النادي الطلابي
كلية الطب

Pathology CNS

Done By Dana Alkhatib

Corrected By Samah Freihat

Neurodegenerative disorders-1

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Classic features:

- Progressive loss of neurons. Slowly , gradually progressing
- Typically affects groups of neurons with functional interconnections.
- 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..

Different symptoms

- Proteins resist degradation, accumulate within the cells, elicit inflammatory response, and is toxic to neurons.

Causes of protein accumulation

- Mutations that alter protein conformation .

Affect folding of the proteins

- Mutations disrupting the processing and clearance of proteins.

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

Different diseases

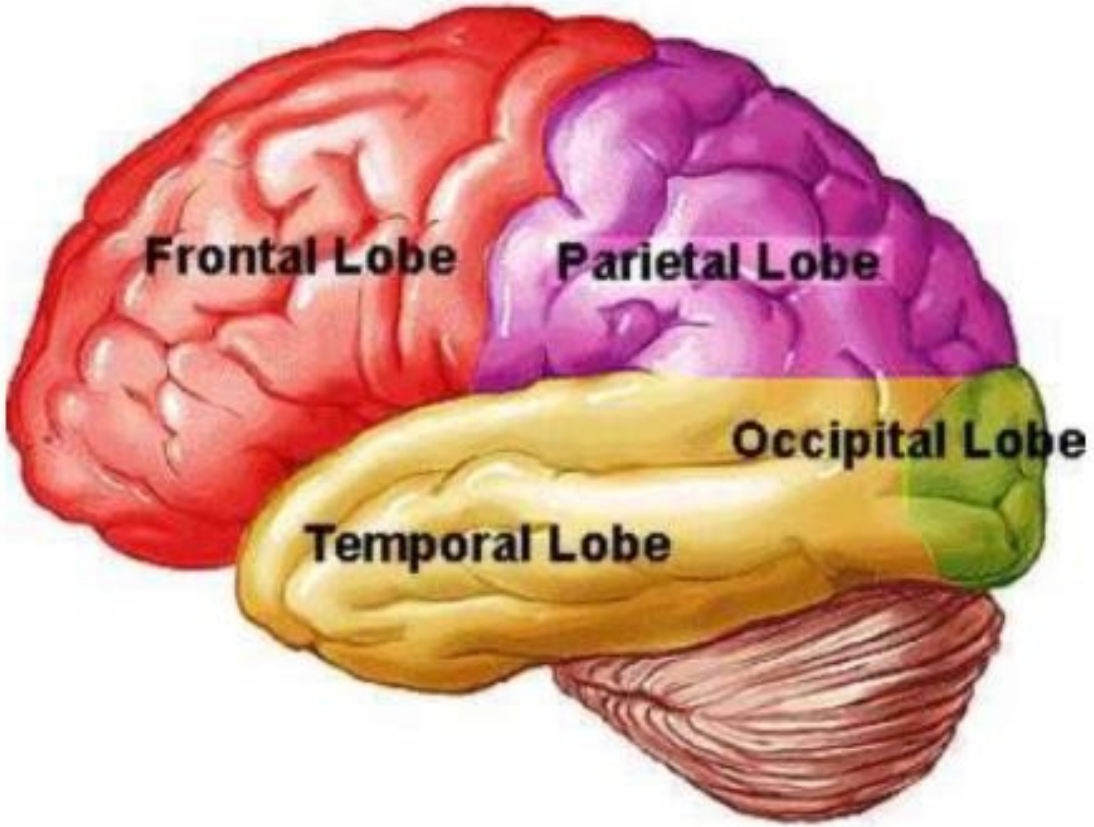
- **Involving the cortex**>>>> cognitive abnormalities of memory, behavior and language >>>> dementia >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

- **Involving the basal ganglia** >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE)

- **Involving the cerebellum** >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA)

Loss of balance

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


Frontal Lobe
Parietal Lobe
Occipital Lobe
Temporal Lobe

Common features to many neurodegenerative diseases:

Severity of the disease correlates with proteins accumulation

- Protein aggregates can seed the development of more aggregates.
- Protein aggregates can spread from one neuron to another in **Prion-like pattern.**
- 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 **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

SYMPTOMS OF DEMENTIA

Cognitive changes	• Memory loss, which is usually noticed by a spouse or someone else	• Difficulty communicating or finding words	•Difficulty reasoning or problem-solving	• Difficulty handling complex tasks
• Difficulty with planning and organizing	•Difficulty with coordination and motor functions	•Confusion and disorientation	**Psychological changes**	• Personality changes
• Depression	• Anxiety	• Inappropriate behavior	• Paranoia	• Agitation
		• Hallucinations		

These symptoms need assessment & excluding all other causes (nutritional problems, toxic drugs use)

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

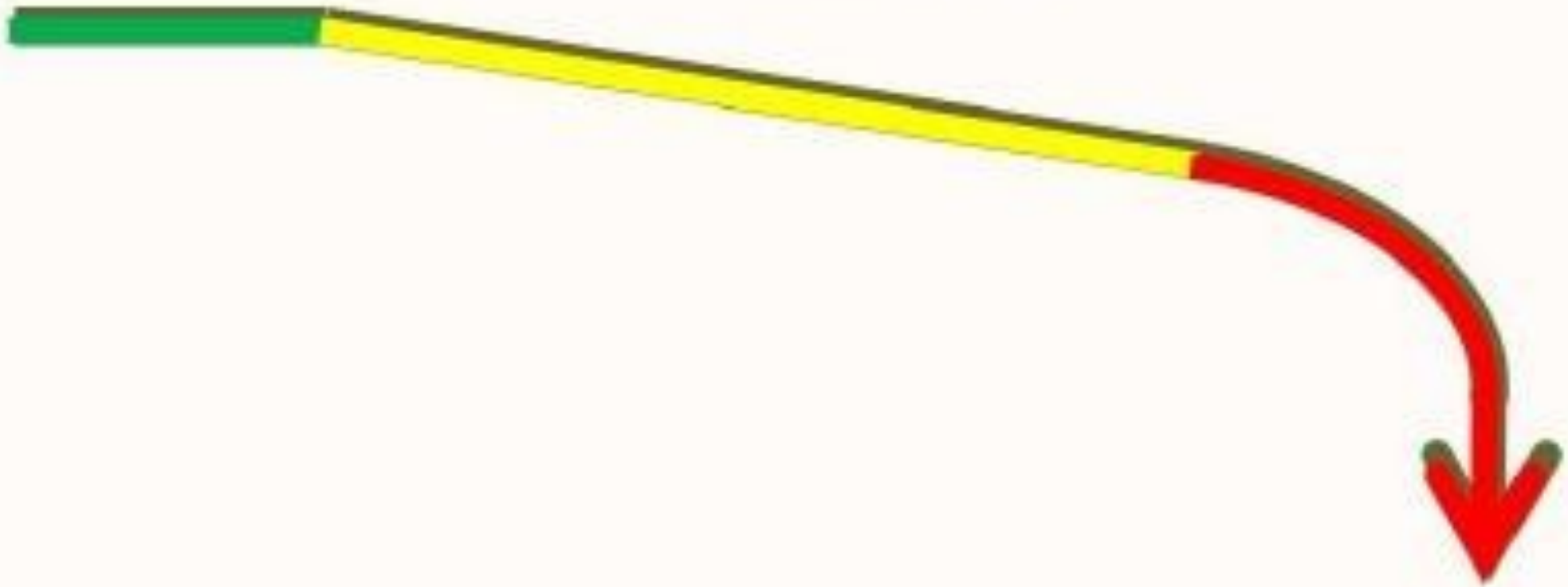
The most common causes of death

Alzheimer disease:

