Neurodegenerative disorders-1

Manar Hajeer, MD, FRCPath

University of Jordan, School of medicine

Classic features:

- **Progressive loss of neurons.**
- **Typically affects groups of neurons with shared functions.**
- **Different diseases involve different neural systems, so different symptoms.**

Different diseases

- **Involving the hippocampus and cortex**>>>> cognitive changes (memory, behavior and language disturbances) >>>> 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, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA)

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

Classic features:

- **The histologic hallmark for ALL diseases is the ACCUMULATION OF PROTEIN AGGREGATES.**
- **Same protein may aggregate in different diseases, BUT AT DIFFERENT DISTRIBUTION..**
- **Proteins resist degradation, accumulate within the cells or in extracellular space, elicit inflammatory response, and is toxic to neurons.**

Causes of protein accumulation

- **Mutations that alter protein conformation.**
- **Mutations disrupting the processing and clearance of proteins.**
- **Subtle imbalance between protein synthesis and clearance (genetic or environmental factors)**

Common features to many neurodegenerative diseases:

- **Protein aggregates can seed the development of more aggregates.**
- **Protein aggregates can spread to healthy neurons 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.**
- **Cognitive deficit must affect the person's performance in his daily life activities.**
- **There is no standard NORMAL COGNITION, always compared to previous level.**

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

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.**
- **Death usually due to infections (pneumonia)**

- **The most recognized 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:

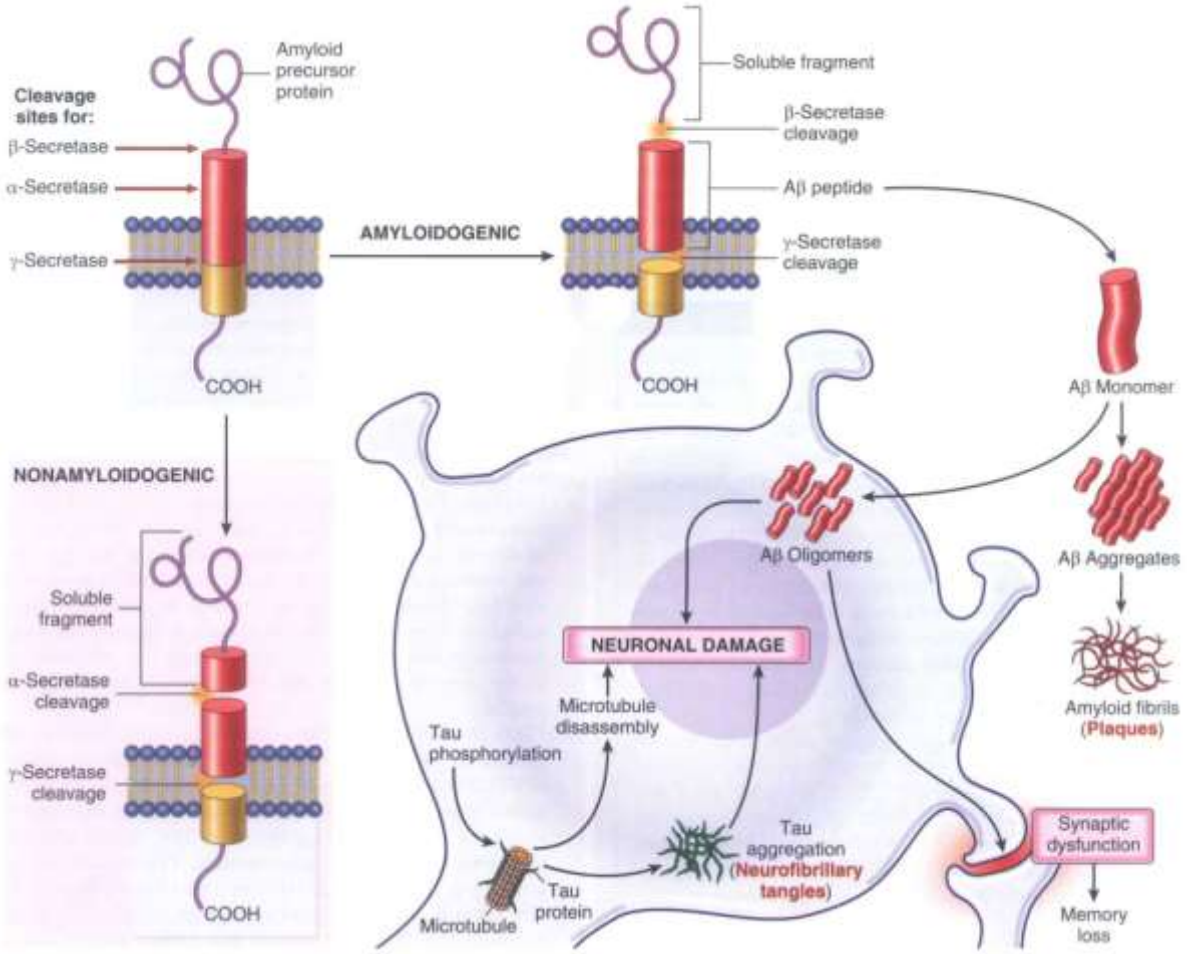
- **Accumulation of two proteins (AB amyloid and Tau)**
- **Plaques (AB amyloid) and neurofibrillary tangles (Tau).**
- **Leads to neuronal dysfunction, death and inflammation.**
- **Plaques deposit in the neuropil, tangles develops intracellularly.**
- **Aβ generation is the critical initiating event.**

