NEUROSCIENCE PATHOLOGY-II

DEMYELINATING DISEASES OF CNS

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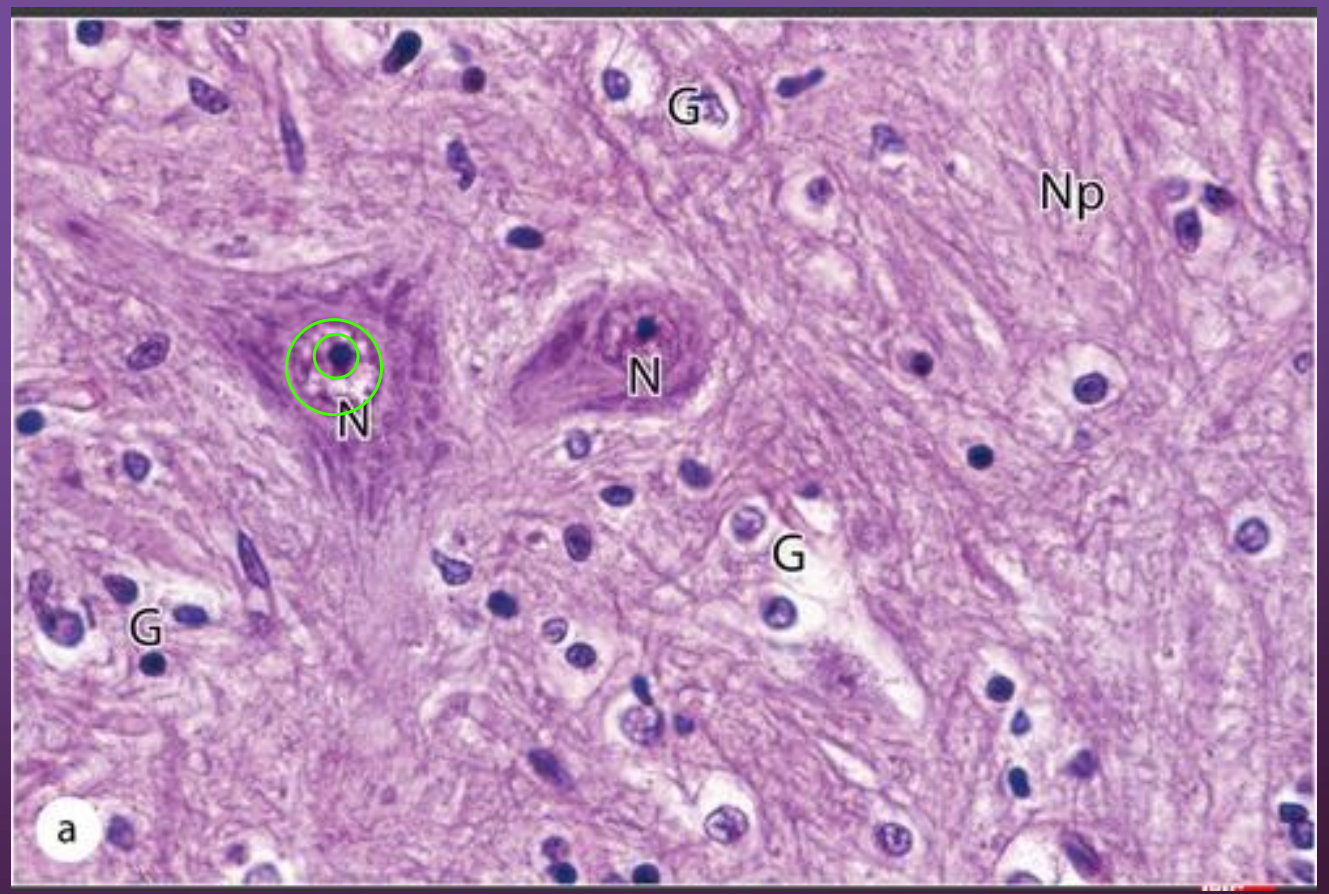
LECTURES TITLES

- Demyelinating diseases of CNS.
- Degenerative diseases of CNS.
- Peripheral Nervous system Pathology.
- Peripheral Nerve Sheath Tumors

