Neuroscience II Pathology

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Topics:

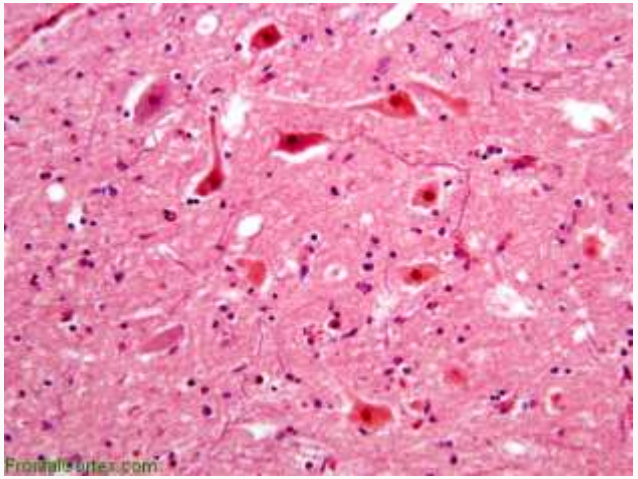
1-Characteristic Features of Cellular Pathology in CNS.
2-DEMYELINATING DISEASES (MS).
3- NEURODEGENERATIVE DISEASES (AZ, PD, HD, ALS).

Central nervous system

Characteristic Features of Cellular Pathology in CNS

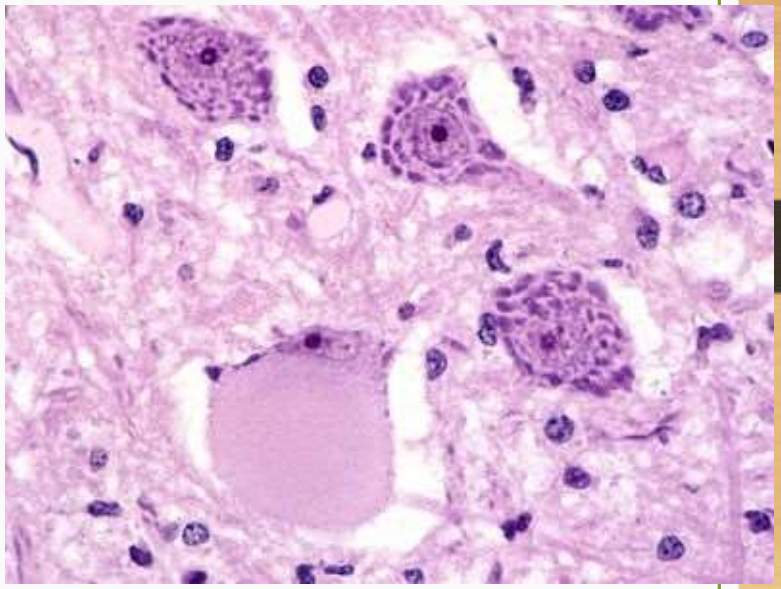
Neurons – Acute neuronal injury

- Within **12-24** hours of an irreversible hypoxic-ischemic insult, **neuronal injury** becomes evident microscopically
- Shrinkage of the cell body, pyknosis of the nucleus, disappearance of the nucleolus, loss of Nissl substance, and intense eosinophilia of the cytoplasm **"red neurons"**



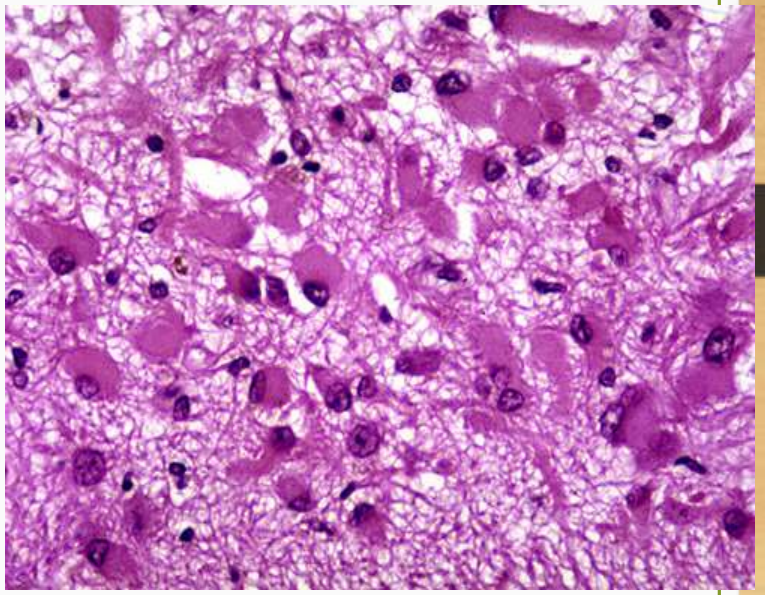
Neurons – Axonal injury/reaction

- **A change observed in the cell body of the neurons during regeneration of the axon (sprouting).**
- Cell body enlargement and rounding, peripheral displacement of the nucleus, enlargement of the nucleolus, and peripheral dispersion of Nissl substance **(central chromatolysis)**



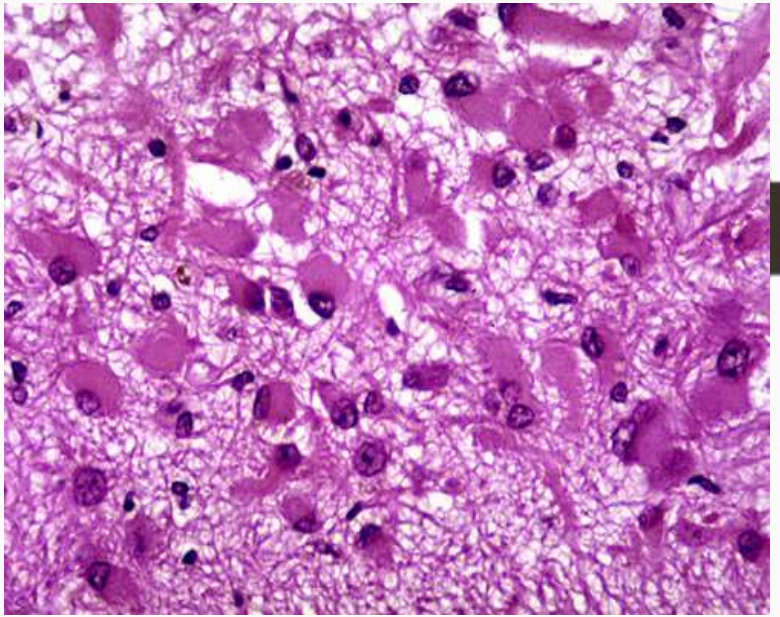
Astrocyte Injury and Repair

- Astrocytes → repair & scar formation in CNS, (**gliosis)**
- After injury they undergo hypertrophy and hyperplasia.
- The nucleus enlarges (more vesicular) & the nucleolus becomes prominent. The cytoplasm expands with bright pink hue & extends multiple processes (**gemistocytic astrocyte).**