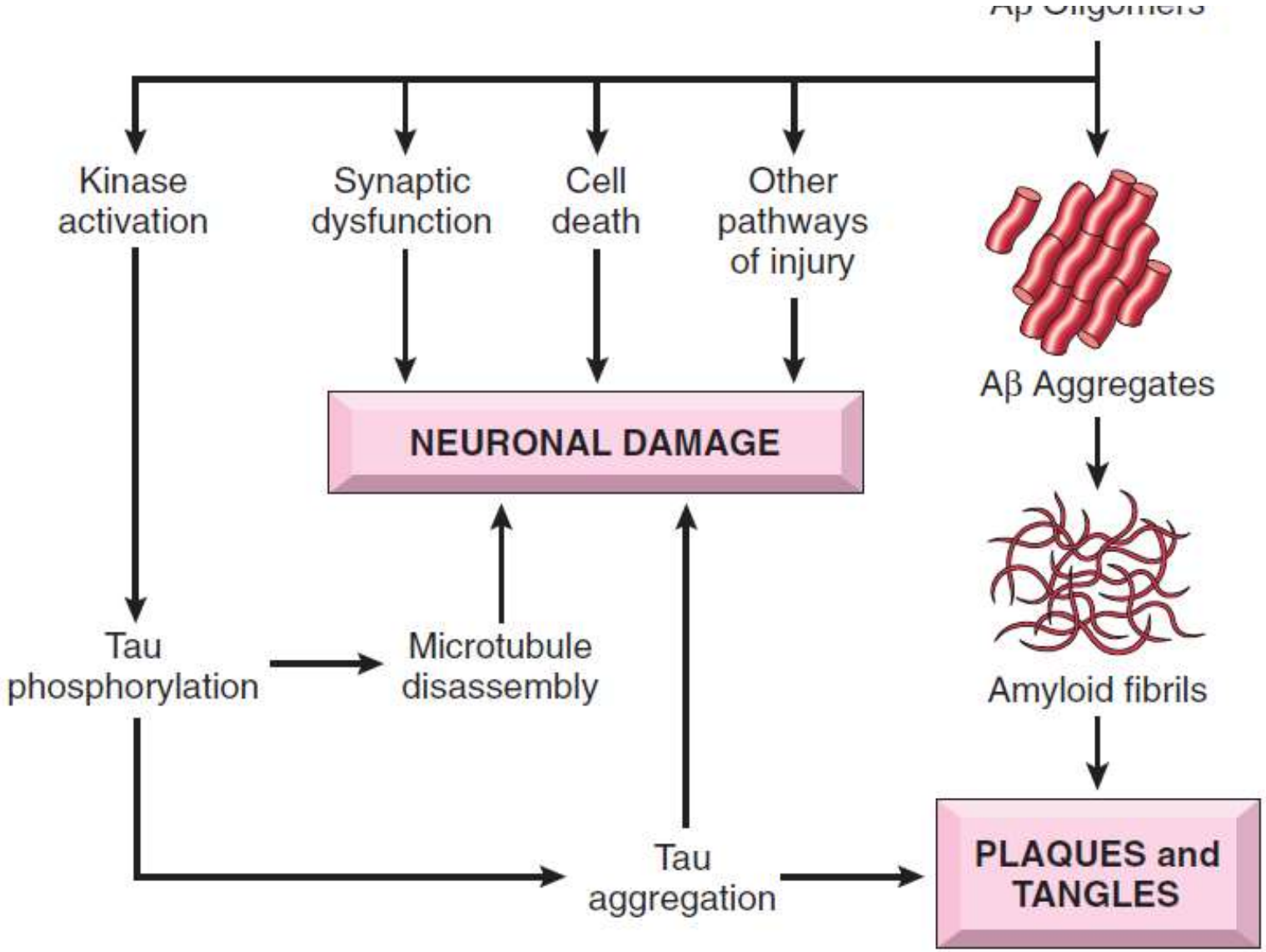
- **Multiple gene loci contribute to the risk of AD.**

Role of Aβ

- **Normally, amyloid precursor protein (APP) is cleaved by α-secretase and γ-secretase, liberating a nonpathogenic peptide.**

- **AD results when APP is cleaved by the enzymes B-secretase (β-amyloid–converting enzyme, BACE) and γ-secretase, creating Aβ amyloid.**
- **Familial AD: Mutations in APP or in components of γ-secretase and others.**
- **The APP 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 >>> synaptic dysfunction >>> memory disruption.**


Amyloid precursor protein
Cleavage sites for:
β-Secretase
α-Secretase
γ-Secretase
COOH
AMYLOIDOGENIC
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH
Aβ Monomer
NONAMYLOIDOGENIC
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage
COOH
Aβ Oligomers
Aβ Aggregates
Amyloid fibrils (Plaques)
NEURONAL DAMAGE
Microtubule disassembly
Tau phosphorylation
Tau aggregation (Neurofibrillary tangles)
Synaptic dysfunction
Tau protein
Microtubule
Memory loss


Aβ Oligomers
Kinase activation
Synaptic dysfunction
Cell death
Other pathways of injury
Aβ Aggregates
NEURONAL DAMAGE
Tau phosphorylation
Microtubule disassembly
Amyloid fibrils
Tau aggregation
PLAQUES and TANGLES

Role of tau:

- Tau is a microtubule-associated protein.
- Present in axons in association with the microtubular network.
- In AD Hyperphosphorylated Tau loses the ability to bind to microtubules >>>> loss of microtubule stability >>> neuronal toxicity and death.
- Responsible for neurofibrillary tangles in AD.

- Tau aggregates can be passed across synapses from one neuron to the next >>> spread of lesions.

Role of inflammation

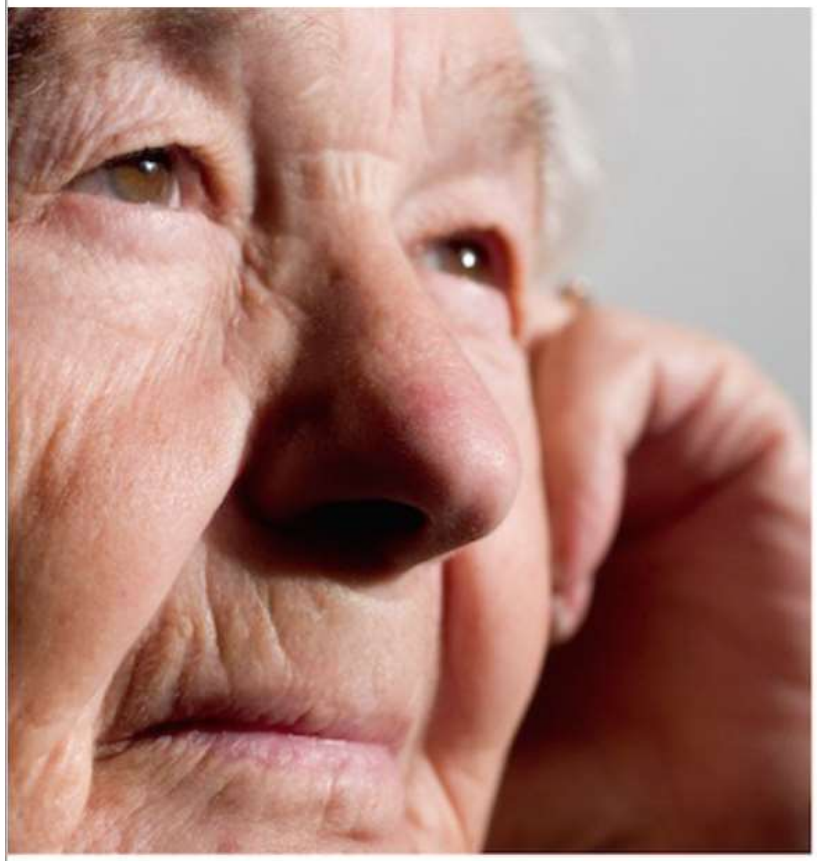
- Deposits of Aβ elicit an inflammatory response from microglia and astrocytes.
- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

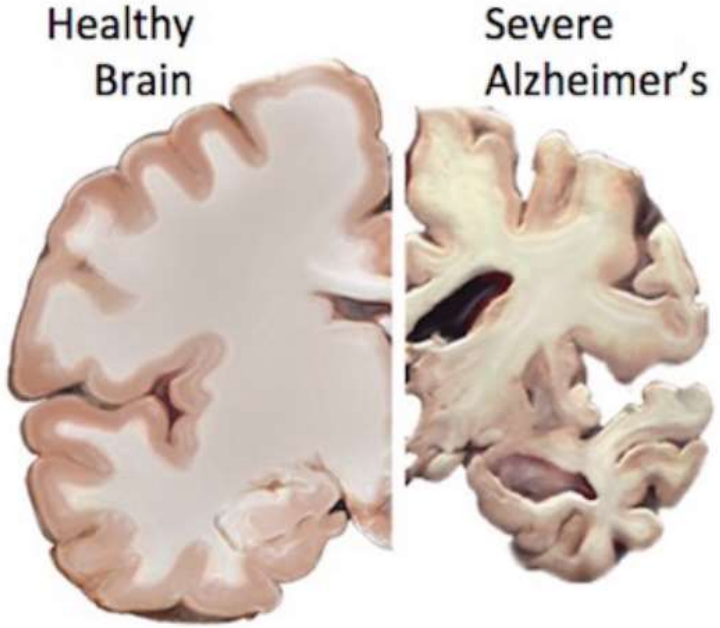
Basis for cognitive impairment

- Deposits of Aβ and tangles appear long 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.**