- 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 (onset before 50)
- Gradual onset.
- Impaired higher intellectual functions, memory impairment and altered mood and behavior.
- Severe cortical dysfunction (disorientation and aphasia, profound disability, mute and immobile)
- Death usually due to infections (pneumonia)

The most common factor is the age

Deterioration Curve



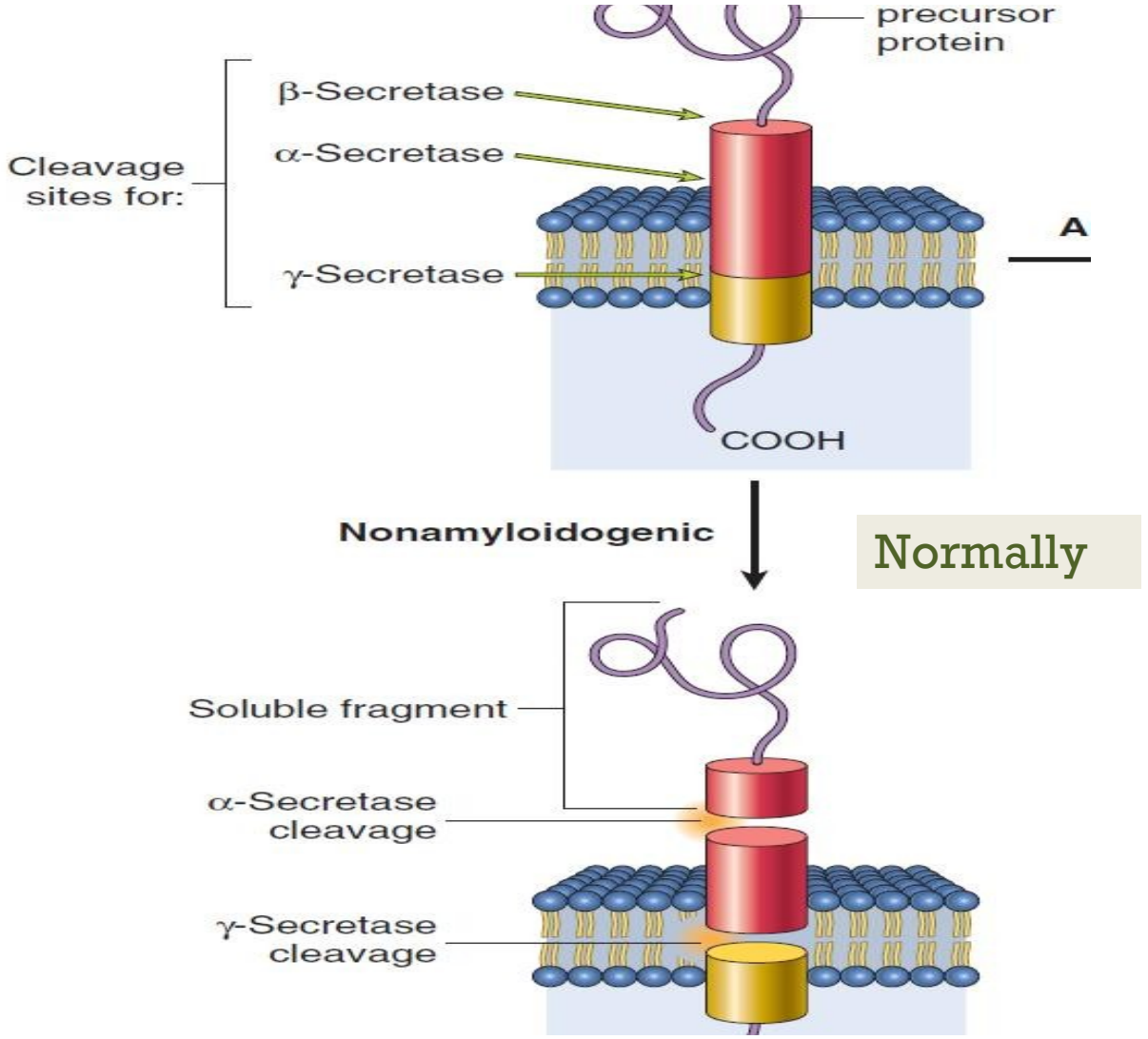
- The most commonly recognised **symptom** of Alzheimer is an inability to acquire **new memories** and difficulty in recalling recently observed facts.
- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.

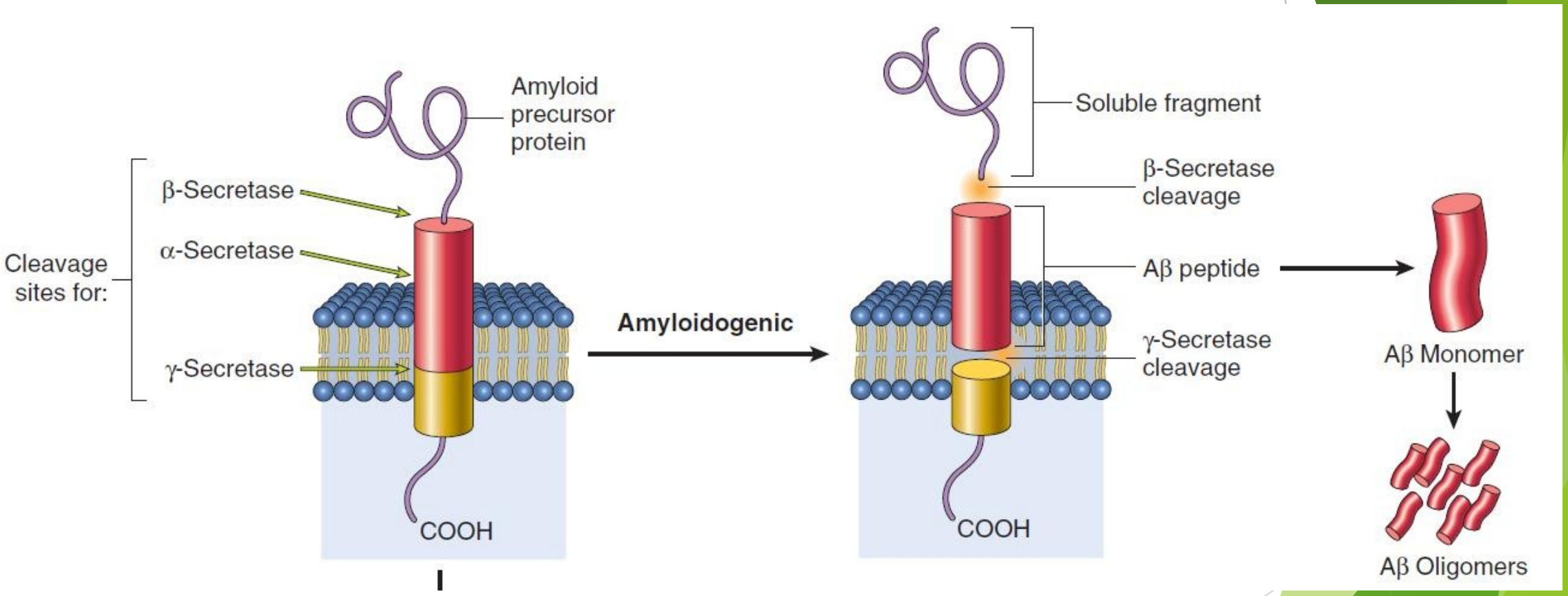
Pathogenesis:

