Neurodegenerative diseases

Neurons — Damage → So: there will be loss of groups of neurons, leading to loss of function

Progressive loss (تدريجي)

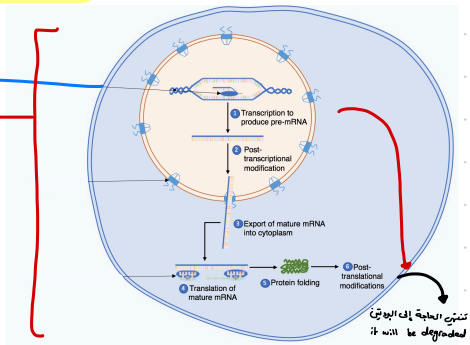
Main cause: accumulation of either normal of abnormal proteins

Causes of aggregation :

1- Mutations that alter protein conformation

2- Disrupt pathway involved in processing of proteins (ممكن يصير في خلل في أي مرحلة من مراحل التصنيع)

3- Imbalance between synthesis and degradation



When protein aggregates it have:

*Toxic effect on neurons

*Elicit inflammation which may lead to apoptosis

2- Disrupt pathway involved in clearance

On what clinical phenotype depends !!?

Answer: It depends on the site of aggregation more than the nature of proteins

(إذا الأعراض تعتمد على مكان التّراكم و ليس على طبيعة البروتين الذي تراكم)

Note

1- Many proteins can spread to other healthy neurons, ex: prions

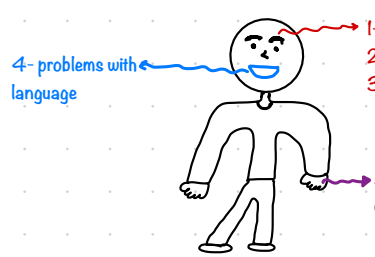
2- Aggregation are resistant to normal cellular proteases

Alzheimer Disease

General definition: progressive neurodegenerative disease in temporoparietal region due to accumulation of (B amyloid , tau proteins)

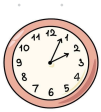
Most common sign: Dementia (it's not a specific disease, it's an umbrella term)

Symptoms of dementia



7- change in mood and behavior

8- change in personality



9- disorientation with time and place

10- loss of initiative (عدم وجود مسؤولية شخصية)

تزداد نسبة الإصابة بالزهايمر مع التقدم في العمر.

Note:

Down syndrome patients have a high percentage to have Alzheimer disease!

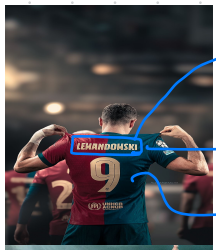
Explanation: because amyloid precursor protein which is carried on chromosome 21, will be degraded into B amyloid

REVERSIBLE DEMENTIA[10-20%]	IRREVERSIBLE DEMENTIA[80-90%]
D= Drugs	Alzheimer
E= Endocrine disorders	Lewy Body dementia
M= Metabolic	Frontotemporal Dementia (Picks disease)
E= Emotional	Parkinson disease
N= Nutritional	Huntington's disease
T = Toxic, Tumor, Trauma	Creutzfeldt-Jakob disease
A= Alcohol	others

Most common cause of dementia: Alzheimer disease

Second most common cause: Vascular dementia due to infarction

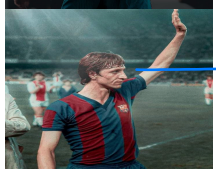
Irreversible dementia



Lewy body dementia

هو مهاجم بكون in front → Frontotemporal dementia

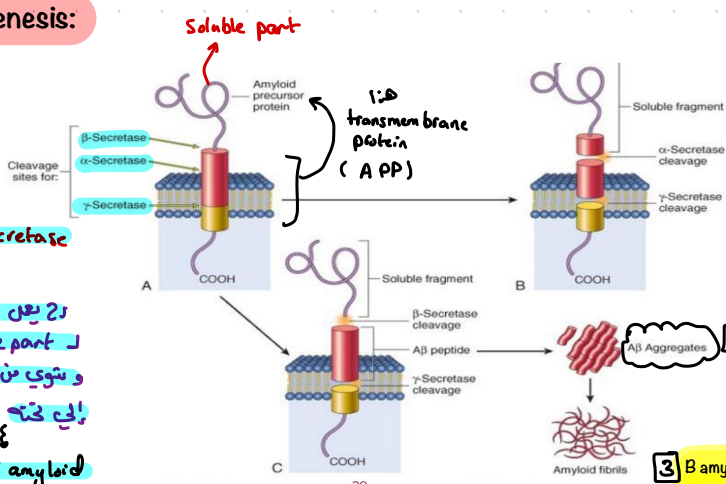
Hunter هو → Huntington disease



(كروتيف) Creuf اسمه → Creutzfeldt Jakob disease

Alzheimer pathogenesis:

1) يتم تكسير APP عن طريق secretases



β Secretase

cleave يقل ال Soluble part leading to form what is called β amyloid.