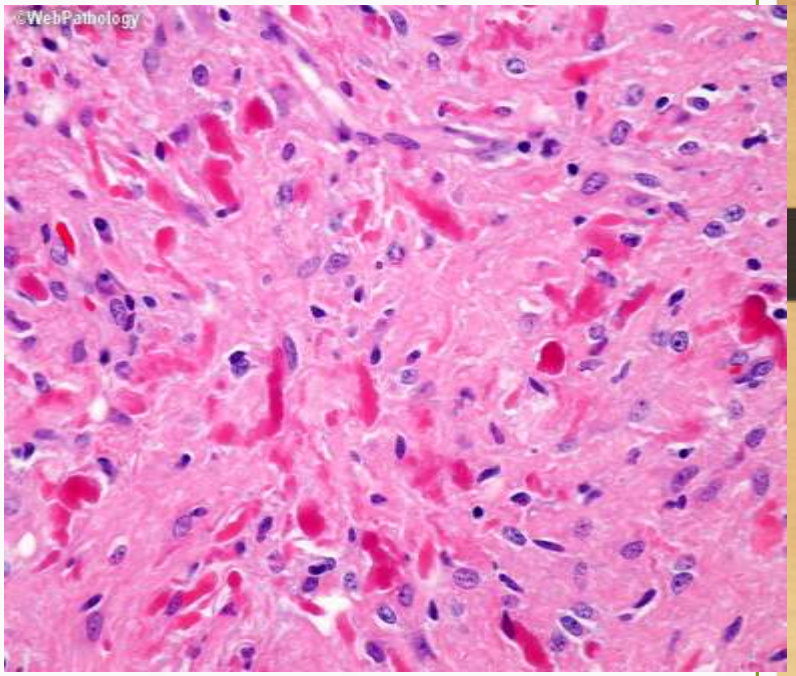
Astrocyte Injury and Repair

- Unlike elsewhere in the body, fibroblasts participate in healing after brain injury to a limited extent except in specific settings (**penetrating brain trauma or around abscesses).**



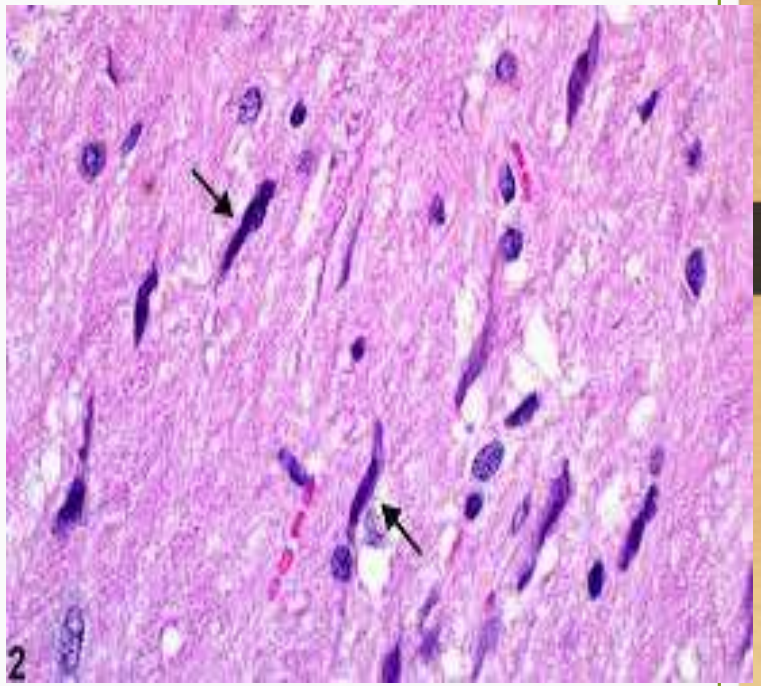
Astrocyte Injury and Repair

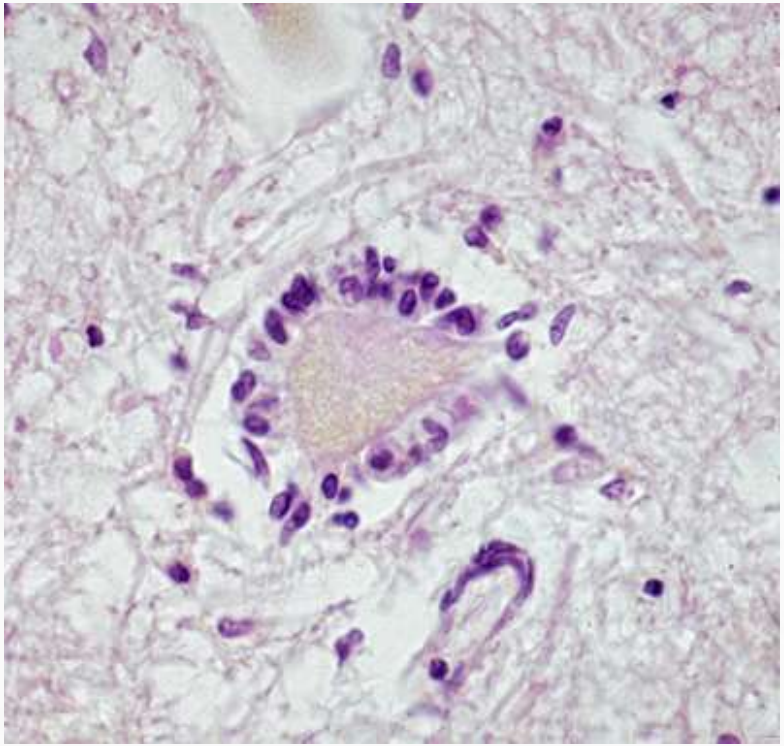
- In long-standing gliosis, the cytoplasm of reactive astrocytes shrinks in size, & cellular processes become tightly interwoven **(fibrillary astrocytes).**
- **Rosenthal fibers:** thick, elongated, brightly eosinophilic protein aggregates in astrocytic processes in chronic gliosis & in some low-grade gliomas. (pilocytic astrocytoma)