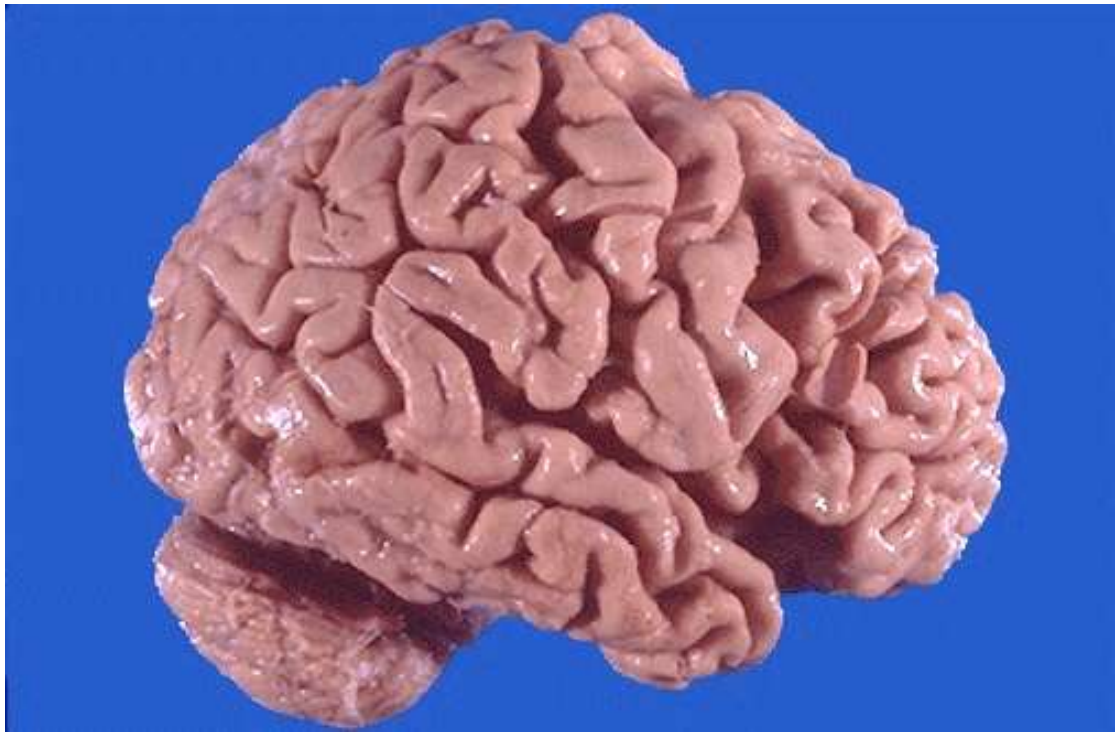
Morphology

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



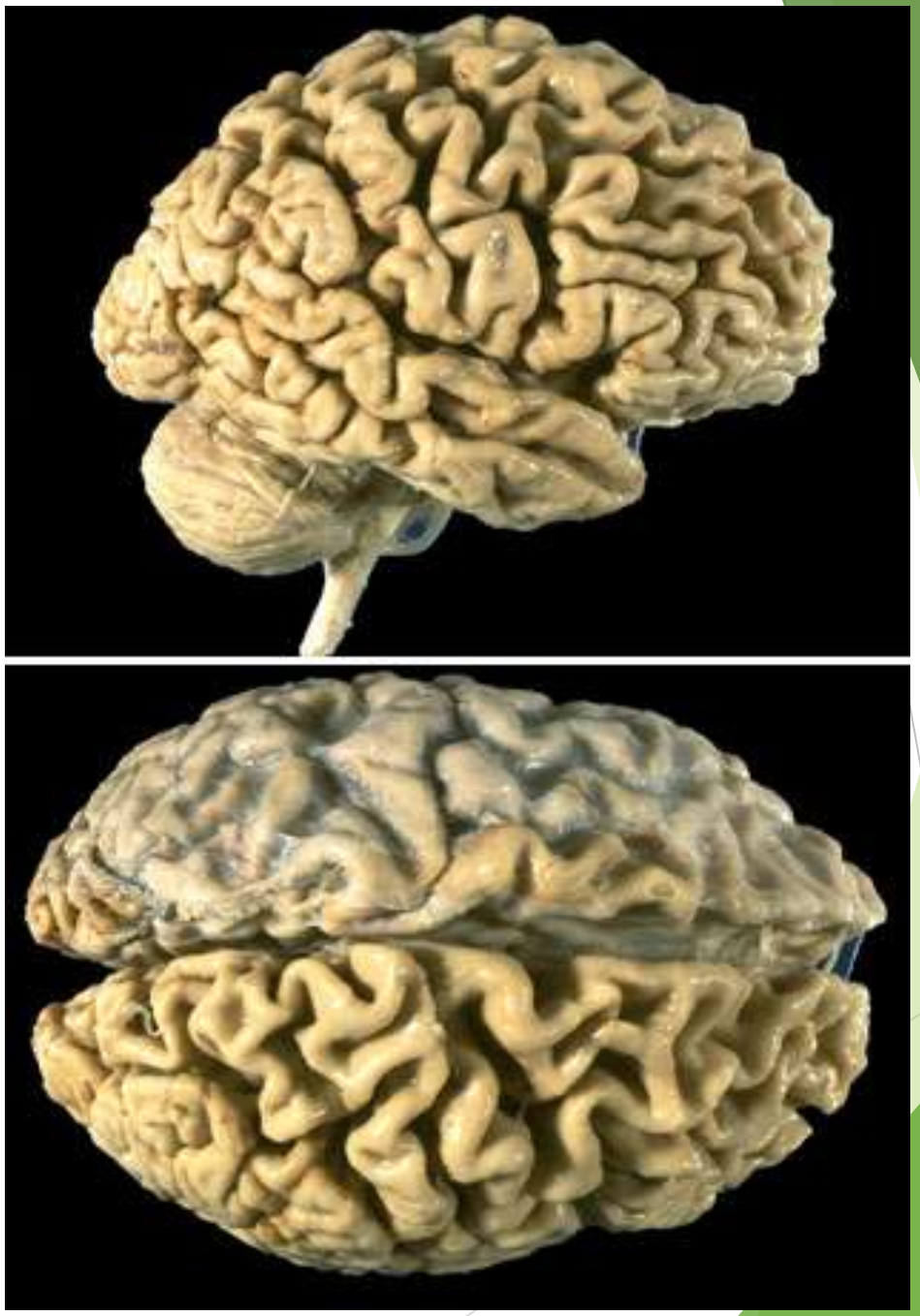


Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).