NORMAL HISTOLOGY

Normal Neuron: cytoplasm, Nucleus, Nucleolus
Cytoplasm Contain → Nissl substance



NEURONS

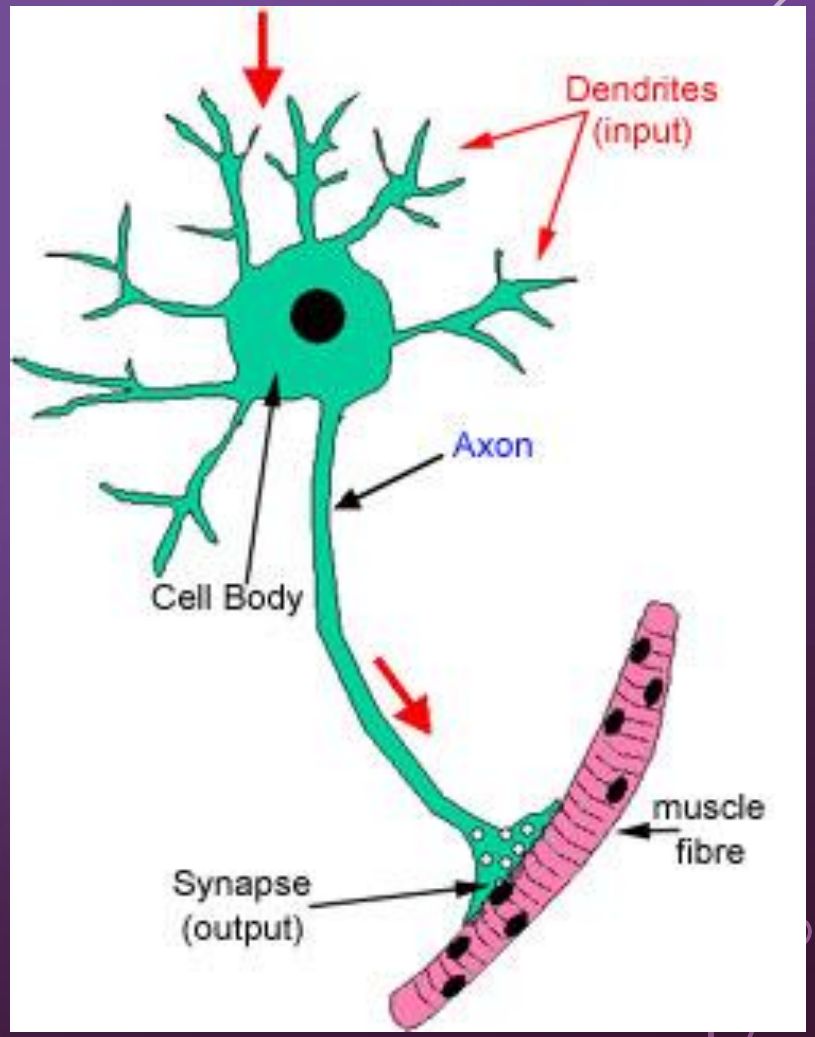
- Are specialized cells that conduct electrical impulses.

- All neurons have the same basic structure:

✓ **Dendrites** extend from the cell body .

✓ The **cell body** .

