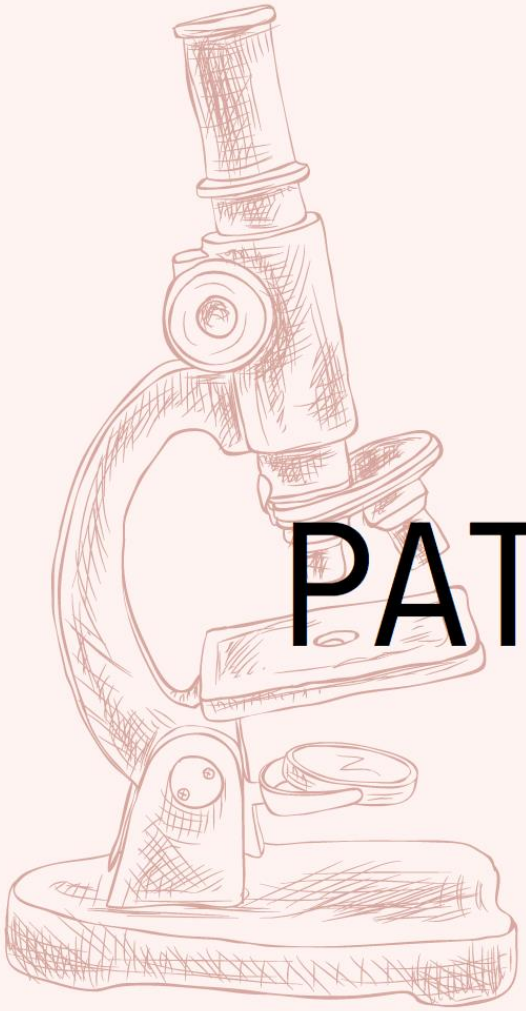
Sheet No. 1



PATHOLOGY

Central Nervous System

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Neurodegenerative disorders-1 :

Classic features : Neurodegenerative diseases are characterised by some features like :

- **Progressive loss of neurons.**(once they start they will progress and become worse with time)

- Typically affects groups of neurons with functional interconnections. (either on **CNS OR PNS**)
- Different diseases involve different neural systems, so different symptoms.
- The histologic hallmark for ALL diseases is the **ACCUMULATION OF PROTEIN AGGREGATES.**

- Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION..as a result they will have different symptoms
- Proteins resist degradation, accumulate within the cells, elicit inflammatory response(with **micoglial proliferation and gliosis** which lead to damage and it is toxic to neurons) .

Causes of protein accumulation:

- Mutations that alter protein conformation.(protein **misfolding** for example)
- Mutations disrupting the processing and clearance of proteins.

- ❖ Subtle imbalance between protein synthesis and clearance(genetic or environmental factors)

Different diseases: according to the site that involved we can classify them into :

1- ***Involving the cortex :*** a group of diseases that are called collectively (***dementia***) it will lead to cognitive abnormalities of memory, behavior and language

Examples : . **ALZHEIMER DISEASE** (AD ; prototype of diseases that affect cerebral cortex) , **FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD) .**

2- ***Involving the basal ganglia :*** the diseases in this group are called (**movement disorders**) which subdivided into either :

- Hypokinesia بطء في الحركة (PARKINSON DISEASE)
- **hyperkinesia** زيادة في الحركة (HUNTINGTON DISEASE)

3- ***Involving the cerebellum:*** collectively called (**ataxia** اختلاج في الحركة)

Examples: **(SPINOCEREBELLAR ATAXIA, Friedrich ataxia, ataxia telangectasia)**

4- ***Involving the motor system :*** difficulty swallowing and respiration with muscle weakness >> (**AMYOTROPHIC LATERAL SCLEROSIS)**

Common features to many neurodegenerative diseases:

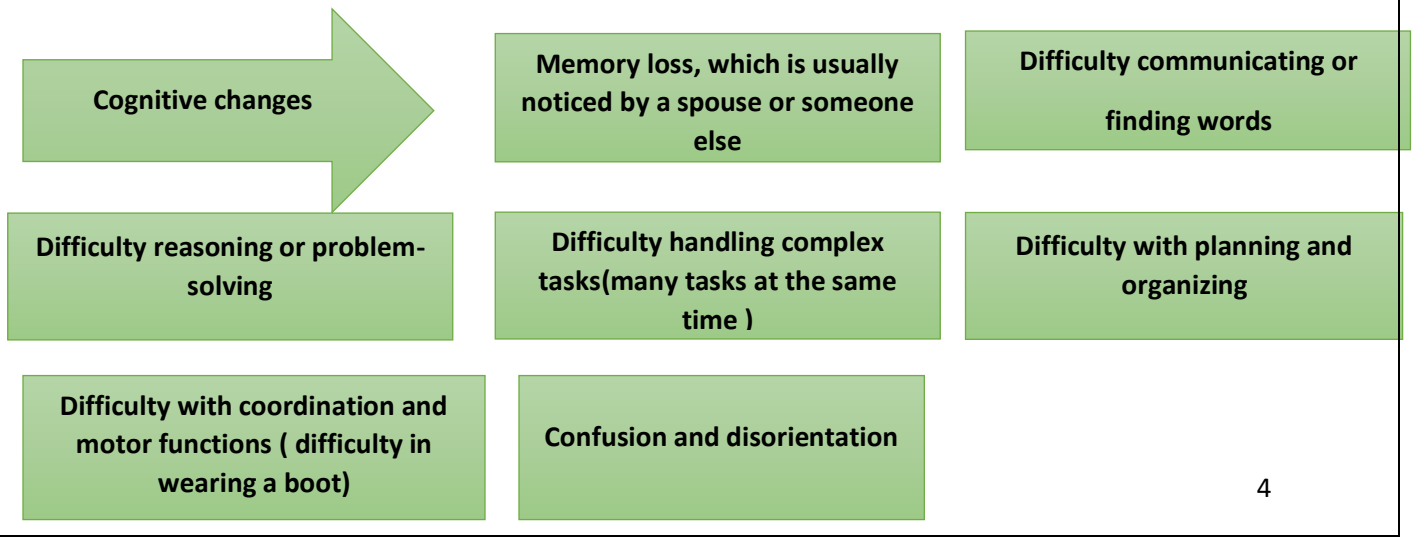
- ❖ Protein aggregates can seed the development of more aggregates.
- ❖ Protein aggregates can spread from one neuron to another in **Prion-like pattern** [it is a pathologic protein they consider it as an infection]
- ❖ No evidence of person-to-person transmission.
- ❖ Activation of the innate immune system is a common feature of neurodegenerative diseases.

**DEMENTIA :*

- ✓ Development of memory impairment and other cognitive deficits severe enough to decrease the person's capacity to function at his (previous level / baseline level)despite **normal level of consciousness.***
- ✓ Note from this definition that the cognitive deficit must affect the person's performance in his daily life activities to be called dementia
- ✓ There is no standard NORMAL COGNITION, always compared to previous level.

SYMPTOMS OF DEMENTIA :

Patients start with:



Note : the disease mainly affects high intellectual functions but it can also affect motor functions .

CAUSES OF DEMENTIA:

1-Neurodegenerative diseases. Differ according to age of patient and other medical illnesses

2-Infections.

3-Nutritional deficiencies.

4- Metabolic and endocrine abnormalities

5-Drugs.

6- Subdural hematoma

7- Poisons.

8- Tumors.

9- Anoxia.