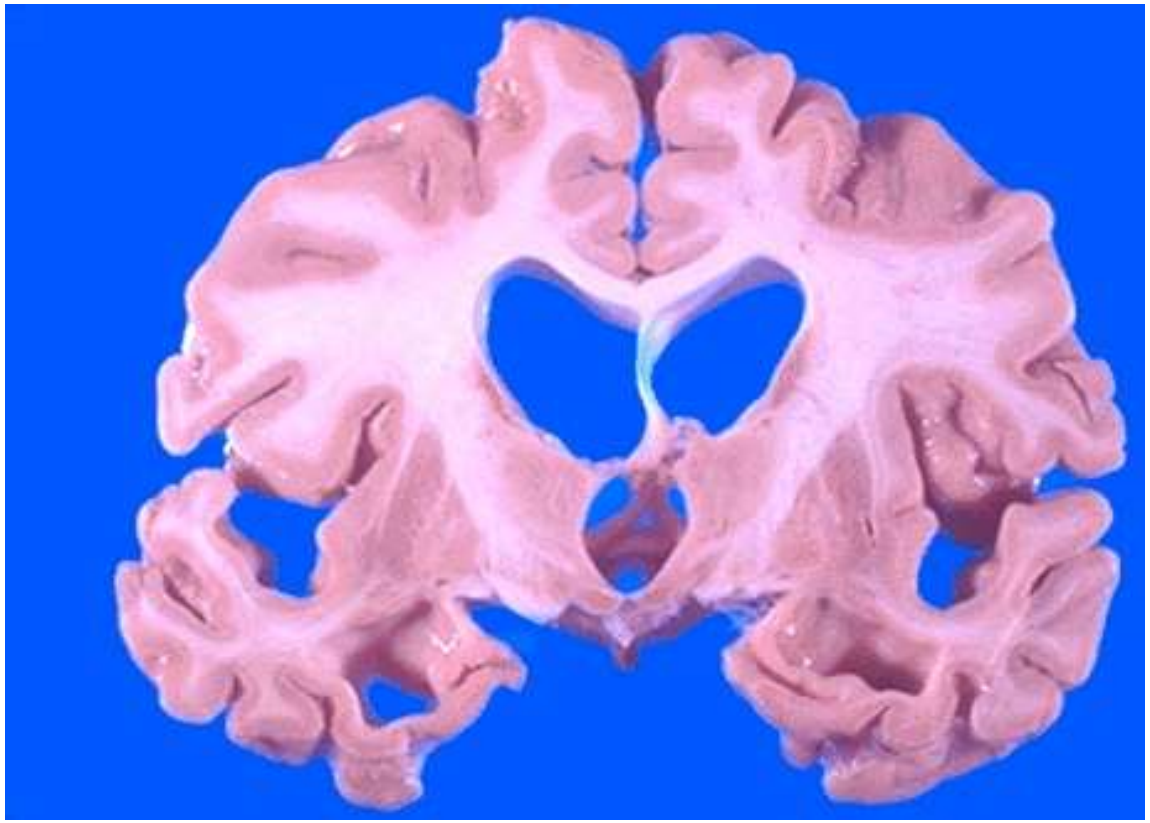


- Mainly in the frontal and parietal regions, characterized by **narrowed gyri** along with **widened sulci**.

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



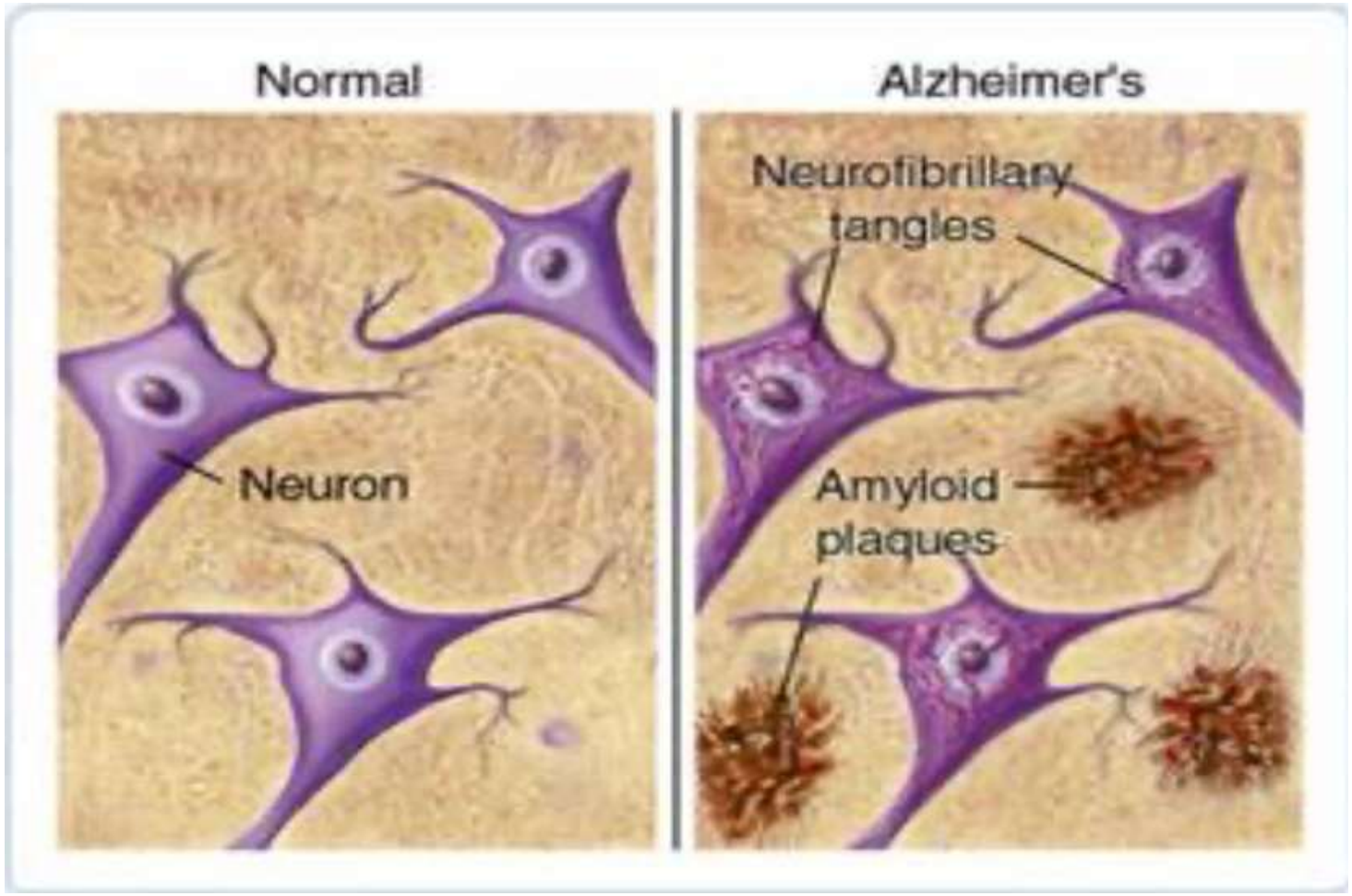
Progressive cortical atrophy with Alzheimer disease leads to compensatory dilation of the **cerebral ventricles** known as "hydrocephalus ex vacuo".



