cases

symptoms of Dementia :-

- Characteristic symptom is loss of Memory ⇒ "the short-term memory" but the long term is effected in the long term. "cases of progression"
- Since it effect the cerebral cortex there will be impairment in some cognitive skills such as language, thinking, judgment, learning ability.
- Normal skills are difficult like eating, wearing close.
- Confusing of Time and place
- others ---

*AD :-

progressive Neurodegenerative disease characterised by Cortical atrophy and loss of Neurons in hippocampus

*Hippocampus is part of the Cerebral
*There is shrinking "Atrophy" in Cerebral
*Most place affected by Atrophy is Hippocampus
*The Disease is Mute Cerebral in women
*Remember: General cause of Neurodegenerative diseases is accumulation of specific Protein in specific area in Brain
*In AD ⇒ ... of β-Amyloid and tau-Proteines in cerebral Cortex Messy

.Main cause of this disease is unknown "Causative agent of accumulation" but there are risk factors

- Age 3% incidence for those 65-74 Y
  20% incidence in the 75-84 Y
  50% incidence in those +85 Y

1/10 of the population of people +65 Y have alzheimers.

⅓ of Population +85 have AD

↳ Genetics
Mutation in some proteins, enzyme
& aggregation of β-Amyloid, ε-Prot

↳ oxidative Stress
Free Radical aggregation of
these proteins in the
Hippocampus

*Pathogenesis:-
initiation of it depend in aggregation
of the two proteins
↳ β-Amyloid
↳ ε-protein

•β-Amyloid: the body synthesize it through
precursor called Amyloid
Precursor protein located in the
cell Membrane in Neurone.
it has two function.

Central growth & Nerves
to Repair damaged Neurones

Two enzymes work on it
- β-Secretase enzyme
- γ-Secretase enzyme

كل البيتا العادي
كل البيتا السفلي

they cause lysis - fragmentation of Amyloid precursor proteins, as Result we get fragments of the process, one of these fragments is the β-Amyloid protein as Monomer

the β-Amyloid proteins located in the CNS, other tissue.
in CNS it
- ⇒ control signalling & synaps
- ⇒ protect against excitotoxic stress
- ⇒ Activation of kinase enzyme causing phosphorelation that have main Role in signal transduction

T-Proteins : group of proteins "b"
They cause interaction,
Binding to Microtubules
cytoskeleton of
skeleton

Stabelization & Shape of Axon

Stability

T-protein

T-proteins Bind to the surface of Microtubules to cause Stabelization of Axon.

The disease occurs due to aggregation of the tau proteins and what causes that is unknown but there are RISK factor ...

a factor causes aggregation >>>
Let Argylent protein it exists in the body of Mohsen does it's function then the body

As said. If it [illegible] then the BBB synthesize it again through transcription factor stimulate Amyloid precursor protein synthesis ,,,

in presence of risk factor that leads to aggregation of Monomer "β-Amyloid protein forming oligomer then this will be further aggregation of the β-Amyloid protein forming β-Amyloid plagues ⇒ if these where formed Now it's AD. → extracellular aggregation

this characteristic that formed plague is very toxic to the Neurones "but the Monomer" the toxicity obtained from the three mechanism

- Distribution in Ca^{+2} homeostasis so cell injury may develop to irreversible cell injury so cell Death "Apoptosis"

- Destruction in Mitochondrial Membrane, as Result Release of Cytochrome C Then Activates Caspase, Pro-Caspase enzymes initiating apoptosis Process " intrinsic Pathway → Bad → Pro-C Caspase

- Hyperactivation of kinase enzymes Ex hyper phosphorlation of T-Proteins

Final Result Neural damage, Synapse Damage

So the T-proteins, they are accumulate, aggregate when ~~they~~ there is hyperphosphorelation by any Risk Factor, So ⇒ Characteristic ~~Aggregate~~ Complex ~~Neurofibrillary~~ Neuro Fibrillary Damage is Main Target → Gives intracellular aggregate inside Neurons

In Advanced Case

Symptoms :-
Similar to dementia,
- early symptoms loss of short term Memory "early stage" Mild case
- Confusion with time, location
- Difficulty complete Normal tasks
- End-Stage can't Recognis his family, he might be aggressive may kill.

* Diagnosis :-
- Symptoms
- image - Two characteristic of Alzeimer Tangles & B-Aggregation inside cell, "Neurone"

B-Amyloid Plaque Formation of B Amyloid extracellular

- Shrinking of cortex "Hippocampus"

* Treatment :-

No treatment, the purpose of treatment is to slow-down progression of symptoms

- Cholinesterase inhibitors
- Drugs work Anti-Beta against proteins
- Drugs to Reduce Symptoms
- glutamate Antagonist "against NMDA" "Memintee"