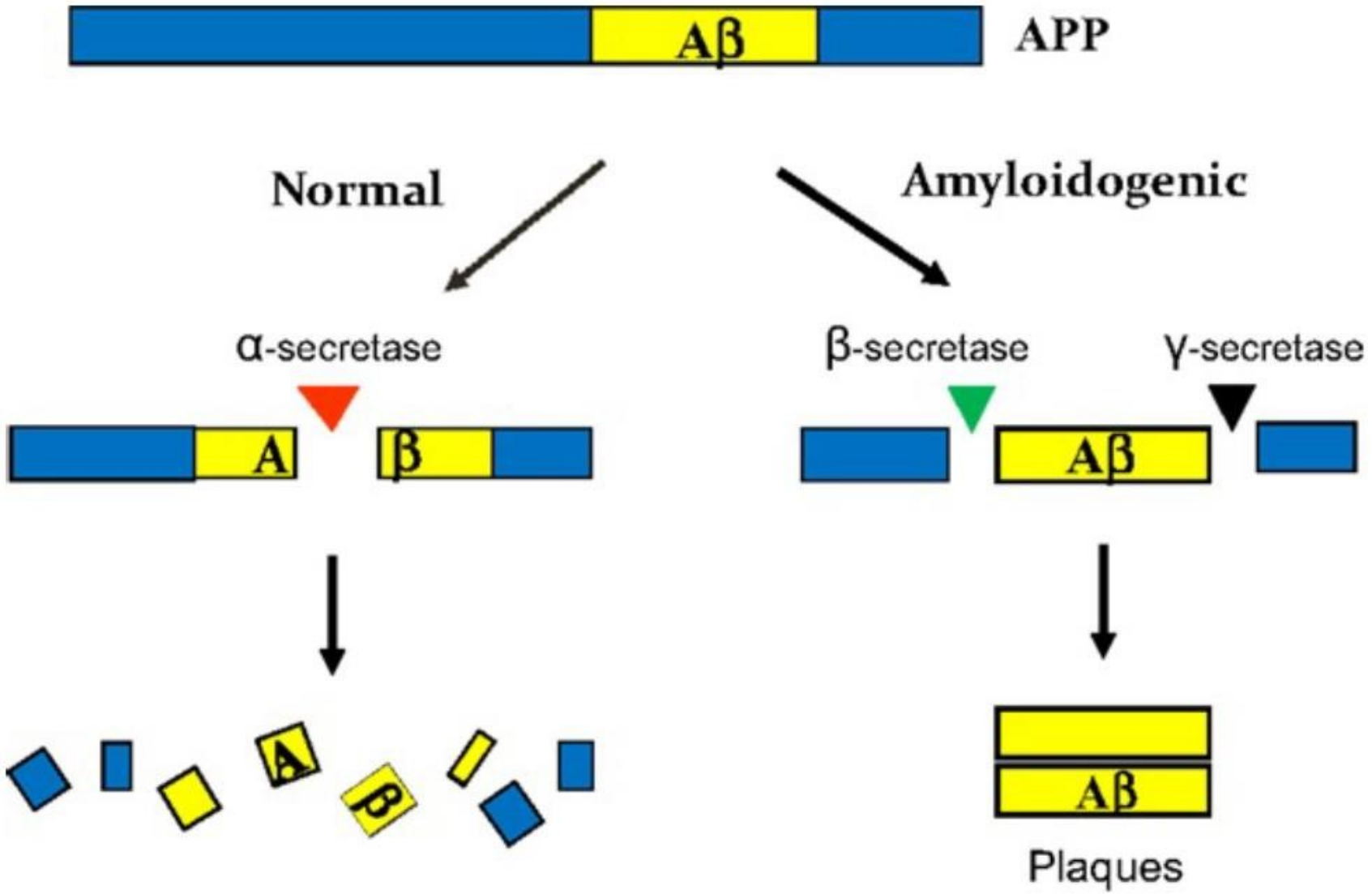
- Accumulation of two proteins (AB amyloid and Tau)
- In the form of plaques and neurofibrillary tangles, respectively.
- This leads to neuronal dysfunction, death and inflammation.
- Plaques deposit in the neuropil. Exracellular
- Tangles develops intracellularly.
- Aβ generation is the critical initiating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