- **We think of 2,3,4,5,6,7,8,9 if the patient at the medium age.but if the patient 70yo or more we should think about Alzheimer .**

COMPLICATIONS OF DEMENTIA:

- ***Inadequate nutrition.*** Many people with dementia eventually reduce or stop their intake of nutrients.
- ***Pneumonia.*** Difficulty swallowing increases the risk of choking or aspirating food into the lungs
- ***Inability to perform self-care tasks.*** As dementia progresses, it can interfere with bathing, dressing, brushing hair or teeth, using the toilet independently and taking medications accurately.
- ***Personal safety challenges.*** Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.
- ***Death.*** Late-stage dementia results in coma and death, often from infection

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ALZHEIMER DISEASE :

Overview:

- Most common cause of dementia in older adults.
- Increase incidence with age (**47% in those over 84 years**).
- Most cases are sporadic.
- **5-10**% are familial / inherited (onset before 50)
- Gradual onset.
- Impaired higher intellectual functions, memory impairment and altered mood and behaviour.
- Severe cortical dysfunction (disorientation and aphasia فقدان القدرة على الكلام, profound disability اعاقة شديدة, mute and immobile)
- **Death usually due to infections (pneumonia**)

- **The most commonly recognised symptom of Alzheimer is an inability to acquire new memories and difficulty in recalling recently observed facts .**

- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.

Pathogenesis :

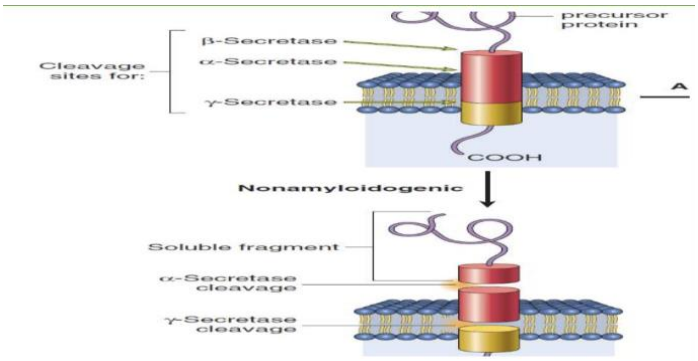
- Accumulation of two proteins (AB amyloid and Tau) AB lead to deposition of the Tau
- In the form of plaques and neurofibrillary tangles (in the cytoplasm of the neurons), respectively.
- This leads to neuronal dysfunction, death and inflammation.
- Plaques deposit in the neuropil.
- Tangles develops intracellularly.
- Aβ generation is the critical initiating event for the development of AD.
- Mutations of the gene encoding the amyloid precursor protein for Aβ >>> elevated risk of AD.
- Mutations of Tau gene do NOT increase risk of AD. (because Tau is a product from AB amyloid)

Role of Aβ :

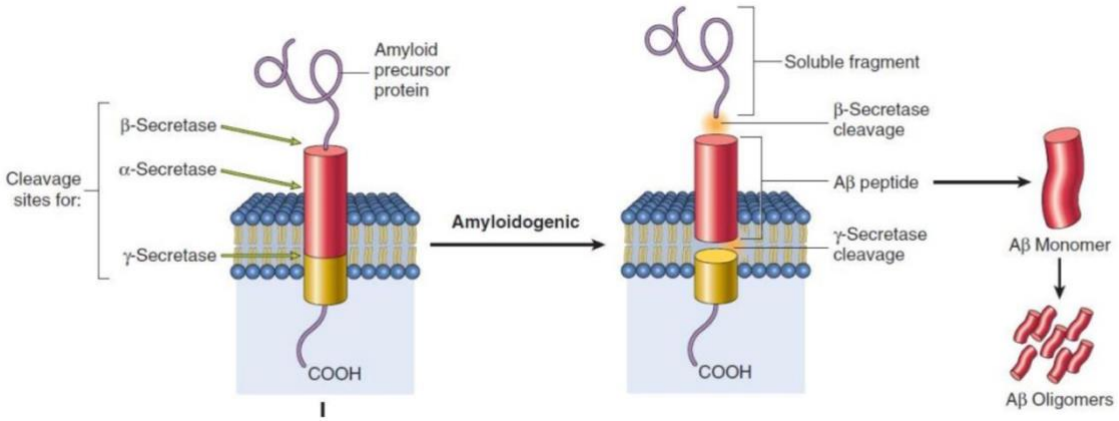
- AD results when the transmembrane protein (amyloid precursor protein APP) is sequentially cleaved by the enzymes β-amyloid–converting enzyme (BACE) (B-secretase ***which***

works when we have a mutation or a problem) and **γ-secretase (it always works**) creating Aβ.