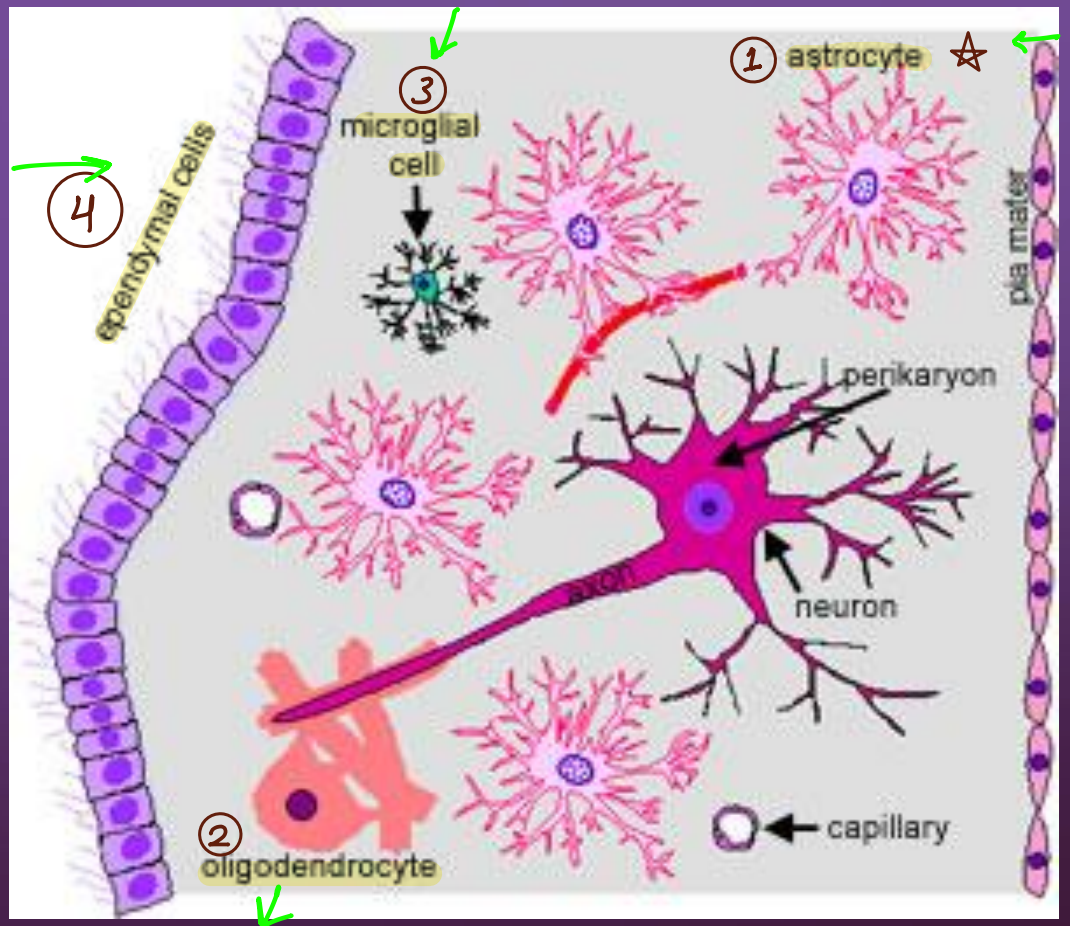
✓ The **axon**.



NEURAL SUPPORTING CELLS ''GLIAL CELLS''

Type of cell that provides physical and chemical support to neurons and maintain their environment. [1,2,3,4]