Role of Aβ

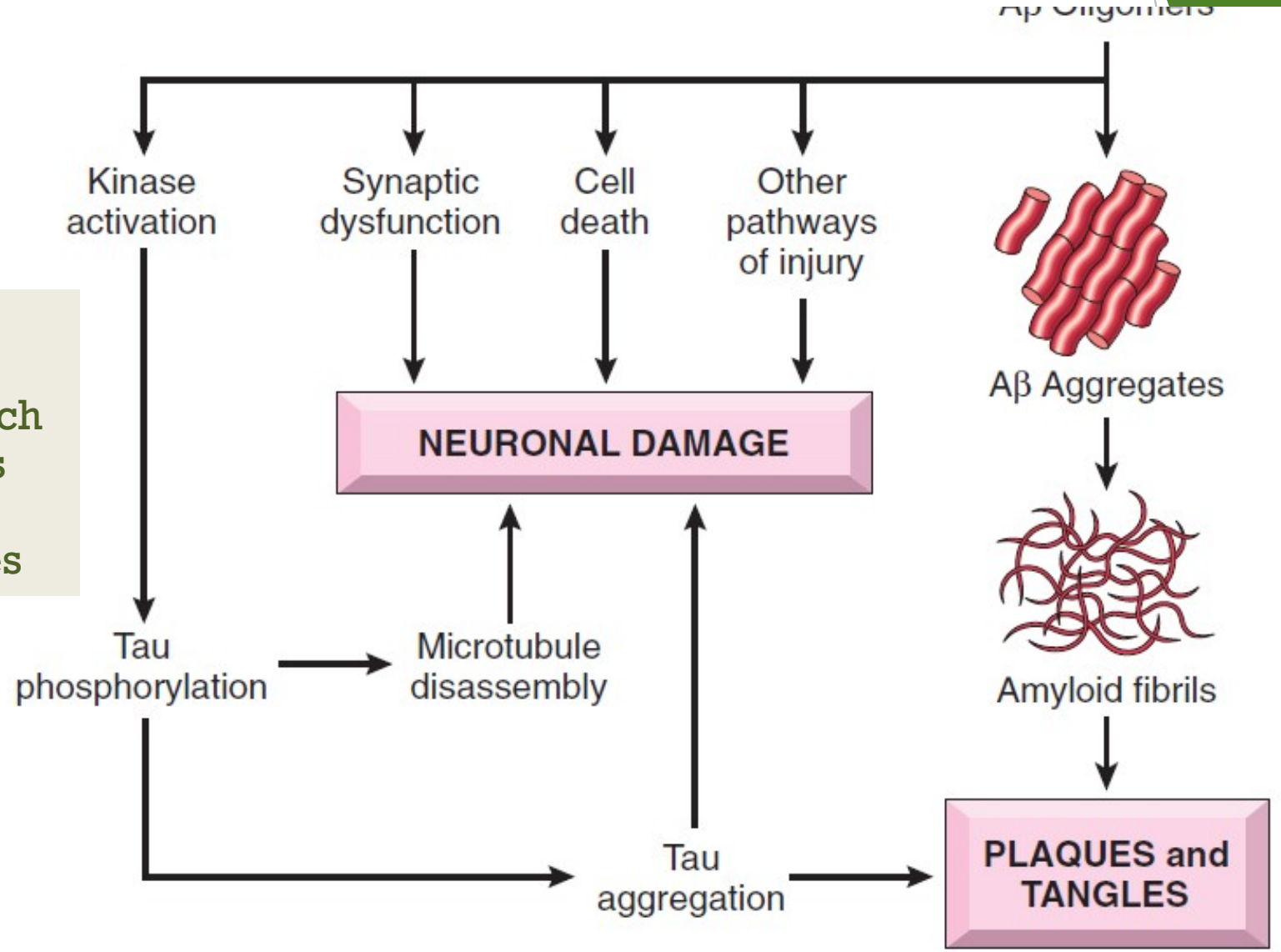
- AD results when the transmembrane protein (amyloid precursor protein APP) is sequentially cleaved by the **enzymes β-amyloid–converting enzyme (BACE) and γ-secretase** creating Aβ.
- Normally, APP can be cleaved by **α-secretase and γ-secretase**, liberating a nonpathogenic peptide.
- Mutations in APP or in components of γ-secretase lead to familial AD.
- The A*PP* gene is located on chromosome 21, increased risk in down syndrome
- Once generated, Aβ is highly prone to aggregation >>>> PLAQUES FORMATION >>> decreased number of synapses and alter their function >>> memory disruption.


precursor protein
β-Secretase
α-Secretase
Cleavage sites for:
γ-Secretase
A
COOH
Nonamyloidogenic
Normally
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage


Amyloid precursor protein
β-Secretase
α-Secretase
γ-Secretase
Cleavage sites for:
COOH
Amyloidogenic
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH
Aβ Monomer
Aβ Oligomers


Aβ
APP
Normal
Amyloidogenic
α-secretase
β-secretase
γ-secretase
A
β
Aβ
A
β
Aβ
Plaques

A beta aggregates activate kinases that phosphorylate tau which results in microtubules disassembly >> tau aggregation >> tangles



Role of tau:

Tau is a subsequent protein deposition not the initial pathogenic cause

- 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.

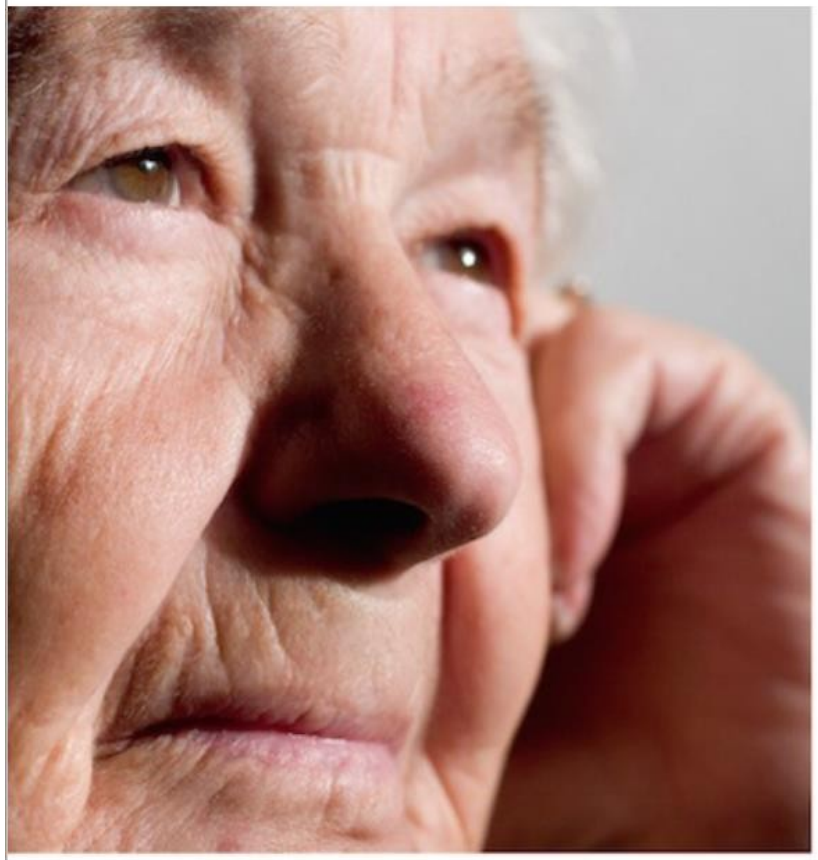
Because it's intracellular deposition

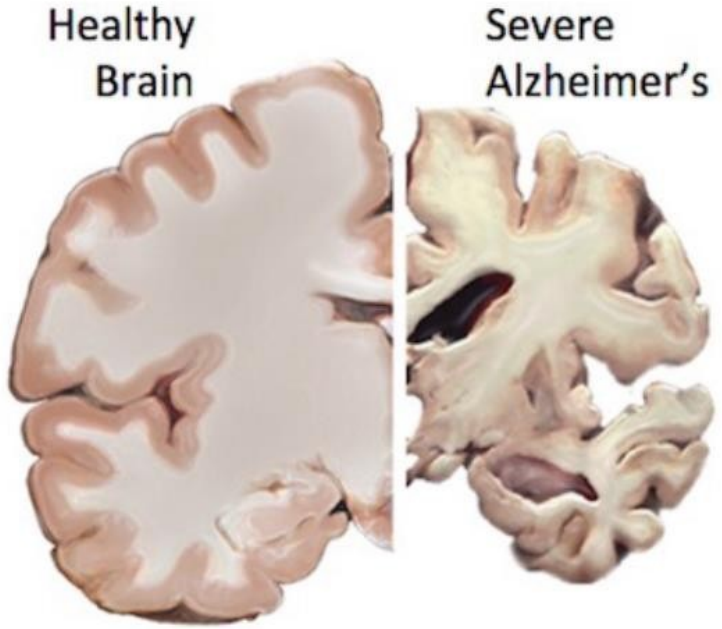
- The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques.