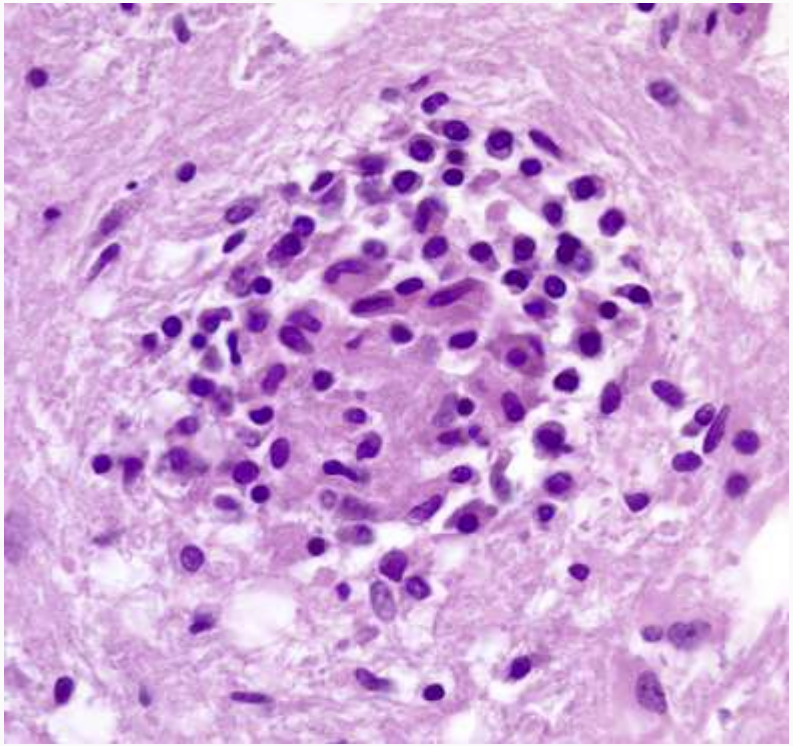


Microglial cells

- Long-lived resident phagocytes in CNS, derived from embryonic yolk sac.
- Activated by tissue injury, infection, or trauma.
- May develop elongated nuclei - **rod cells** (infections).
- Aggregates around necrosis → **microglial nodules .**
- Or around a dying neuron → **Neuronophagia.**







Demyelinating diseases of CNS

Myelin..

- Axons in CNS are tightly ensheathed by myelin.
- It is an electrical insulator → allows rapid propagation of neural impulses.
- Consists of multiple layers of highly specialized, closely apposed plasma membranes.
- Assembled by oligodendrocytes.
- Dominant component in the white matter, so most diseases of myelin are primarily white matter disorders.

Differences b/w CNS & PNS Myelin

1) PNS myelin is made by Schwann cells, CNS myelin is made by oligodendrocytes.
2) In PNS each Schwann cells provides myelin for only one internode, while in the CNS, many internodes are created by processes coming from a single oligodendrocyte.
3) The specialized proteins and lipids are also different.
4) Most diseases of CNS myelin do not involve the PNS to any significant extent, and vice versa.

Diseases of myelin are separated to two groups:

I. Demyelinating diseases

+acquired conditions. Damage to previously normal myelin.

+causes:

(1)immune mediated.

(2)oligodendrocytes viral infection (progressive multifocal Leukoencephalopathy → JC virus, a polyomavirus).

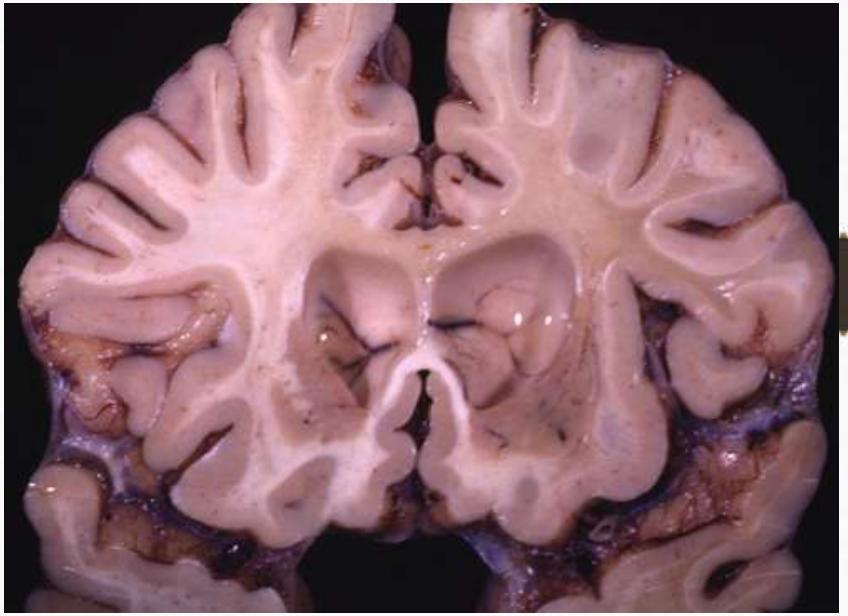
(3) injury caused by drugs or other toxic agents.

diseases of myelin are separated to two groups:

II. Leukodystrophy or dysmyelinating diseases:

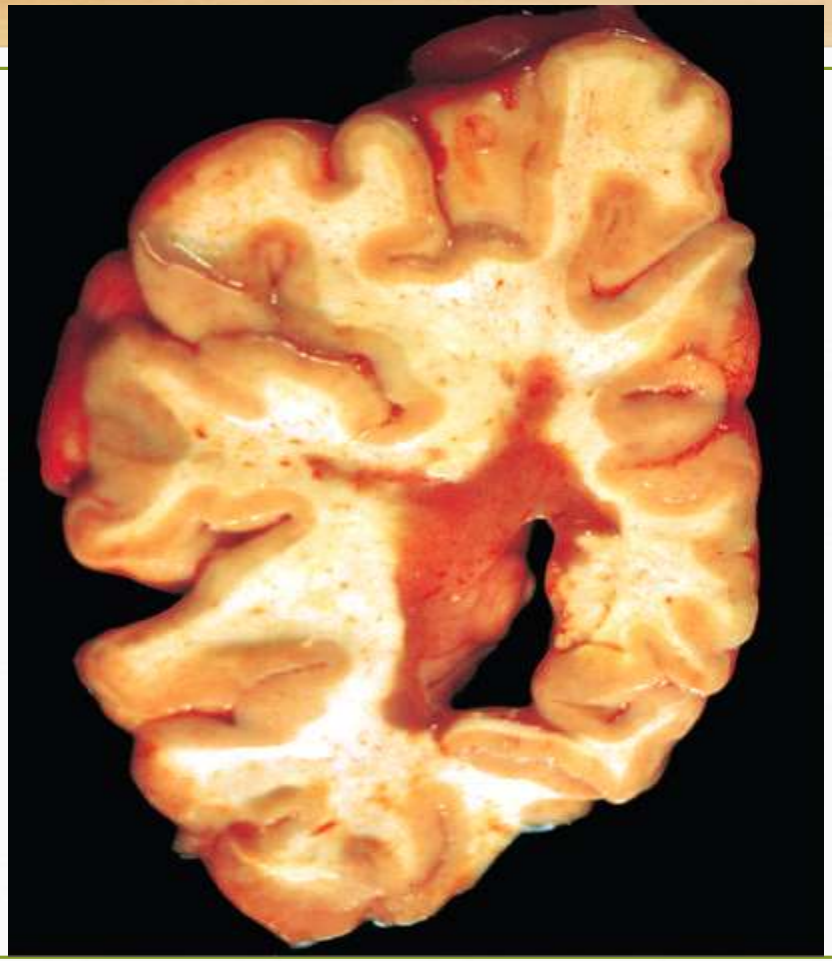
+Myelin is not formed properly or has abnormal kinetics

+Caused by mutations that disrupt the function of proteins required For the formation of normal myelin sheaths.