- Normally, APP can be cleaved by α-secretase and γ-secretase, liberating a nonpathogenic peptide as you can see in the following picture :



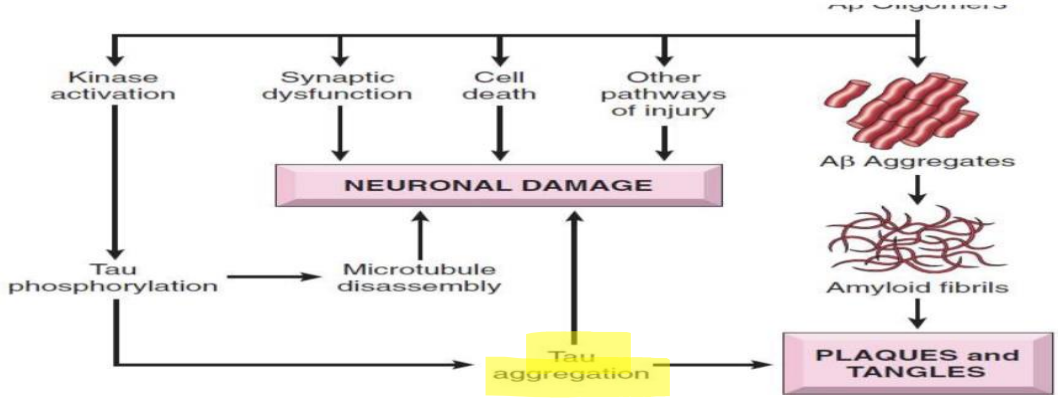
- AD results when the (APP) is sequentially cleaved by the enzymes β- amyloid converting enzyme (BACE) and γ-secretase creating **Aβ amyloid .**



- Mutations in APP or in components of γ-secretase lead to familial AD.
- The APP gene is located on chromosome **21** (so patient who have extra copy of this chromosome like dawn syndrome patient will be at high risk of dementia and Alzheimer at low age) ,

- Once generated, Aβ is highly prone to aggregation >>>> PLAQUES FORMATION >>> decreased number of synapses and alter their function >>> memory disruption.
  - Amyloidogenic: once deposition starts , it will be progressive

Role of tau:



What is tau ?

it will be non-functional

- Tau is a microtubule-associated protein. Present in axons in association with the microtubular network.

- Responsible for tangles in AD >>> Tau aggregates leads to cell death
- Hyperphosphorylated and loses the ability to bind to microtubules >>>> loss of microtubule stability >>> neuronal toxicity and death.
- Tau aggregates can be passed across synapses from one neuron to the next >>> spread of lesions.

Role of inflammation :

- Innate immune system responds to Aβ and tau.
- Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.

- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

Basis for cognitive impairment :

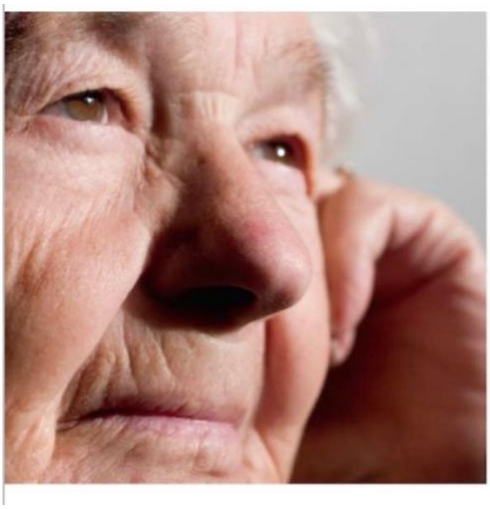
- Deposits of Aβ and tangles appear before cognitive impairment
- In familial AD, deposition of Aβ and the formation of tangles precede cognitive impairment by as much as **15 to 20** years.