Morphology

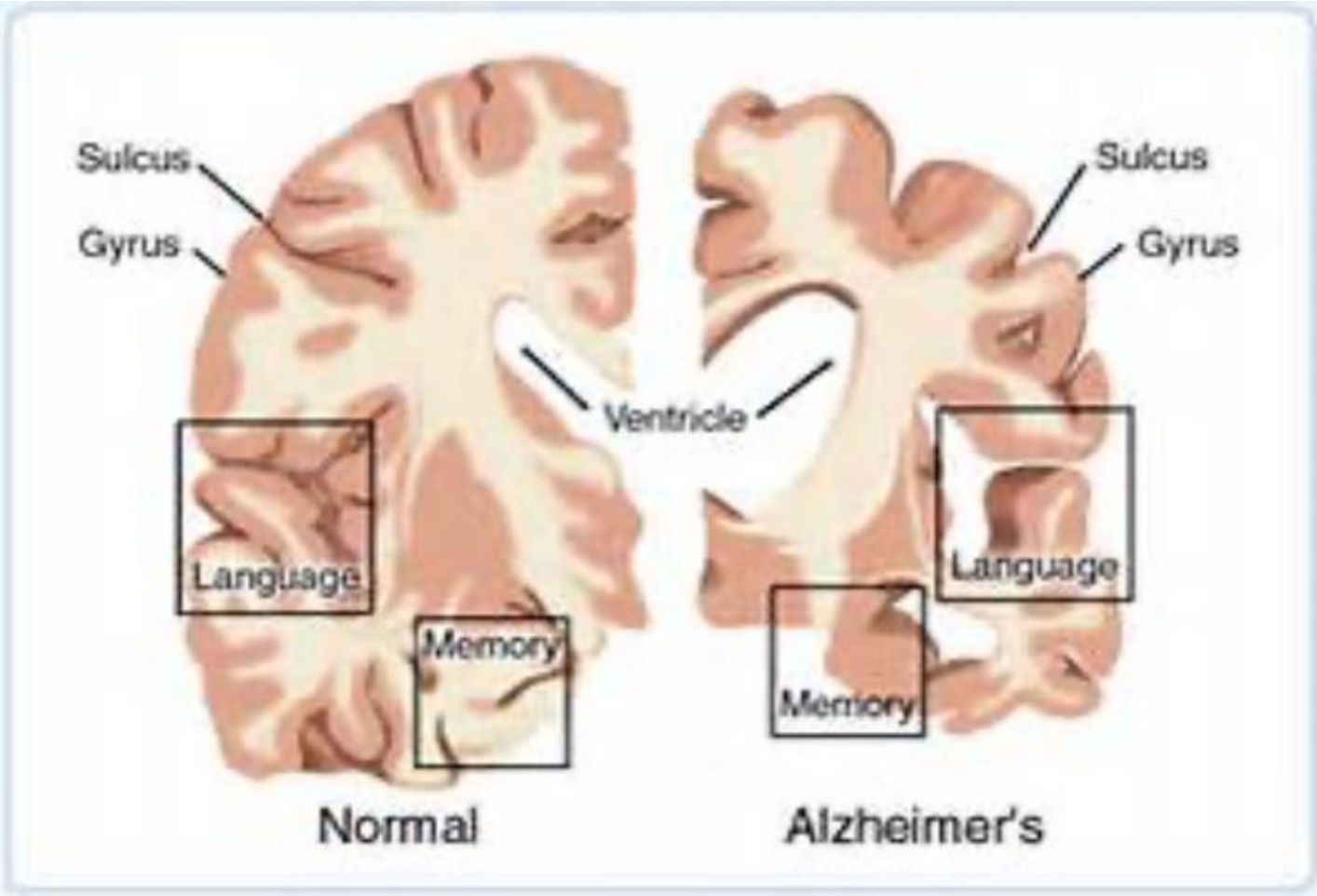
Secondary ventricles enlargement

- Cortical atrophy,
- Widening of the cerebral sulci
- Most pronounced in the frontal, temporal, and parietal lobes.
- Compensatory ventricular enlargement (hydrocephalus ex vacuo).





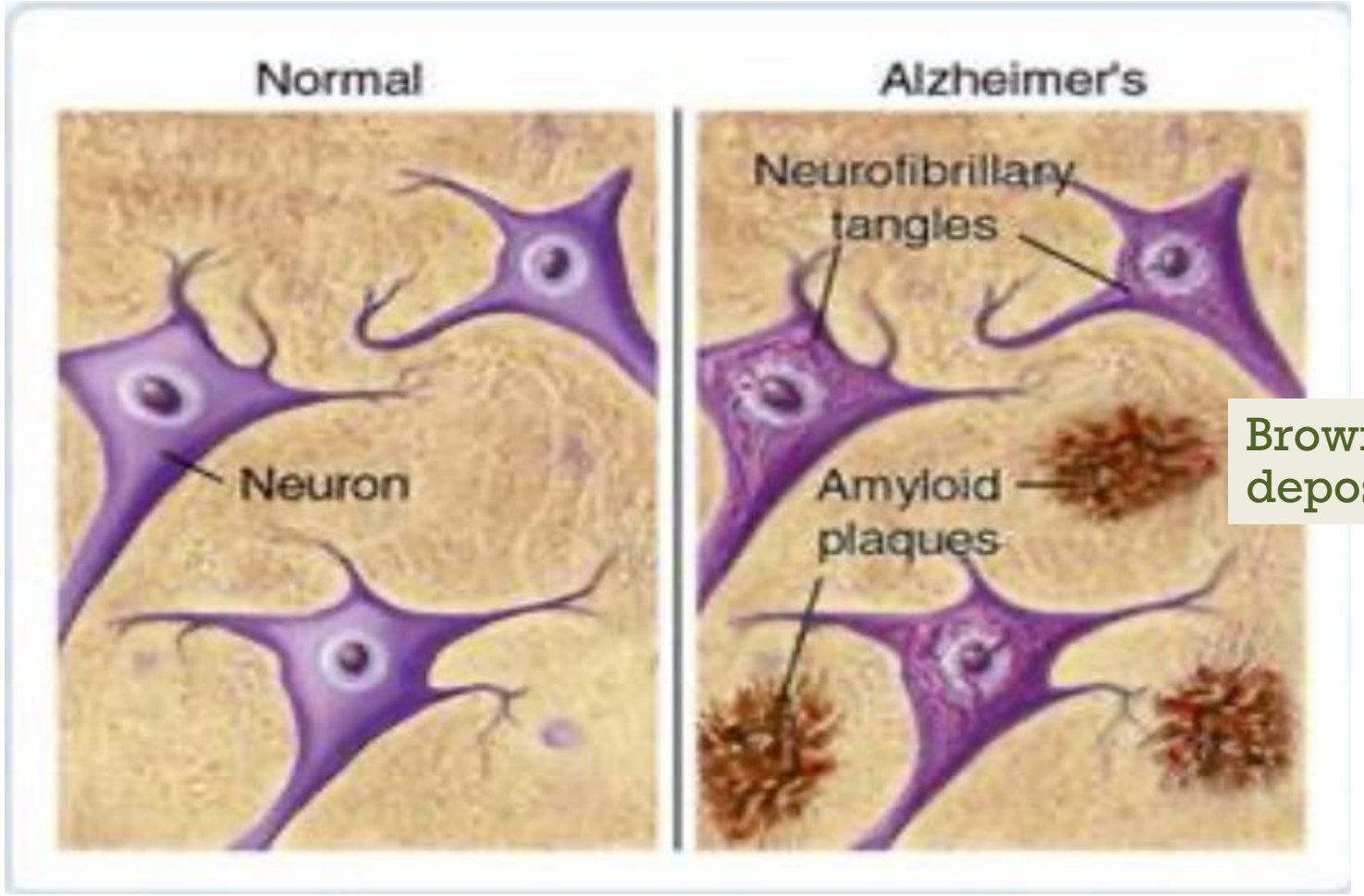
Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).


Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

Alzheimer disease neuropathologic changes.

- **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

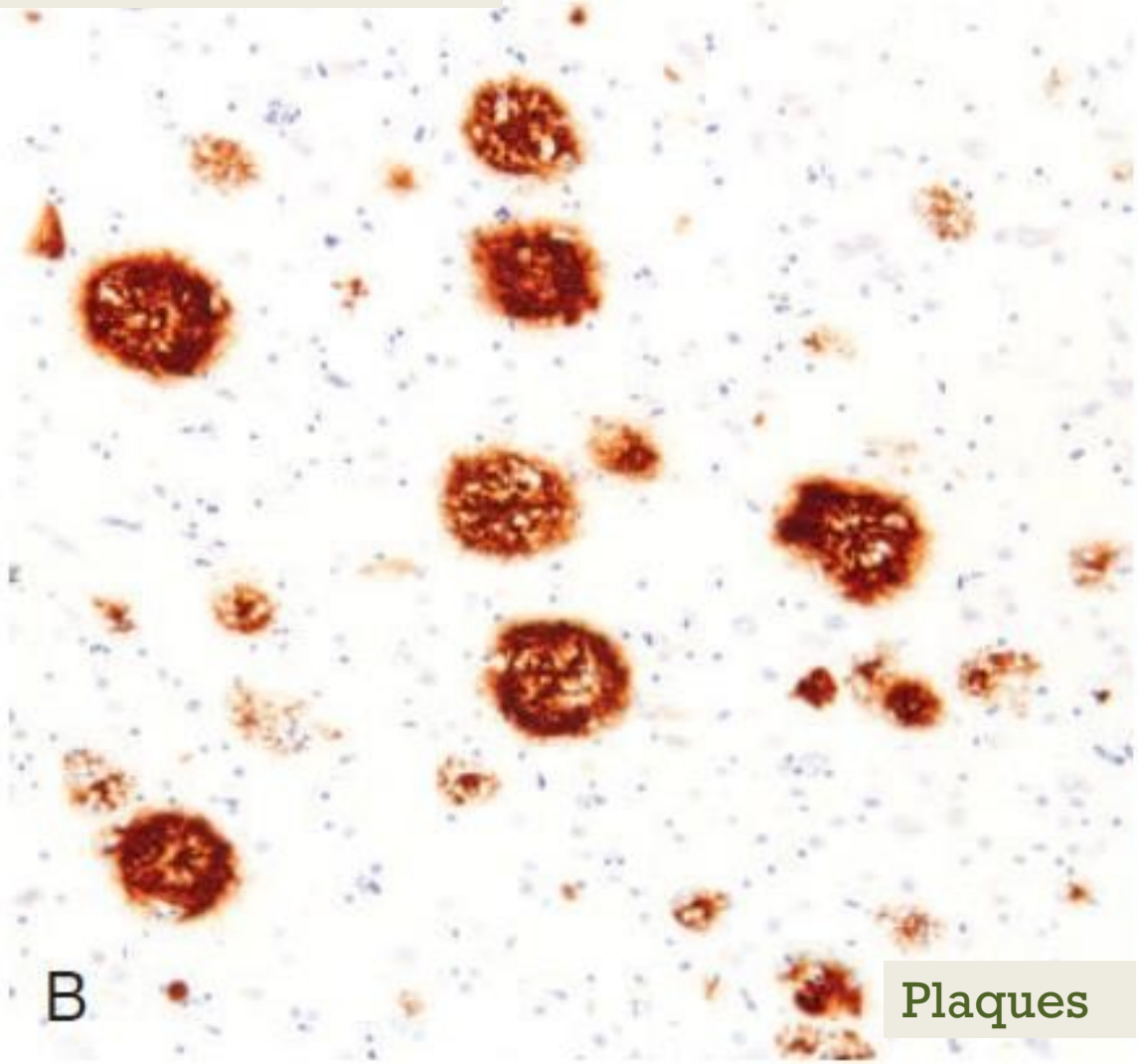
- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Hyperphosphorylated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