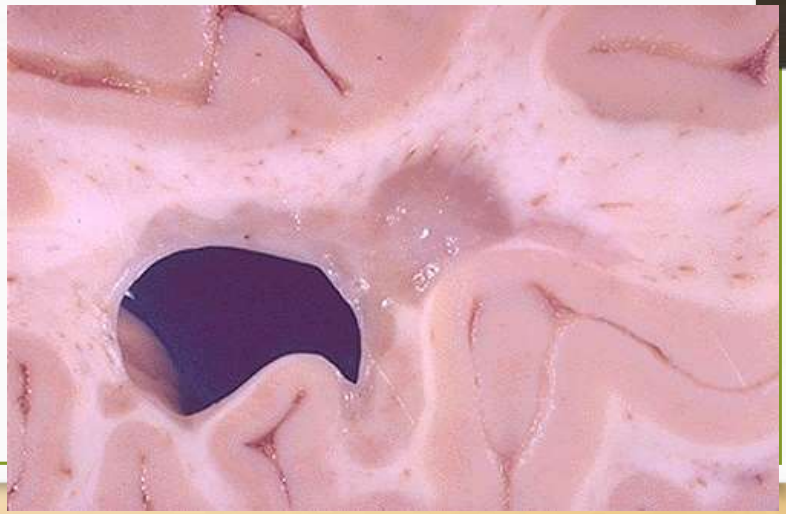


Multiple Sclerosis (MS)

- The most common demyelinating disease.
- An autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits that are separated in time and are attributable to patchy white matter lesions that are separated in space.
- M:F 1:2, rare in childhood & after the age of 50.
- The lesions of are caused by an autoimmune response directed against components of the myelin sheath.
- The clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual and partial recovery of neurologic function.

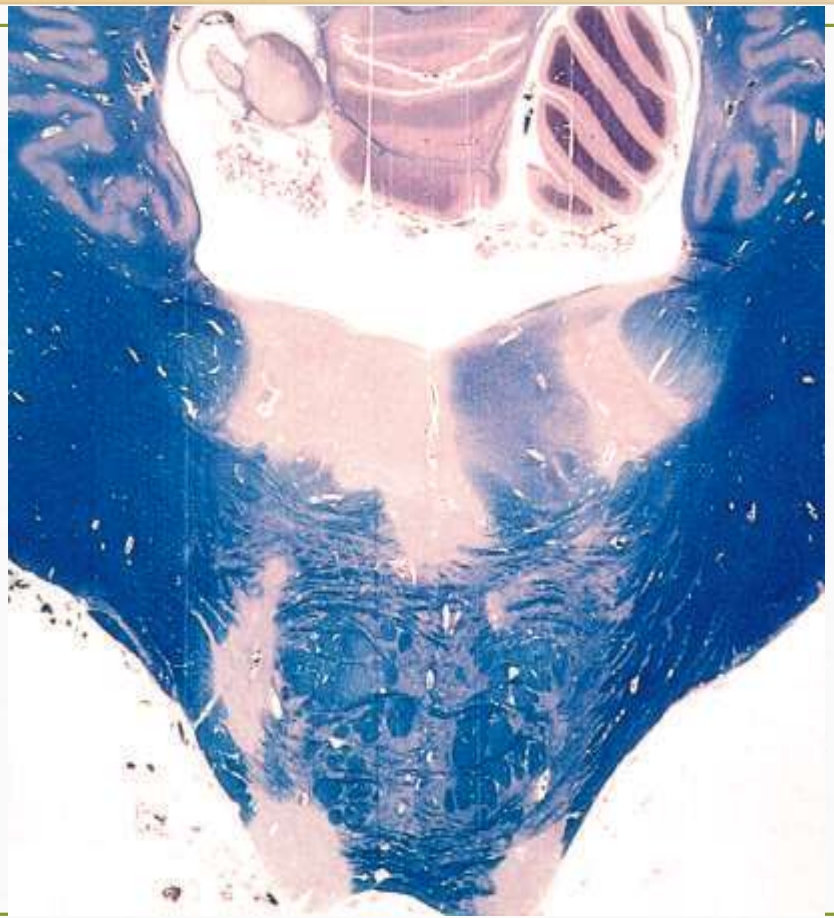


A white matter disease.
Lesions → **plaques**: **discrete**, slightly depressed, glassy-appearing, and gray in color, and commonly near the ventricles.



Microscopically:
The active plaque, there is ongoing myelin breakdown associated with abundant foamy macrophages; lymphocytes are also present, mostly as perivascular cuffs, especially at the outer edge of the lesion. Active lesions are often centered on small veins; myelin is usually completely absent. but axons are relatively preserved.

In time, astrocytes undergo reactive changes. As lesions become quiescent, the inflammatory cells slowly disappear. Within inactive plaques, there is no macrophage-rich infiltrate, little to no myelin is found, and there is a reduction in the number of oligodendrocyte nuclei; instead, reactive gliosis is prominent. Axons in old gliotic plaques are usually greatly diminished in number



lesions are sharply defined microscopically:

+ **Active plaques** (ongoing myelin breakdown): contain abundant macrophages stuffed with myelin debris (lipid), also perivascular cuffs of Lymphocytes.

+**Inactive plaques** (quiescent): inflammation mostly disappears, leaving little to no myelin, & gliosis.

Multiple Sclerosis (MS)

- So over time there is usually a gradual accumulation of neurologic deficits.
- Unilateral visual impairment due to optic nerve involvement is a frequent initial manifestation.
- Brainstem involvement produces cranial nerve signs; ataxia & nystagmus, while spinal cord lesion give rise to motor & sensory impairment.
- The CSF in patients shows a mildly elevated protein level, moderate pleocytosis, & increased immunoglobulin(Ig) with oligoclonal bands.