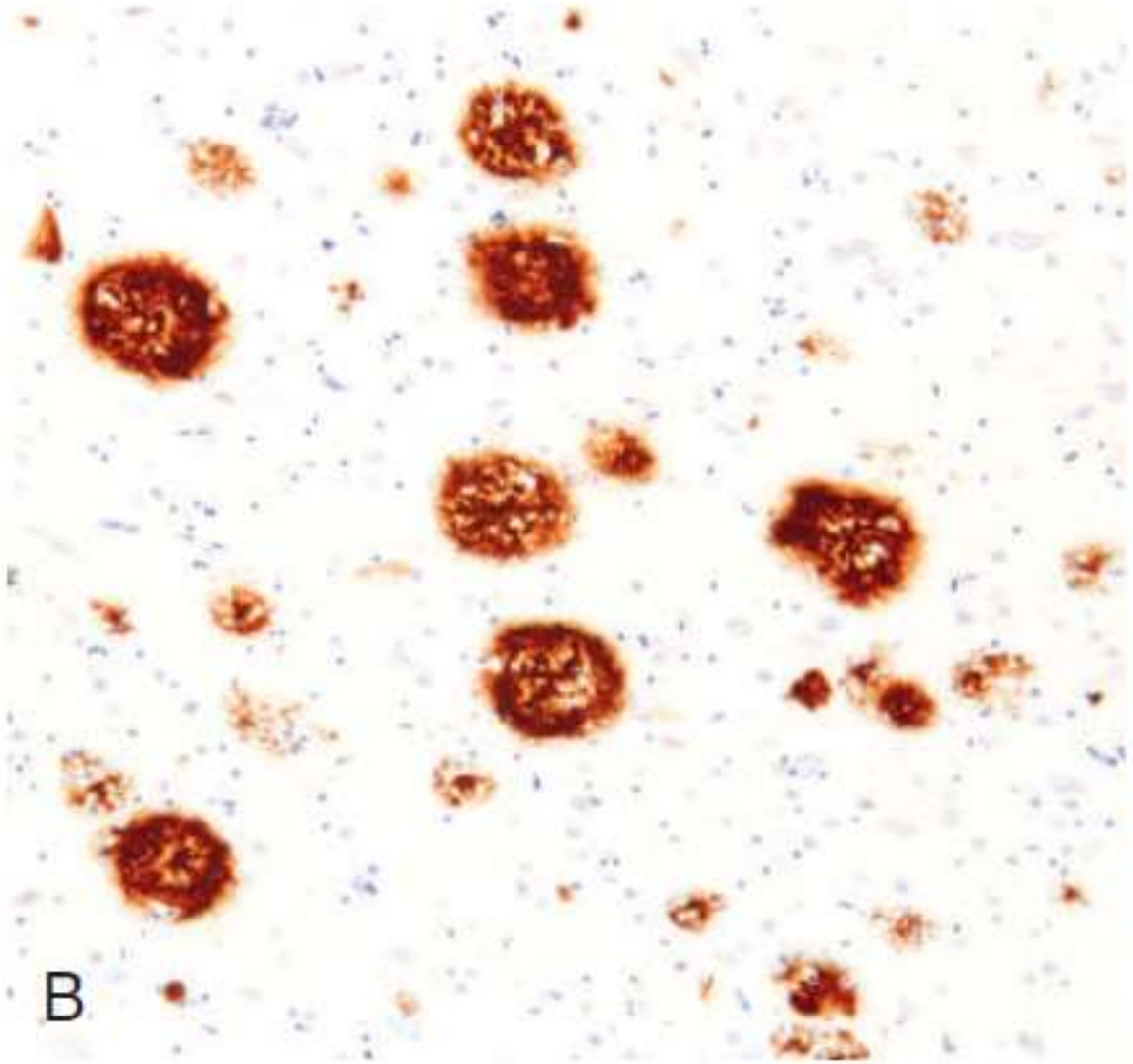
Microscopy:

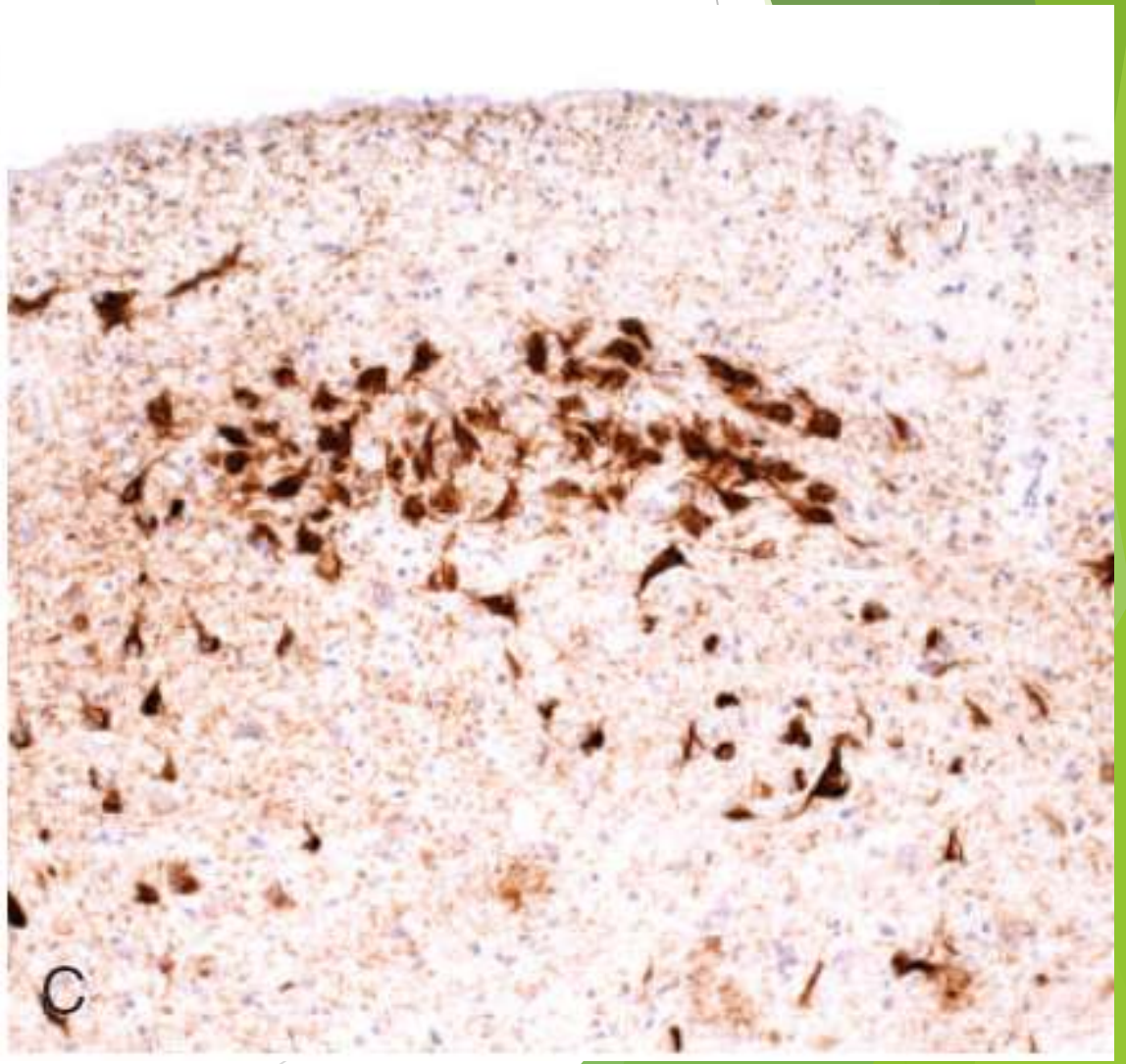
- **Neuritic plaques** (an extracellular lesion): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites.
- Hippocampus and amygdala and neocortex, (sparing of primary motor and sensory cortices until late)
- The amyloid core contains Aβ