Brownish deposition

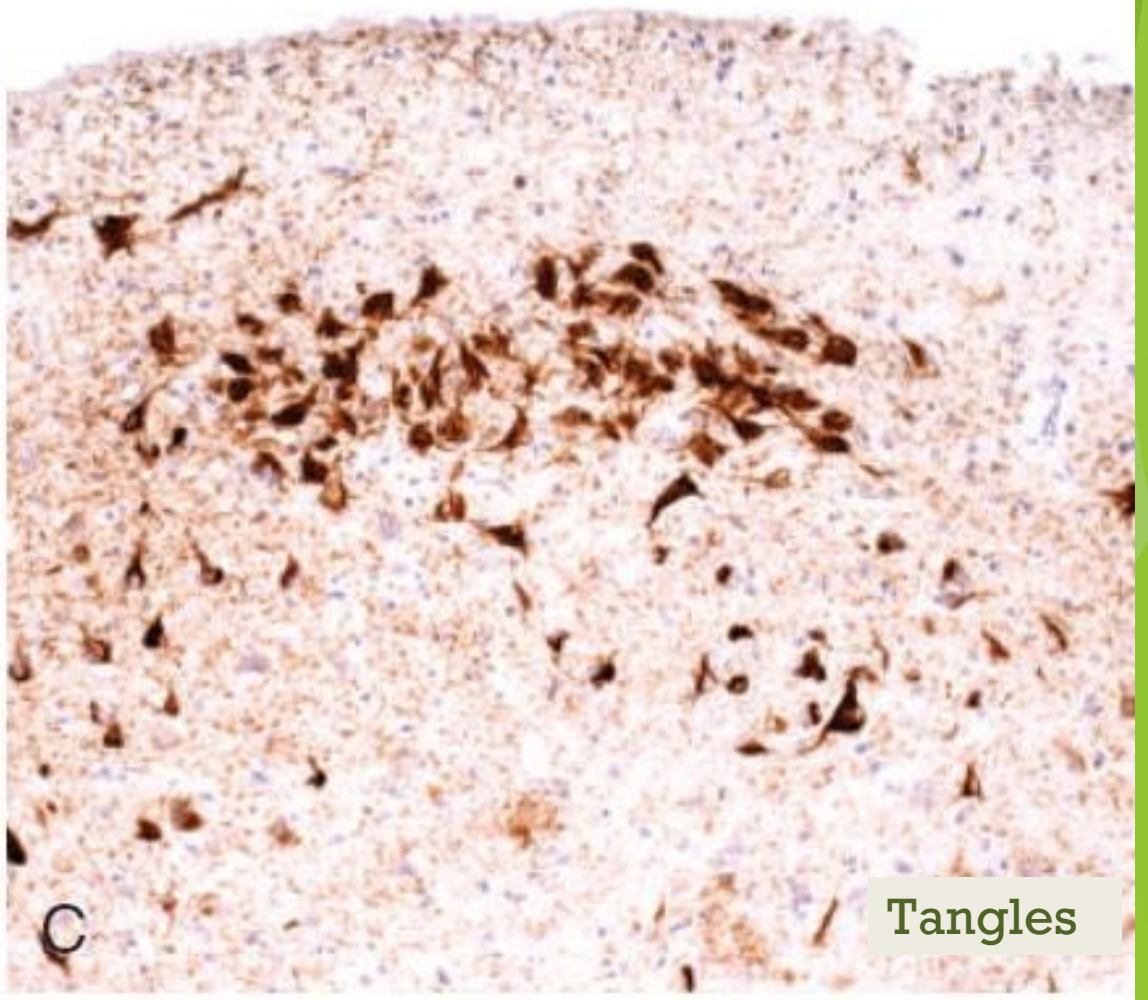
Plaques and tangles

Immune stains

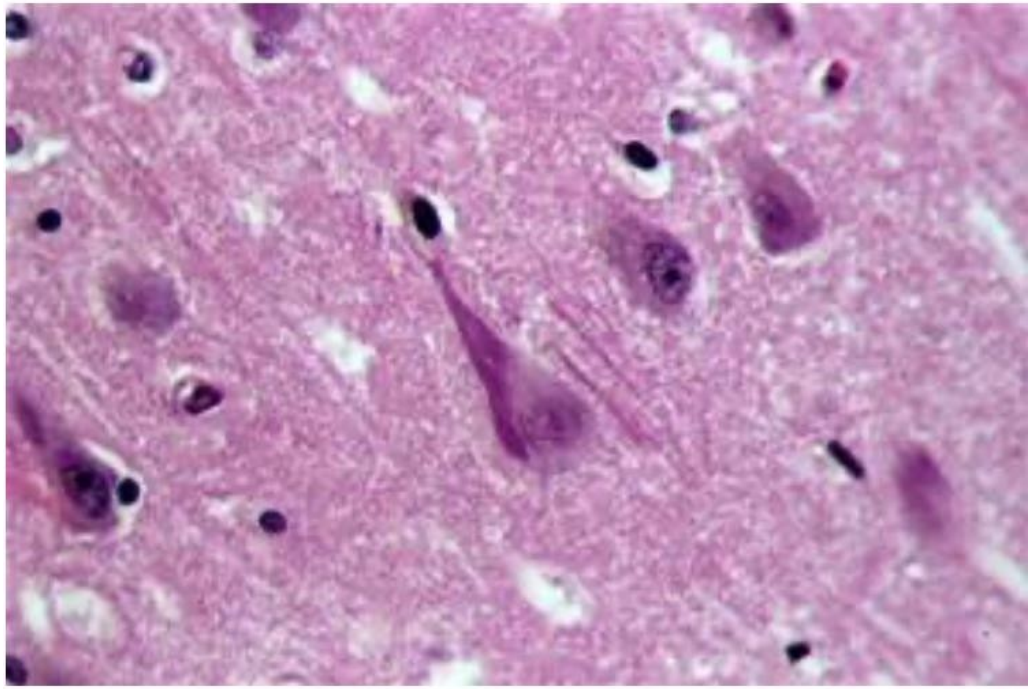


Plaques

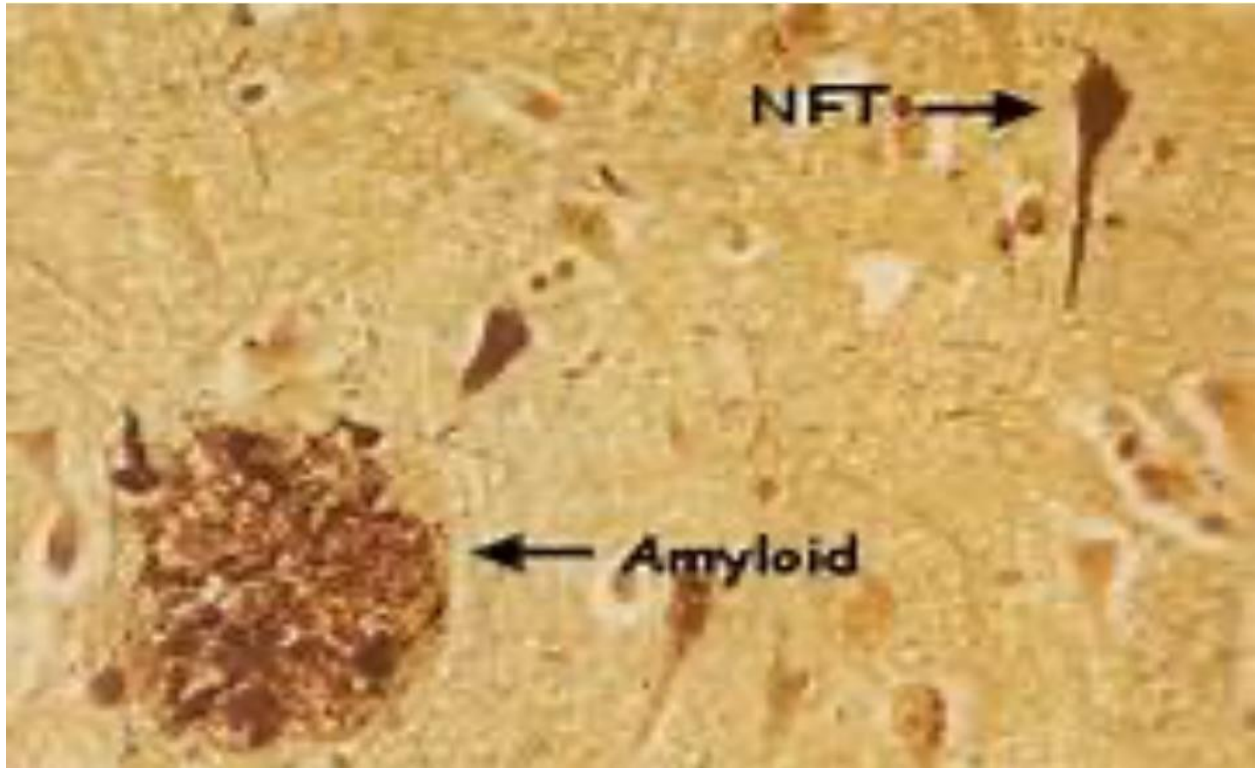
Triangle in shape



Tangles



NEUROFIBRILLARY TANGLES


NFT
Amyloid

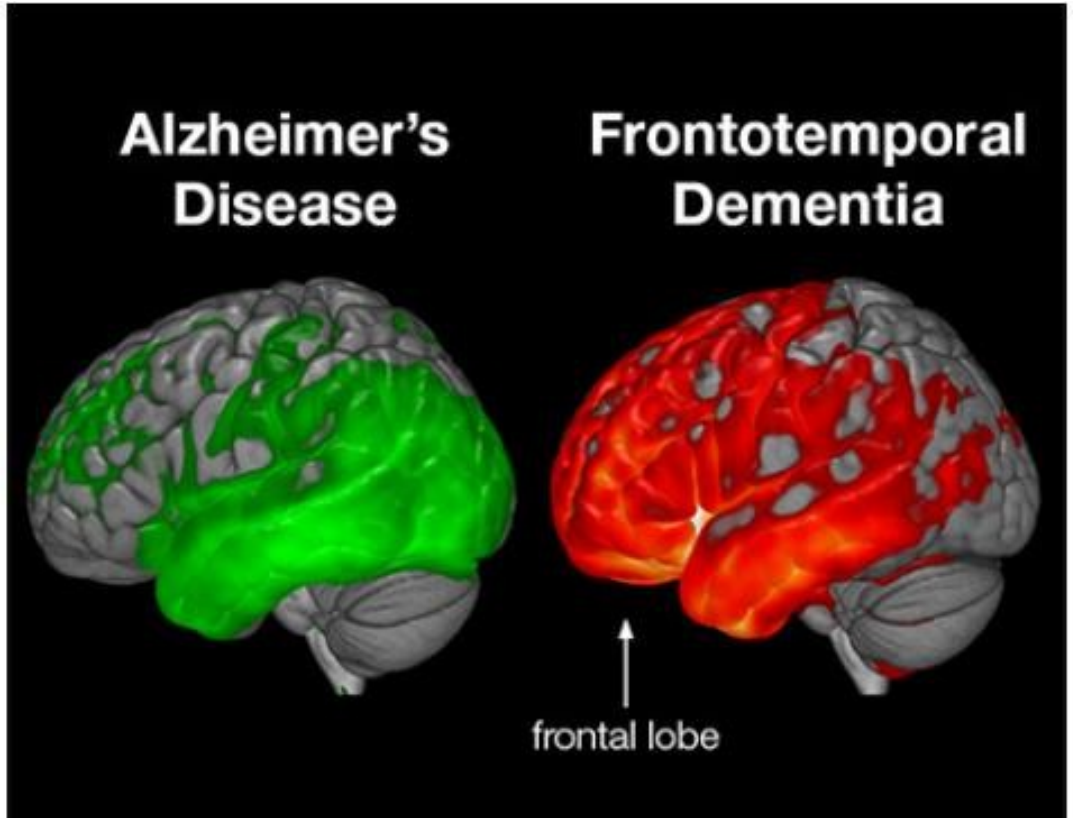
Frontotemporal Lobar Degeneration

- Several disorders.
- Preferentially affect the frontal and/or temporal lobes.
- Progressive deterioration of language and changes in personality
- Clinically, frontotemporal dementias

Because of the frontal lobe degeneration

- **Behavioral and language problems precede memory disturbances, in contrast to AD.**
- The onset of symptoms occurs at younger ages than for AD.