NEURODEGENERATIVE DISEASES

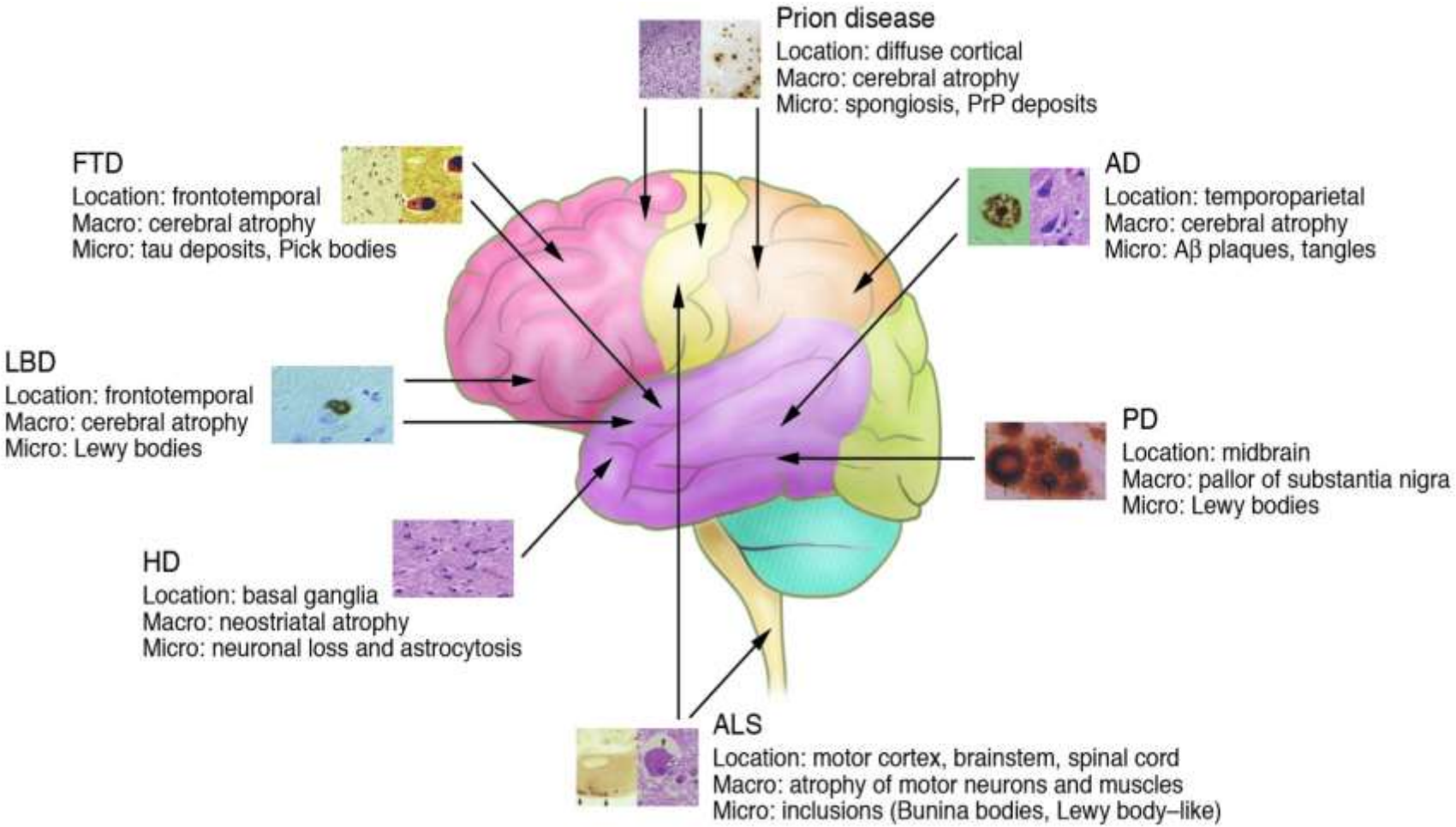
- Neurodegenerative diseases are disorders characterized by the progressive loss of particular groups of neurons, which often have shared functions.

- The pathologic process that is common across most of the neurodegenerative diseases is the accumulation of protein aggregates (hence the occasional use of the term “proteinopathy”).

Neurodegenerative diseases can be classified using two different approaches:

• Symptomatic/anatomic: based on the anatomic regions that are most affected, which is typically reflected in the clinical symptoms (e.g., neocortical involvement results in cognitive impairment and dementia).

• Pathologic: based on the types of inclusions or abnormal structures observed (e.g., diseases with inclusions containing tau or containing synuclein


Prion disease
Location: diffuse cortical
Macro: cerebral atrophy
Micro: spongiosis, PrP deposits
FTD
Location: frontotemporal
Macro: cerebral atrophy
Micro: tau deposits, Pick bodies
AD
Location: temporoparietal
Macro: cerebral atrophy
Micro: Aβ plaques, tangles
LBD
Location: frontotemporal
Macro: cerebral atrophy
Micro: Lewy bodies
PD
Location: midbrain
Macro: pallor of substantia nigra
Micro: Lewy bodies
HD
Location: basal ganglia
Macro: neostriatal atrophy
Micro: neuronal loss and astrocytosis
ALS
Location: motor cortex, brainstem, spinal cord
Macro: atrophy of motor neurons and muscles
Micro: inclusions (Bunina bodies, Lewy body–like)

Alzheimer Disease (AD)

Alzheimer Disease (AD)

- The most common cause of **dementia** in older adults.
- Rare before 50, incidence increases with age (1% → 60 to 64, reaching 47% in 85 and older).
- Manifests with the insidious onset of impaired higher intellectual function, **memory impairment**, & altered mood and behavior.
- **Aβ** (amyloid β) and ***tau*** proteins accumulation is the fundamental abnormality.
- AD is an eventual feature of the cognitive impairment in trisomy 21 individuals (Down syndrome).