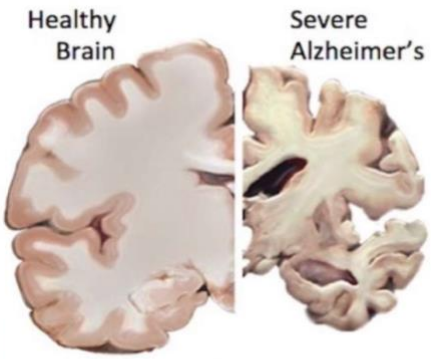
- Large burden of plaques and tangles is strongly associated with severe cognitive dysfunction.

- **The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques**

Morphology: macroscopic

1- Cortical atrophy:

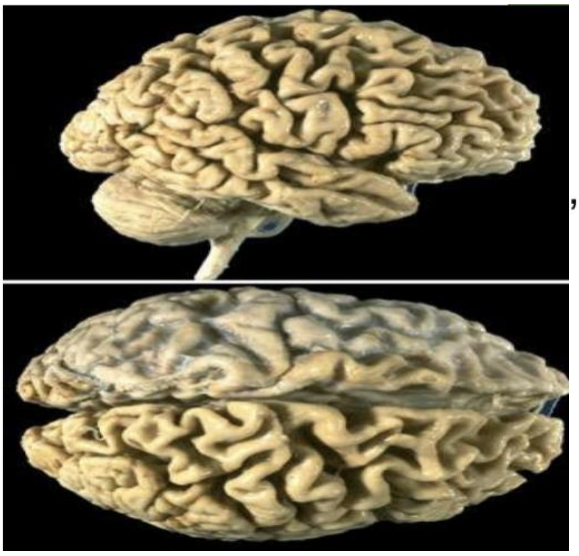




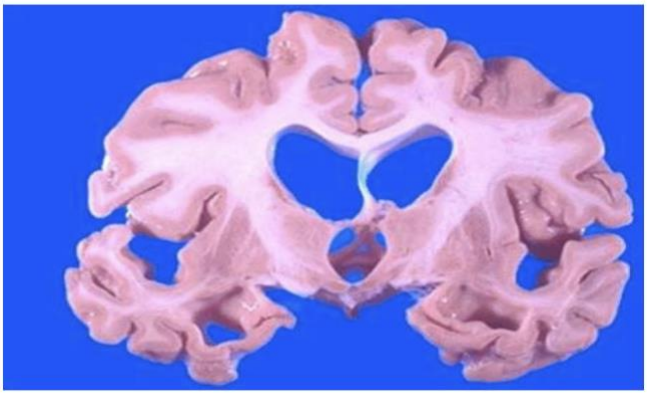
Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).

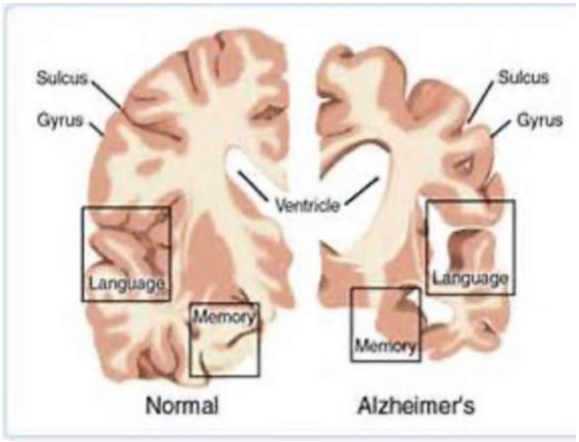
2- Widening of the cerebral sulci , Most pronounced in the frontal, temporal, and parietal lobes.the occipital lobe is separated .