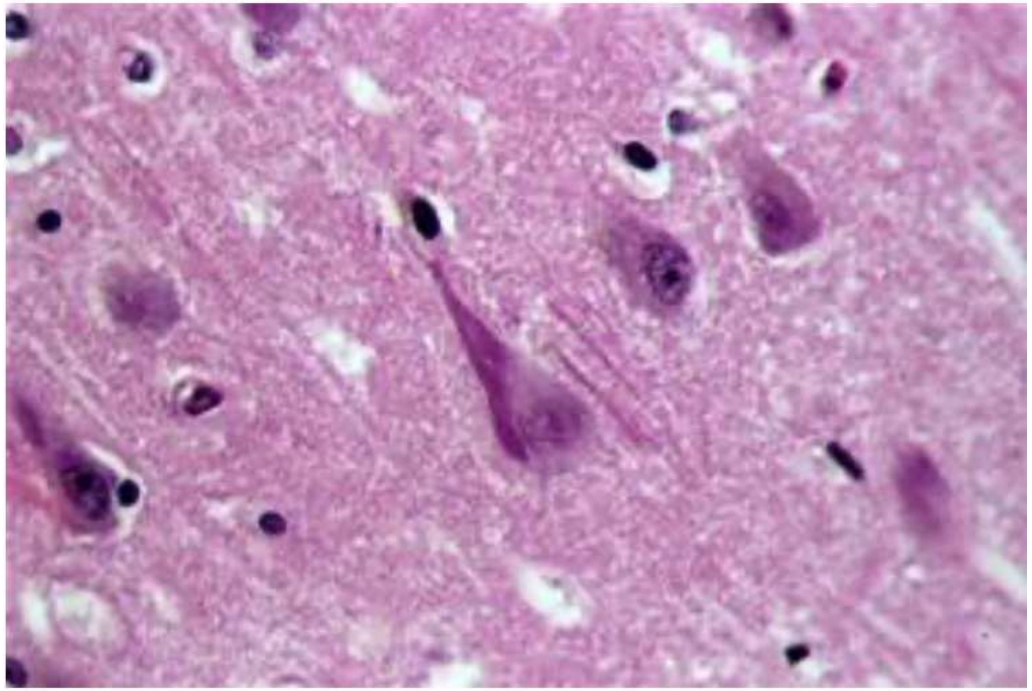
- **Neurofibrillary tangles**, basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.
- Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.
- Contains hyperphosphorylated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


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

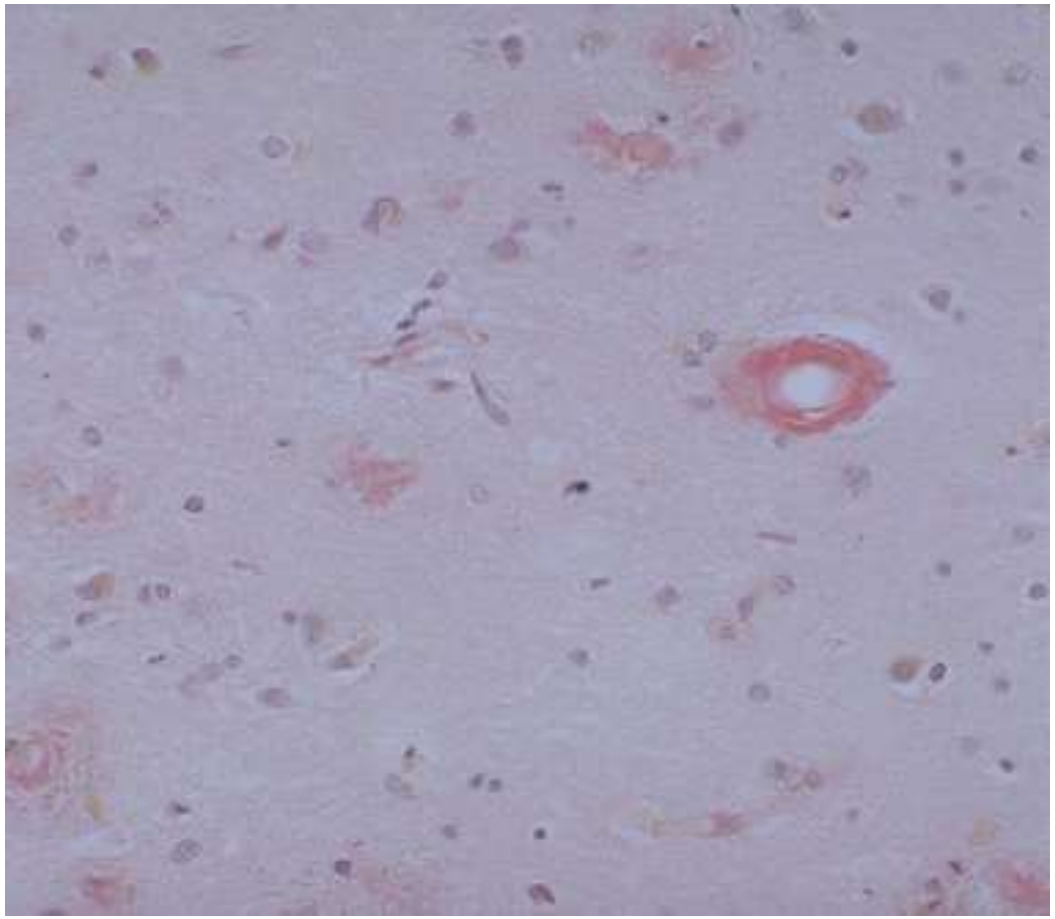
Plaques and tangles







NEUROFIBRILLARY TANGLES



Congo red stain for amyloid core of plaques.