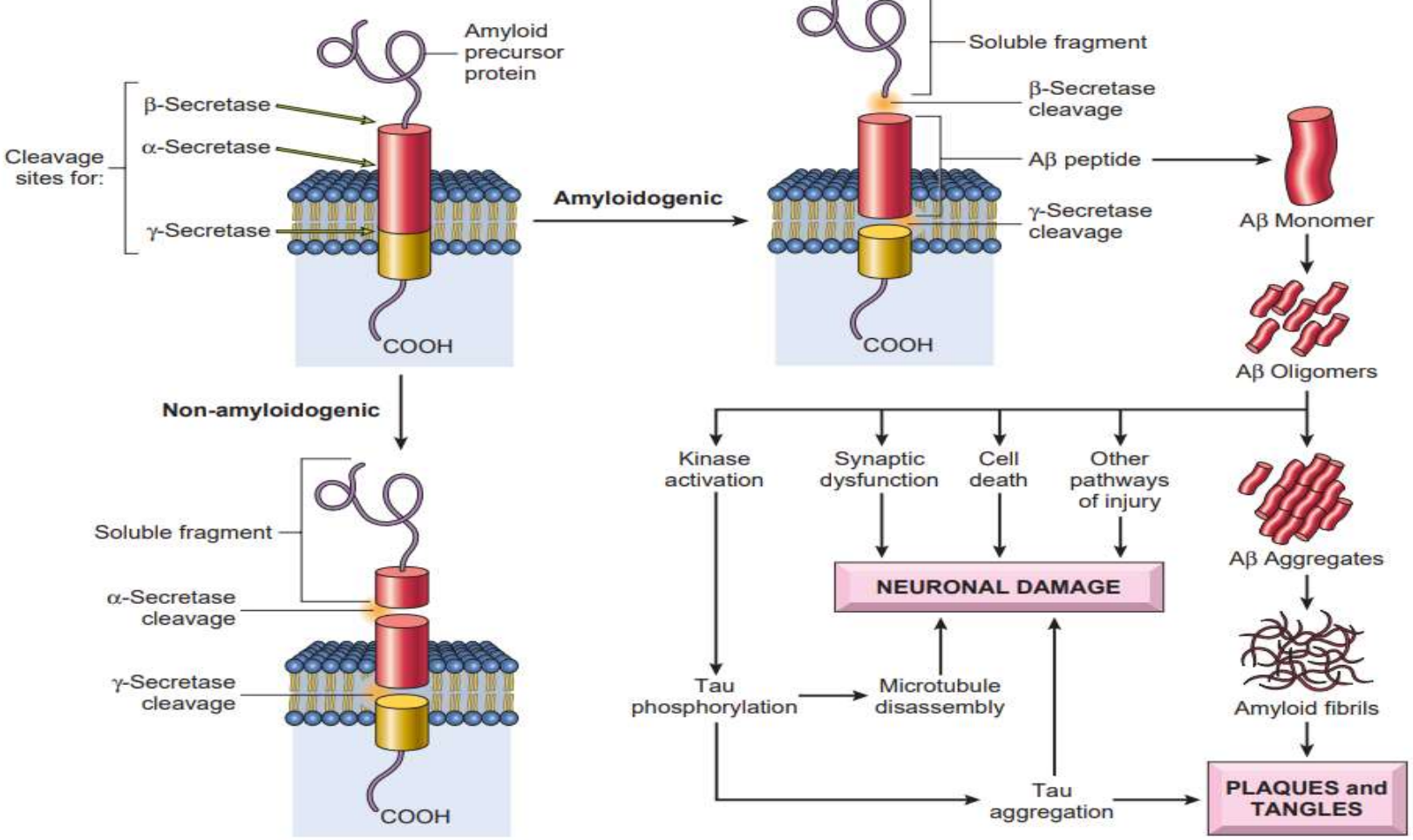
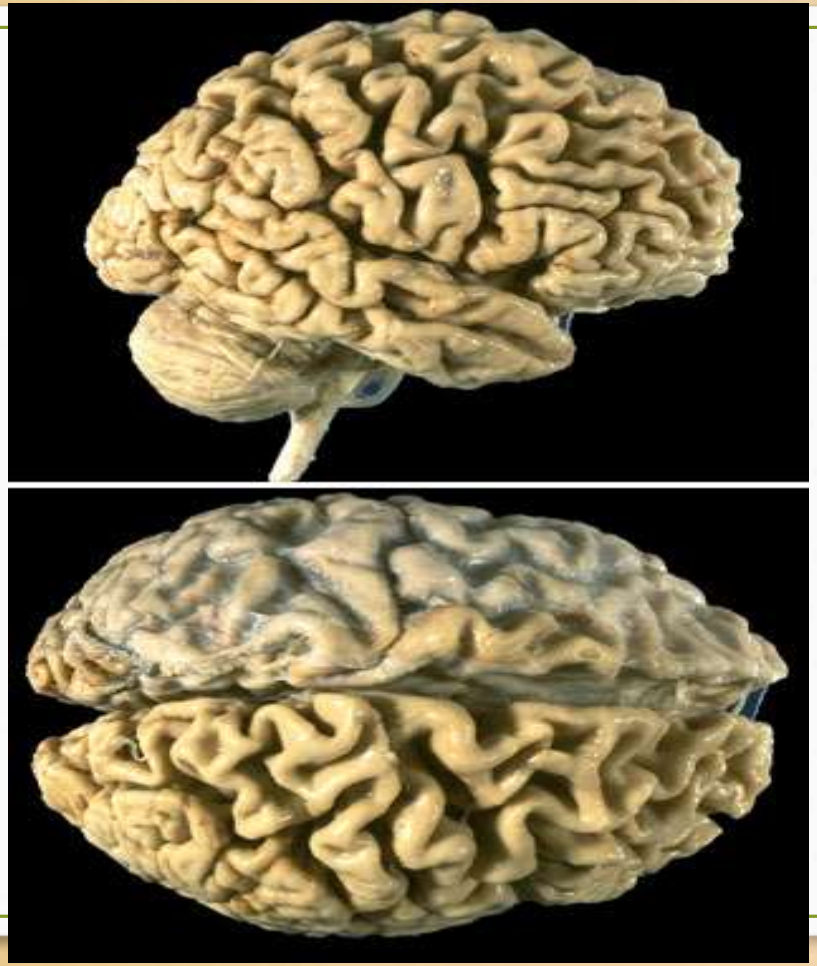


Figure 28.35 Protein aggregation in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

Dementia is a general term for loss of memory and other mental abilities severe enough to interfere with daily life of a conscious patient → it is not a specific disease it's an umbrella term.