- More marked atrophy seen superiorly and laterally, with sparing of the occipital region.



3- Compensatory ventricular enlargement (hydrocephalus ex vacuo).

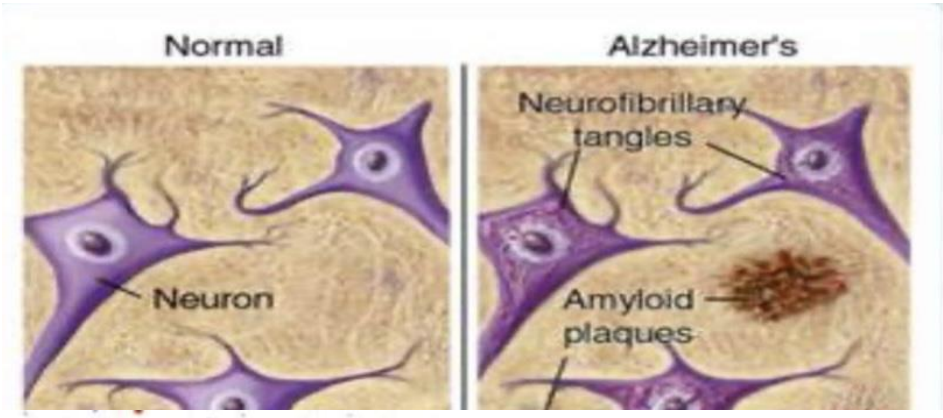


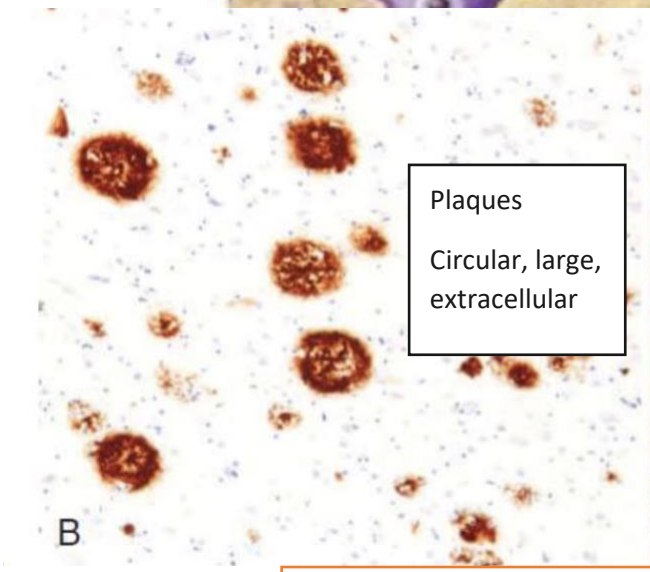


Alzheimer disease neuropathologic change:

- **Neuritic plaques (an extracellular lesion)**: central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.
- Hippocampus and amygdala and neocortex, (relative sparing of primary motor and sensory cortices until late)
- The amyloid core contains Aβ

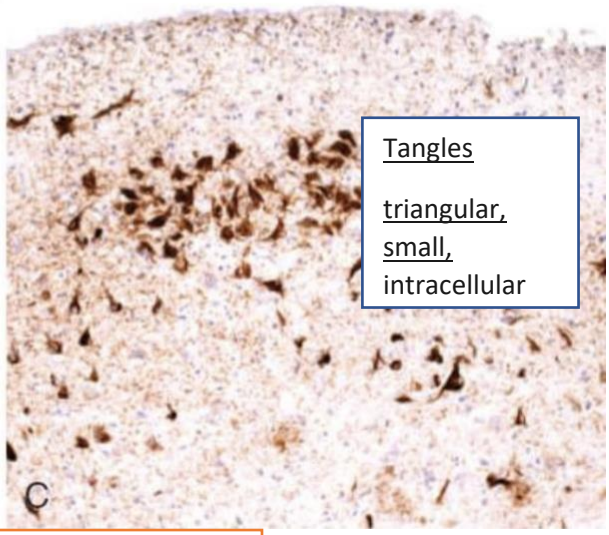
- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Hyperphosphorylated tau