- Neuronal inclusions, which may contain tau or TDP43.
- *Pick disease (subtype of* FTLD-tau*),* associated with smooth, round inclusions known as *Pick bodies*

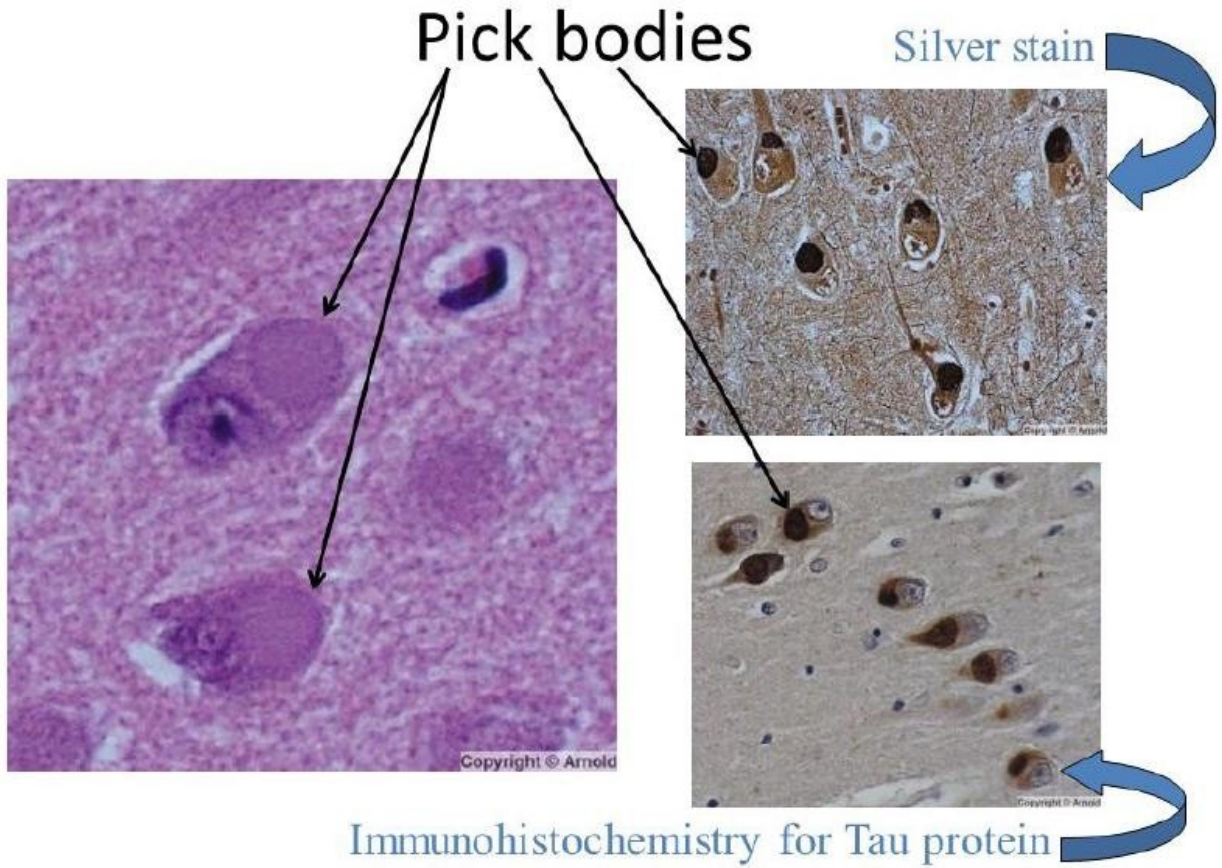
Tau aggregates



- In AD there is sparing of the frontal lobe, at least at the beginning so behavioural changes are a late manifestation.
- In FTLD frontal is affected from the beginning so patients present with behavioural problems first.

MORPHOLOGY

- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis
- In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD .
- Pick bodies.


Pick bodies
Silver stain
Copyright © Arnold
Immunohistochemistry for Tau protein

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