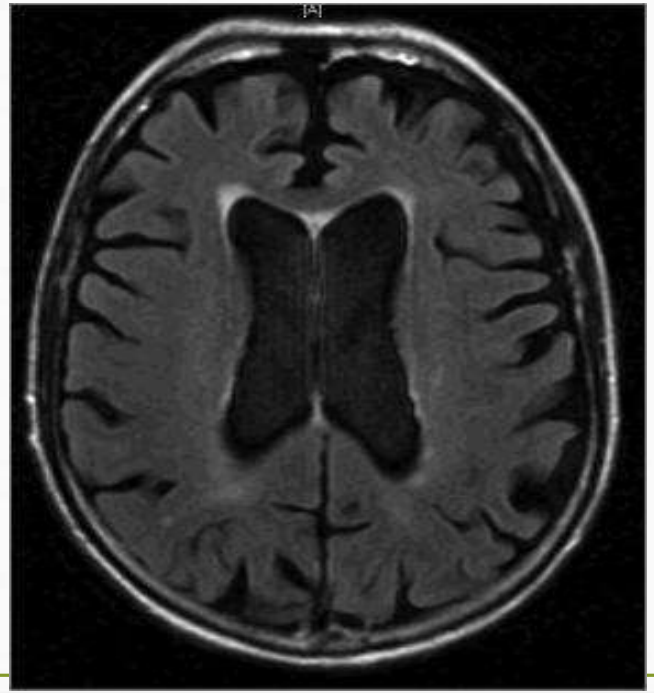
AD – Pathogenesis

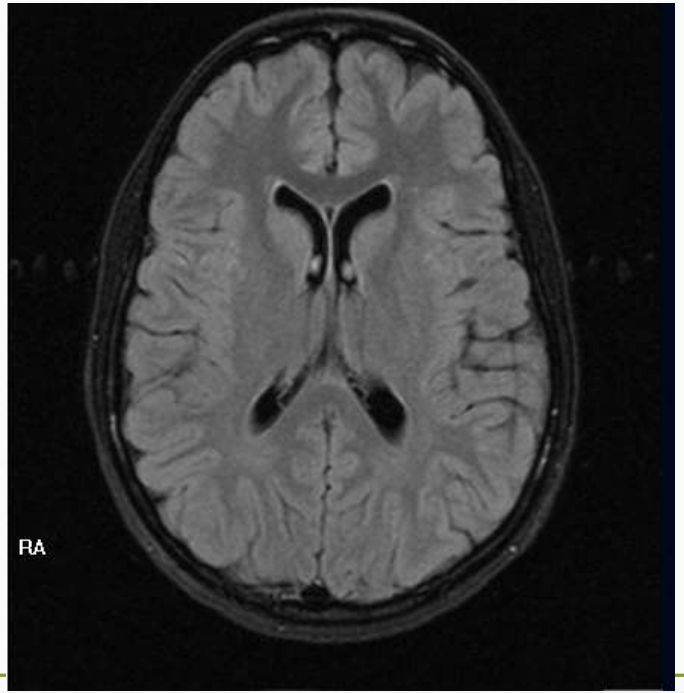
- **Aβ generation is the critical initiating event to develop AD,** it's derived from a membrane protein → amyloid precursor protein (APP).
- APP processed in 2 ways pathways:
  (1) Starts with α-secretase (non-amyloidogenic), **no Aβ generation.**
  (2) Starts with β-secretase (amyloidoigenic), **Aβ generation.**
- APP gene located on chr. 21 (~Down syndrome).
- Aβ is highly prone to aggregation and causing neural dysfunction, & elicits a local inflammatory response that can result in further cell injury.



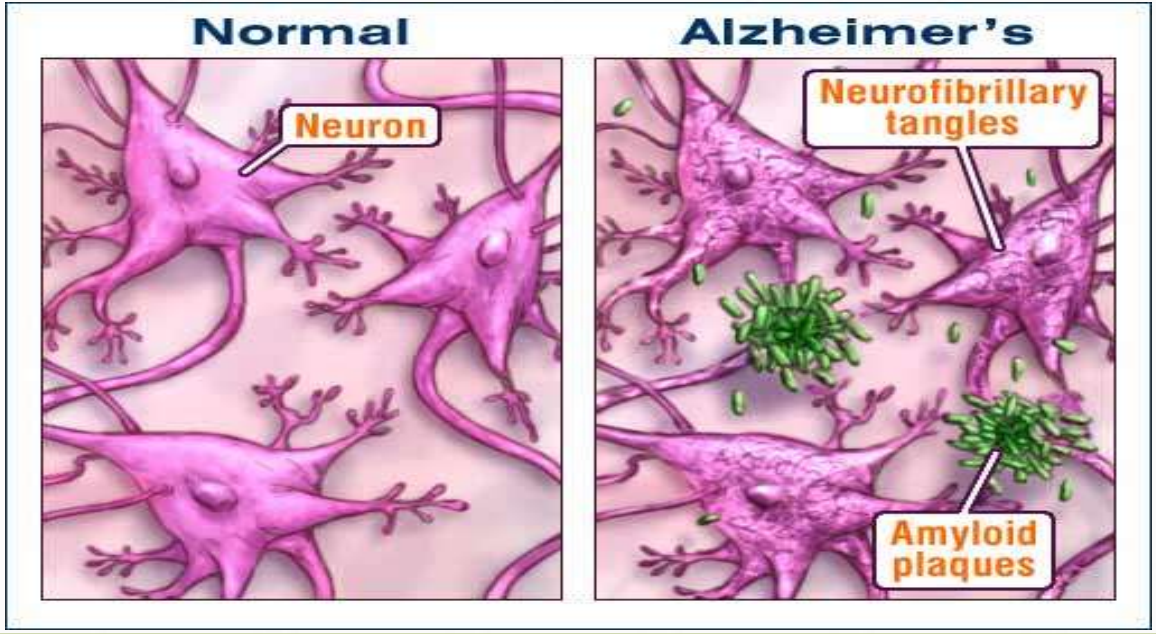
A variable degree of cortical atrophy, resulting in a widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.

The atrophy produces a compensatory ventricular enlargement (hydrocephalus ex vacuo)