Clinical features

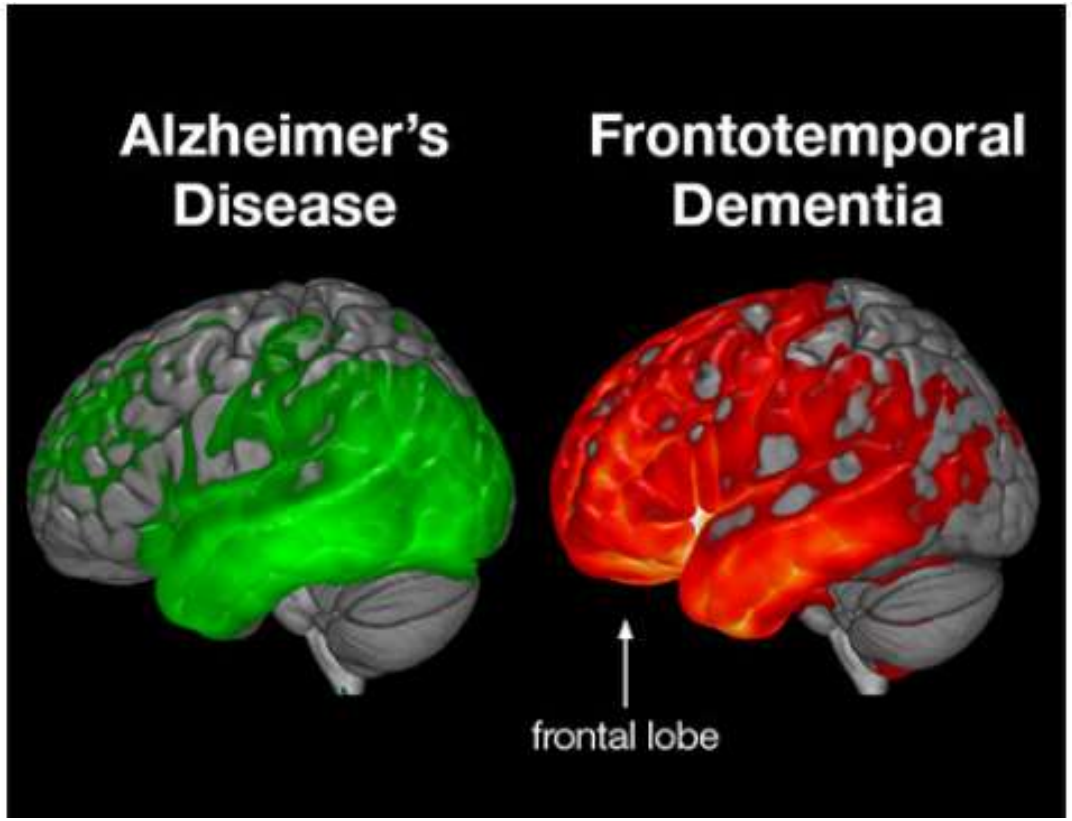
- **Slow relentless progression over more than 10 years**
- **Initially forgetfulness and memory disturbances**
- **With progression language deficits, loss of mathematical skills and learned motor skills**
- **Late stages: incontinent, mute and unable to walk**
- **Pneumonia in usually the terminal event.**
- **Early intervention in preclinical stages, drugs or antibodies to clear AB amyloid from brain or prevent alterations in Tau.**
- **Detection of biomarkers of AD for early intervention: imaging methods , CSF studies (phosphorylated Tau and reduced AB in CSF).**

Frontotemporal Lobar Degeneration

Frontotemporal dementias

- **Heterogenous group, preferentially affect the frontal and/or temporal lobes.**
- **Behavioral and language problems precede memory disturbances, in contrast to AD.**
- **The onset of symptoms occurs at younger ages than for AD.**
- **The most common forms according to neuronal inclusions:**
- **1-FTLD-tau.**
- **2-FTLD-TDP43: also deposited in ALS.**

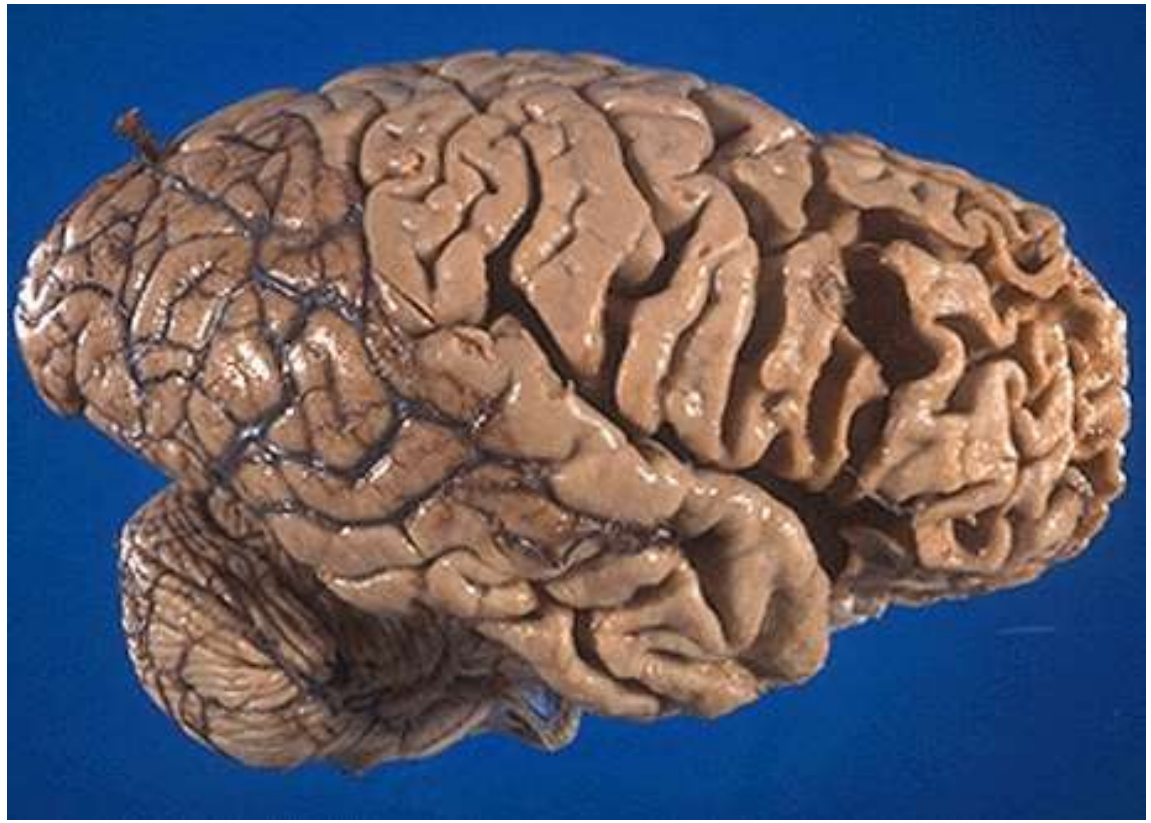
In FTLD, frontal lobe is affected from the beginning, so patients present with behavioral problems first.



- In AD there is sparing of the frontal lobe, at least at the beginning so behavioral changes are a late manifestation.