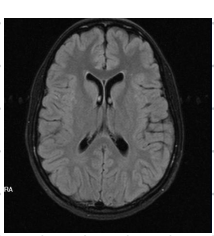
α-secretase

cleave يقل ال Soluble part و بتوي من الجزء اللي جنب

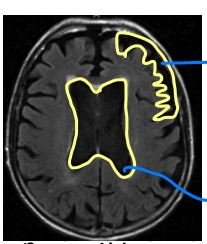
no β amyloid (non Amyloidogenic)

3 B amyloid as we said: It has toxic effect and may elicit inflammation leading to apoptosis

B amyloid is highly prone to accumulation



Normal brain



Brain in Alzheimer disease

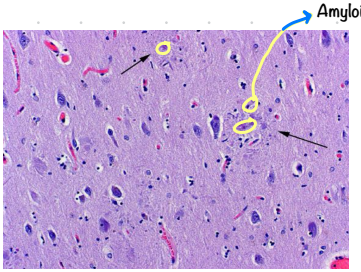
1- There will be brain atrophy leading to widening of sulci and narrowing of gyri

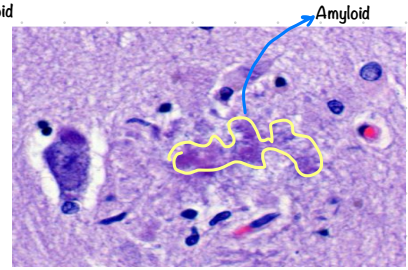
Mostly in: temporal, parietal and frontal regions

2- Ventricular enlargement called hydrocephalus ex vacuo (to be filled with fluid and compensate brain atrophy)

Note:

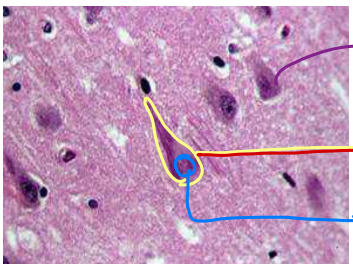
In Alzheimer disease there will be accumulation of beta amyloid (intercellular=extracellular) and accumulation of tau proteins (intracellular)





*When amyloid is surrounded by dilated, tortuous dystrophic (died) neurons it's named " Neuritic plaques "

*Without neurites it's called " diffuse plaques "



Neurofibrillary tangles (accumulation of tau proteins)

Bundles of filaments in cytoplasm encircling nucleus That will give " flame shape "

Nucleus

Note:

Neurofibrillary tangles usually located in:
1- Hippocampus
2- Amygdala
3- Pyramidal cells
4- Basal forebrain
5- Raphe nuclei

In Alzheimer:

Impaired intellectual functions, memory and altered mood and behavior —> Disorientation and aphasia ——> Disabled, immobile and mute

*Death may occur due to pneumonia or other infections

Parkinson Disease

General definition: Neurodegenerative disease due to accumulation of alpha synuclein protein in substantia nigra forming Lewy bodies

Pathogenesis:

Accumulation of alpha synuclein (Lewy bodies)

↓

Normally it's cleared with autophagy, but now there is problem with autophagy and lysosomal degradation

↓

loss of dopaminergic neurons in substantia nigra

↓

Loss of nigrostriatal pathway

↓

Leading to Parkinson disease

Some changes in Parkinson disease:

1- Accumulation of alpha synuclein protein
2- Neuronal loss in substantia nigra forming
3- Mitochondrial abnormalities

Note:

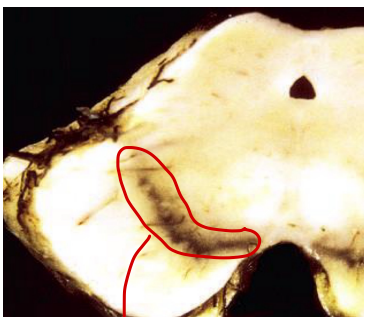
**Parkinsonism: clinical syndrome can be seen with Parkinson disease and other cases that damage dopaminergic neurons (damage nigrostriatal pathway) that control motor activity, as antidopaminergic drugs for example

Parkinson disease progress over 10-15 years at final stages patient nearly immobile

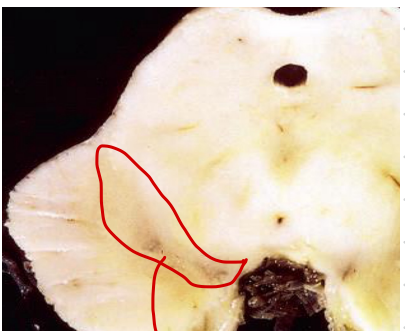
Diagnosis based on triad: 1-Rigidity 2-Tremor 3-Bradykinesia

Giving L-Dopa will relief symptoms but it doesn't prevent slow disease progression

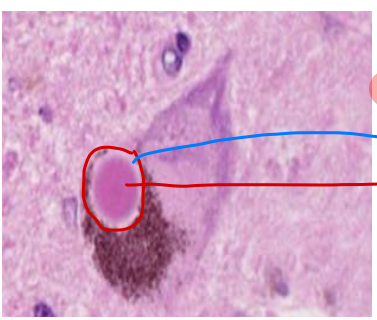
**Death may occur due to: 1-Pneumonia 2-Trauma



Normal substantia nigra and locus ceruleus



Substantia nigra and locus ceruleus become pallor due to loss of catecholaminergic=dopaminergic neurons



Lewy body features:

1- Pale halo

2- Dense core

3- Single or multiple

4- Eosinophilic

5- Round inclusions