Plaques

Circular, large, extracellular

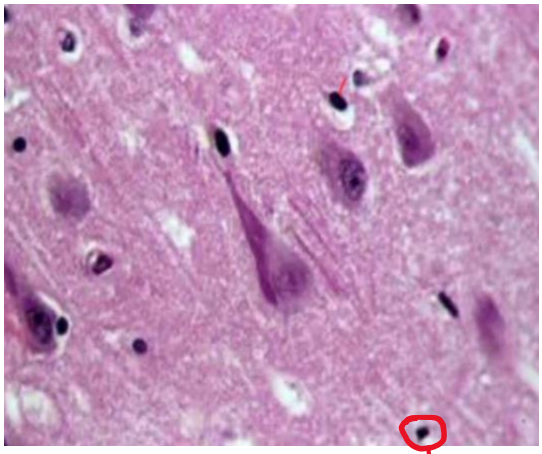


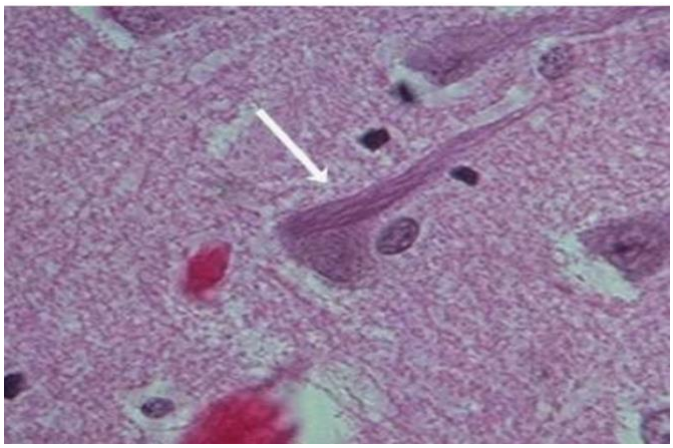
Tangles

triangular, small, intracellular

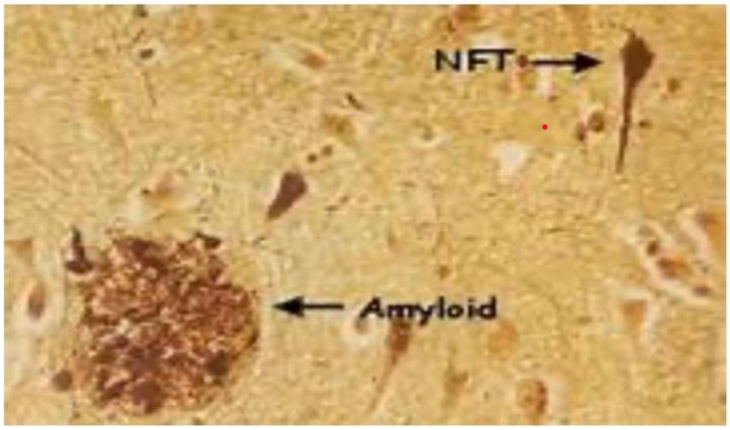
These are immunostains that give brown color if the antigen is found.