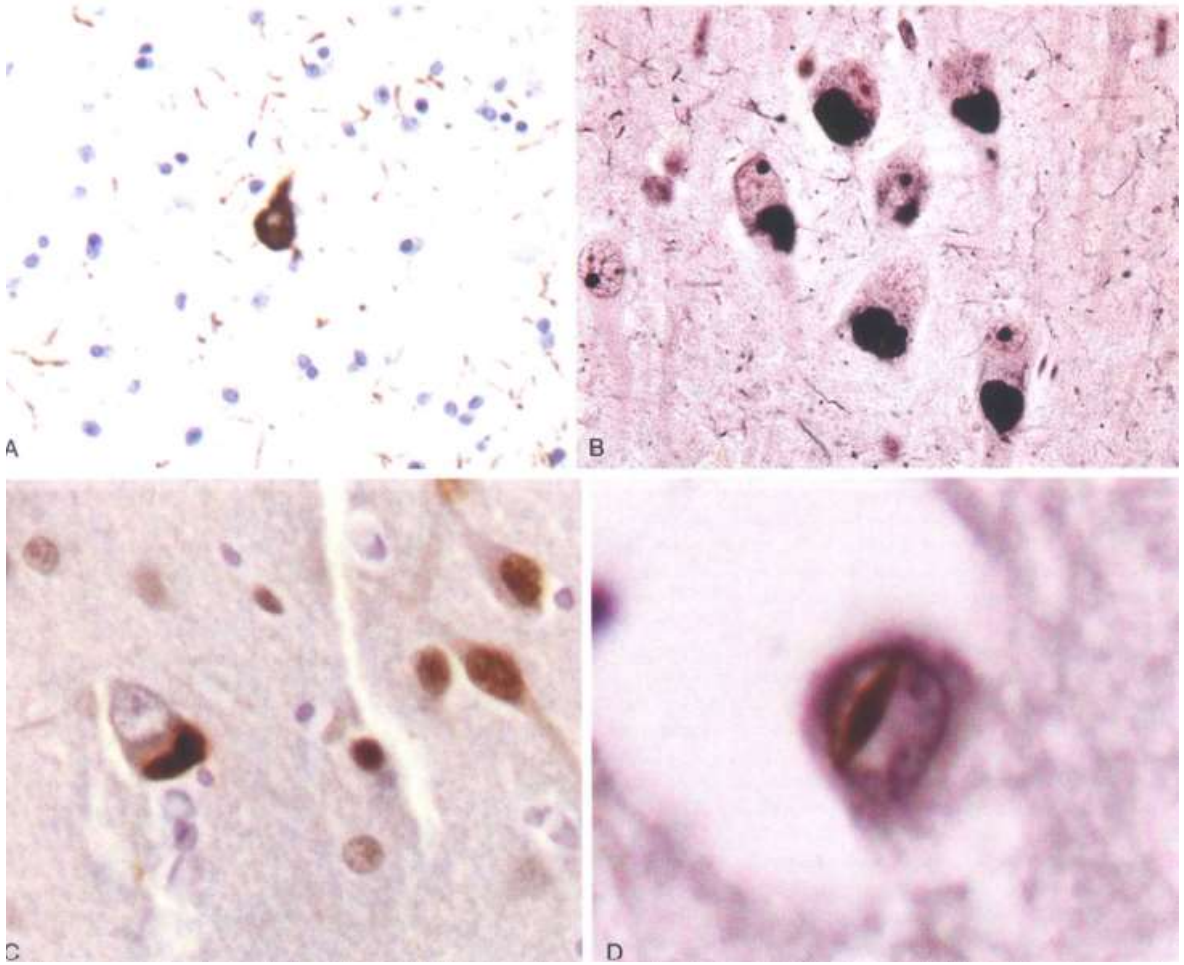
MORPHOLOGY

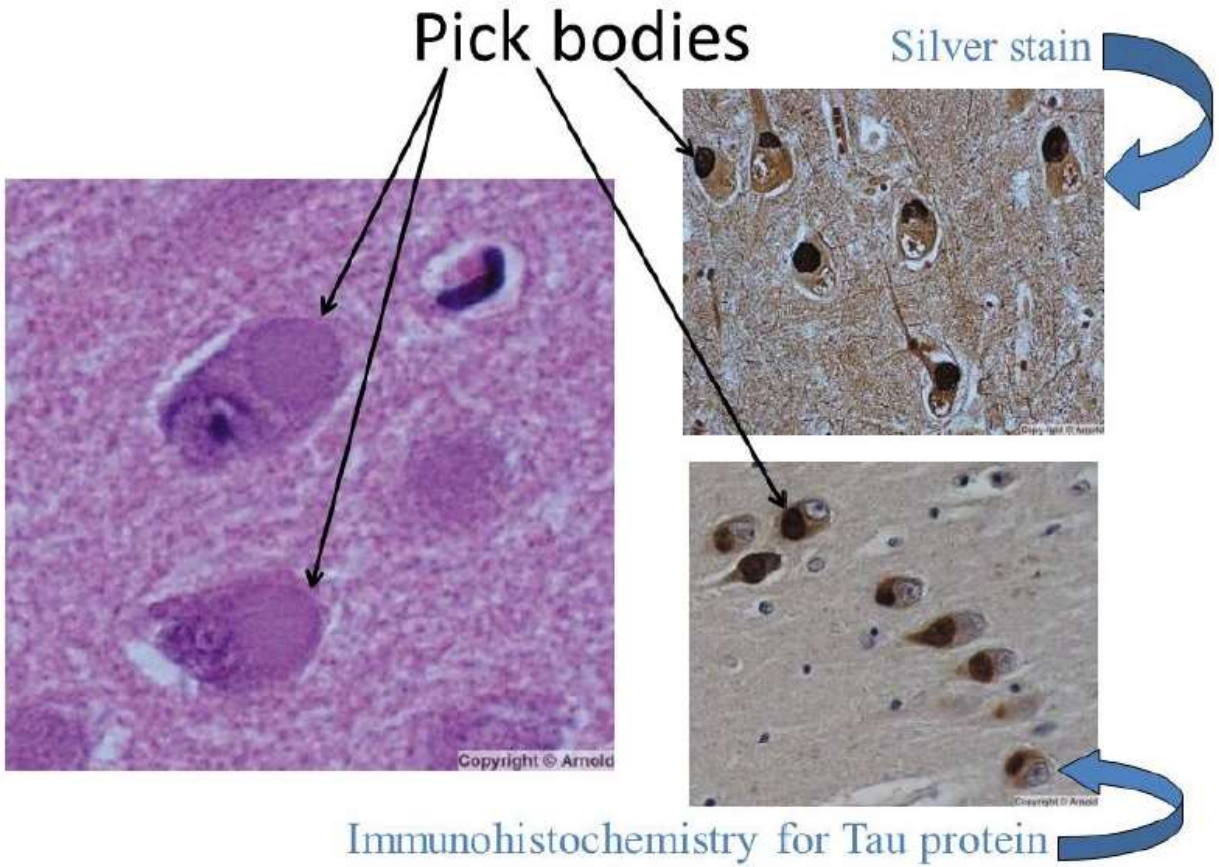
- **Atrophy of frontal and temporal lobes.**
- **Neuronal loss and gliosis**
- **In FTLD-tau: neurofibrillary tangles like in AD.**
- **In FTLD-TDP43: cytoplasmic inclusions.**
- **In Pick disease: pronounced and asymmetric atrophy of frontal and temporal lobes with sparing of posterior two thirds of superior temporal gyrus. And pick bodies (round oval cytoplasmic filamentous inclusions stain strongly with silver stain.**



- Very marked **frontal lobe atrophy** and **temporal lobe atrophy**

Frontal lobes are markedly thinned


A
B
C
D


Pick bodies
Silver stain
Copyright © Arnold
Immunohistochemistry for Tau protein