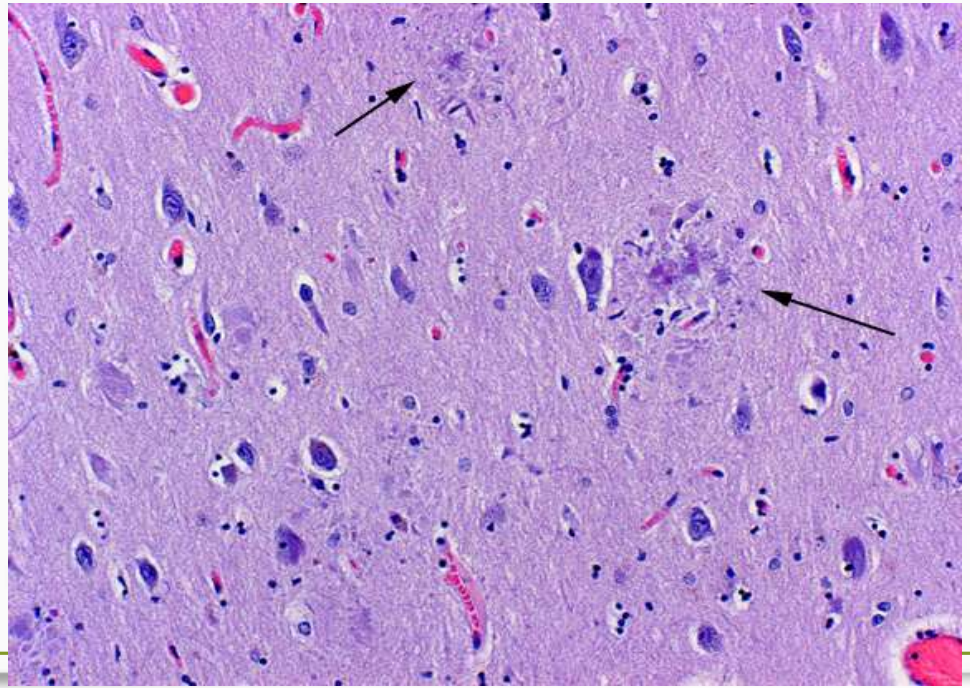


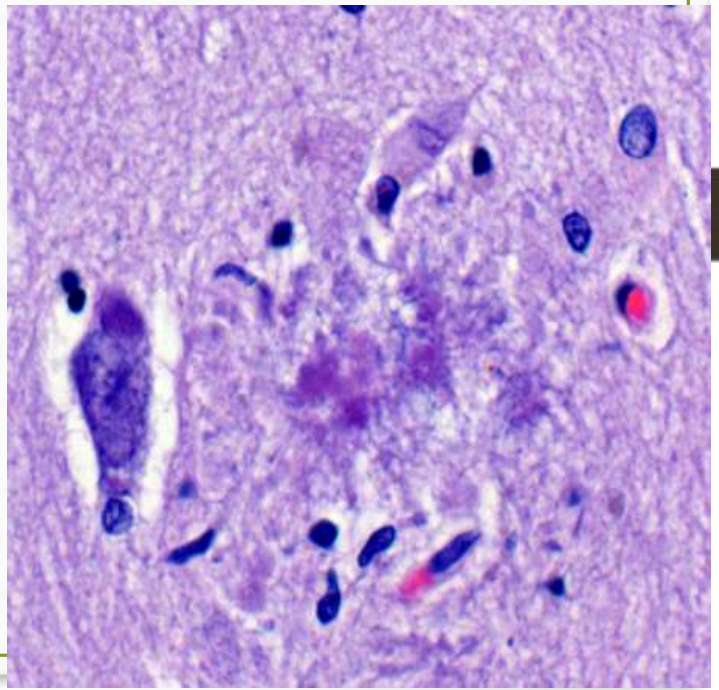


- Microscopy: Amyloid plaques (extracellular - accumulation of Aβ amyloid) and neurofibrillary tangles (intracellular -*Tau* accumulation).



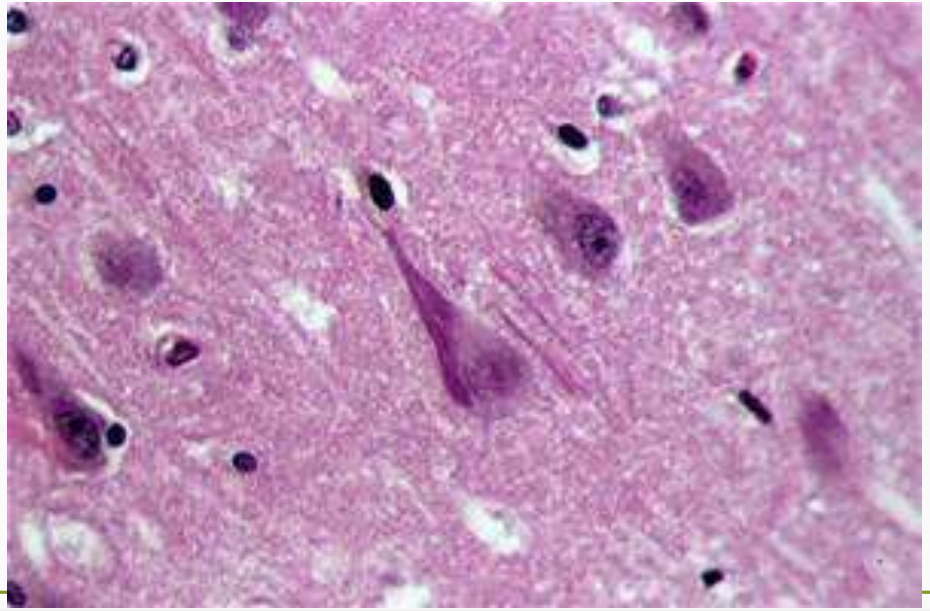
Neuritic plaques are focal, spherical collections of dilated, tortuous, processes of dystrophic neurites around a central amyloid (Aβ) core. Aβ deposition without neurites termed **diffuse plaques.**

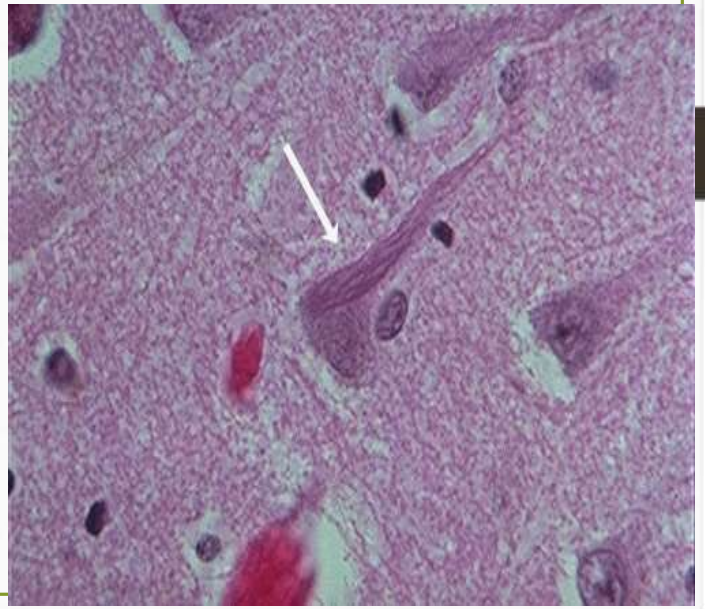




Neurofibrillary tangles: Tau containing bundles of filaments in neurons cytoplasm (encircle the nucleus), <**flame** shapes>

Where ? cortical neurons (entorhinal cortex), & the pyramidal cells of hippocampus, amygdala, basal forebrain, the raphe nuclei.





Clinically: Insidious onset of impaired higher intellectual function & memory, & altered mood & behavior.

Over time, disorientation & aphasia. In final stages they are disabled, mute & immobile.

Death → intercurrent pneumonia or other infections.