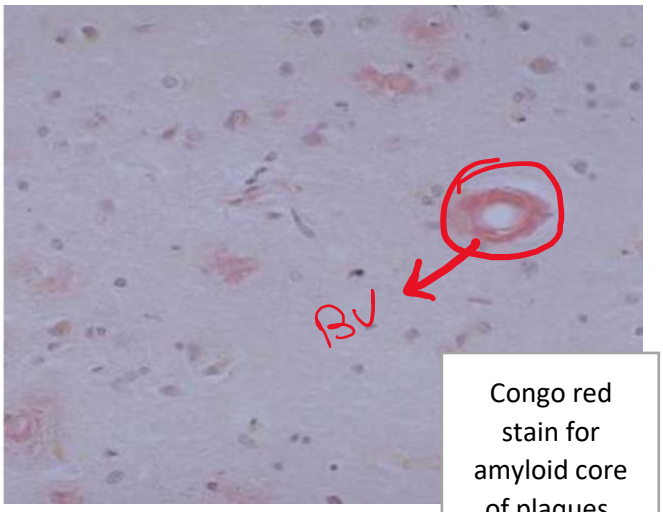
- **Neurofibrillary tangles**



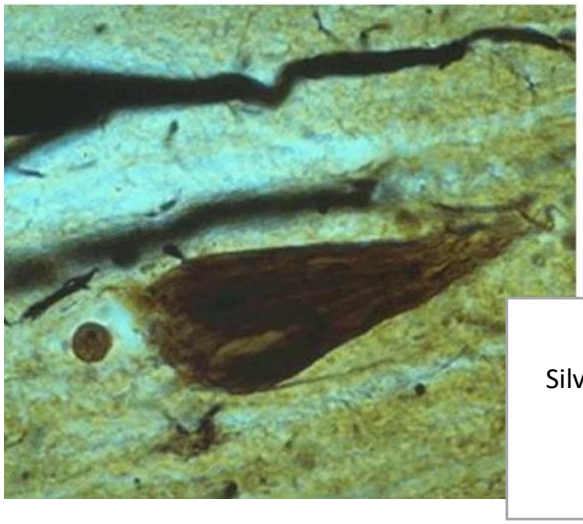


Astrocytes





Congo red stain for amyloid core of plaques.



Silver stain for NFT

This is might be helpful 😬

https://youtu.be/v5gdH_Hydes

TEST YOURSELF!

1.Alzheimer's is the most common form of which of these?
A. MalnutritionB. DementiaC. FatigueD. Psychosis
2. How is Alzheimer's diagnosed?
A. Mental-status testsB. Blood testsC. Neurological testsD. All of the above
3. Physiologically, what happens to the brain as Alzheimer's progresses?
A. Tissue swellsB. Fluid collectsC. Many cells dieD. Brain-stem atrophies
4. Which of these is the strongest risk factor for developing the disease?
A. HeredityB. AgeC. Exposure to toxinsD. None of the above
5. Occasionally, other medical conditions may mimic this disease. What are they?
A. Side effects to medicationB. DehydrationC. Poor nutritionD. All of the above
6. Signs of Alzheimer's include which of these symptoms?
A. Loss of memoryB. Increase in irritabilityC. RestlessnessD. All of the above

7. Which age group has the highest rate of Alzheimer's cases reported?
A. 85 and olderB. 74 to 84C. 65 to 74D. 55 to 65
8. Because no drugs cure this condition, emphasis is put on delaying the onset of severe symptoms. Which of these strategies helps?
A. ExerciseB. HobbiesC. Good nutritionD. All of the above
9. The average time from the onset of symptoms to death is how long?
A. 20 yearsB. 8 yearsC. 6 yearsD. 4 years
10. If you care for a relative with Alzheimer's, which of these measures will help stabilize the patient mentally?
A. Move to a small apartmentB. Correct "bad" behavior gentlyC. Establish a regular routineD. Repaint or buy new furniture

ANSWERS

1	2	3	4	5	6	7	8	9	10
b	d	c	b	d	d	a	d	b	c

- Note: sometimes we give AD patients b12.

تم بحمد الله....