immune defense

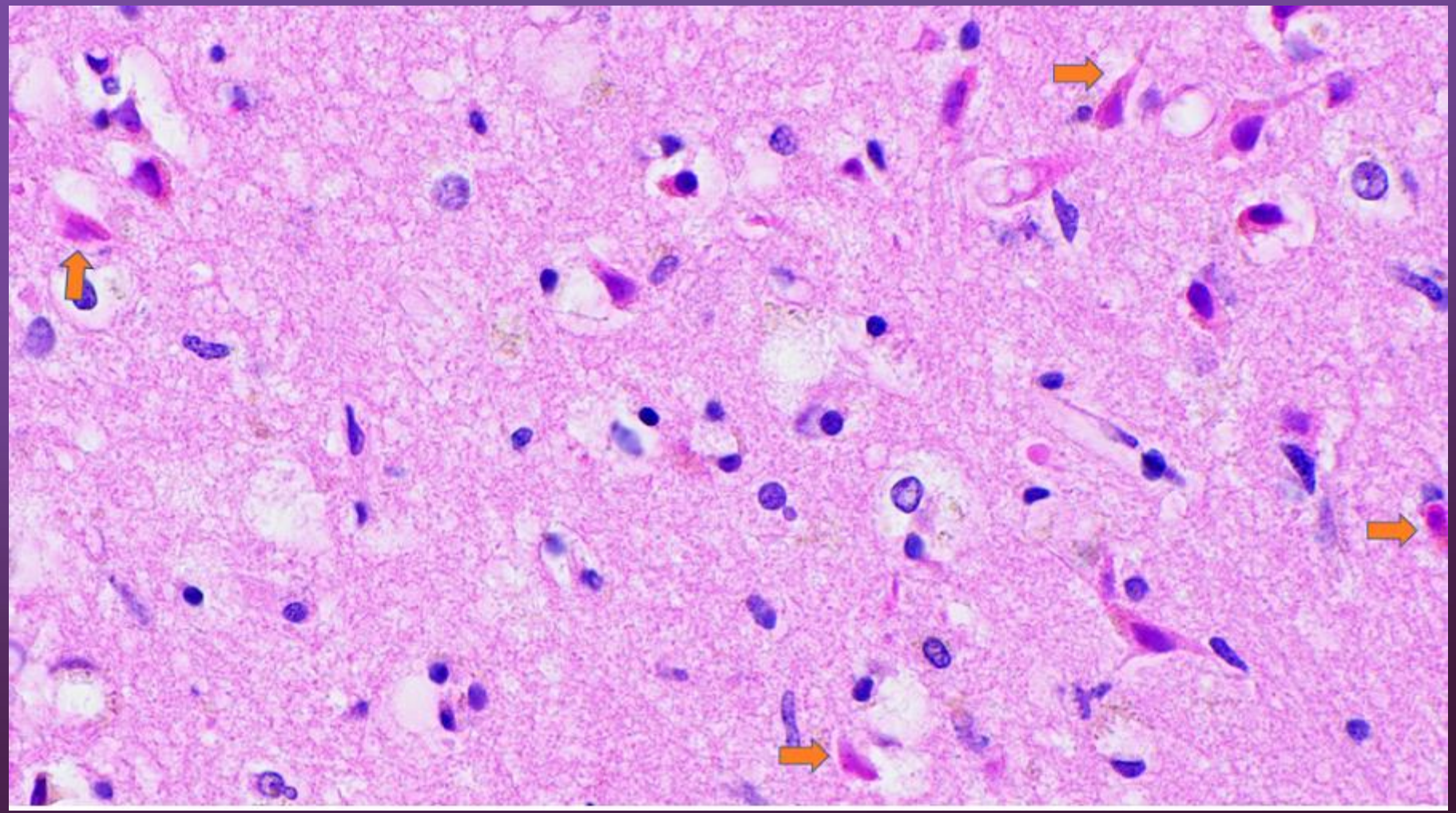


involved in metabolic exchange between neurons and blood.

line the ventricles and spinal canal.

Myelin formation

ACUTE NEURONAL INJURY



ACUTE NEURONAL INJURY

- **1. Neuronal changes "red neurons"**

- Within **12-24** hours of an irreversible hypoxic-ischemic insult, **neuronal injury** becomes evident microscopically as:

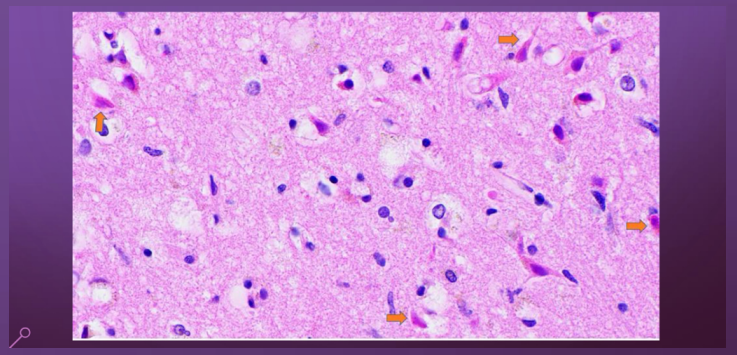
✓ Shrinkage of the cell body.

✓ pyknosis of the nucleus. [small]

✓ disappearance of the nucleolus.

✓ loss of Nissl substance.

✓ intense eosinophilia of the cytoplasm



Nissl substance & Nucleolus ← انعدام

Nucleus [Pyknosis] & cell Body [shrink] ← قلة

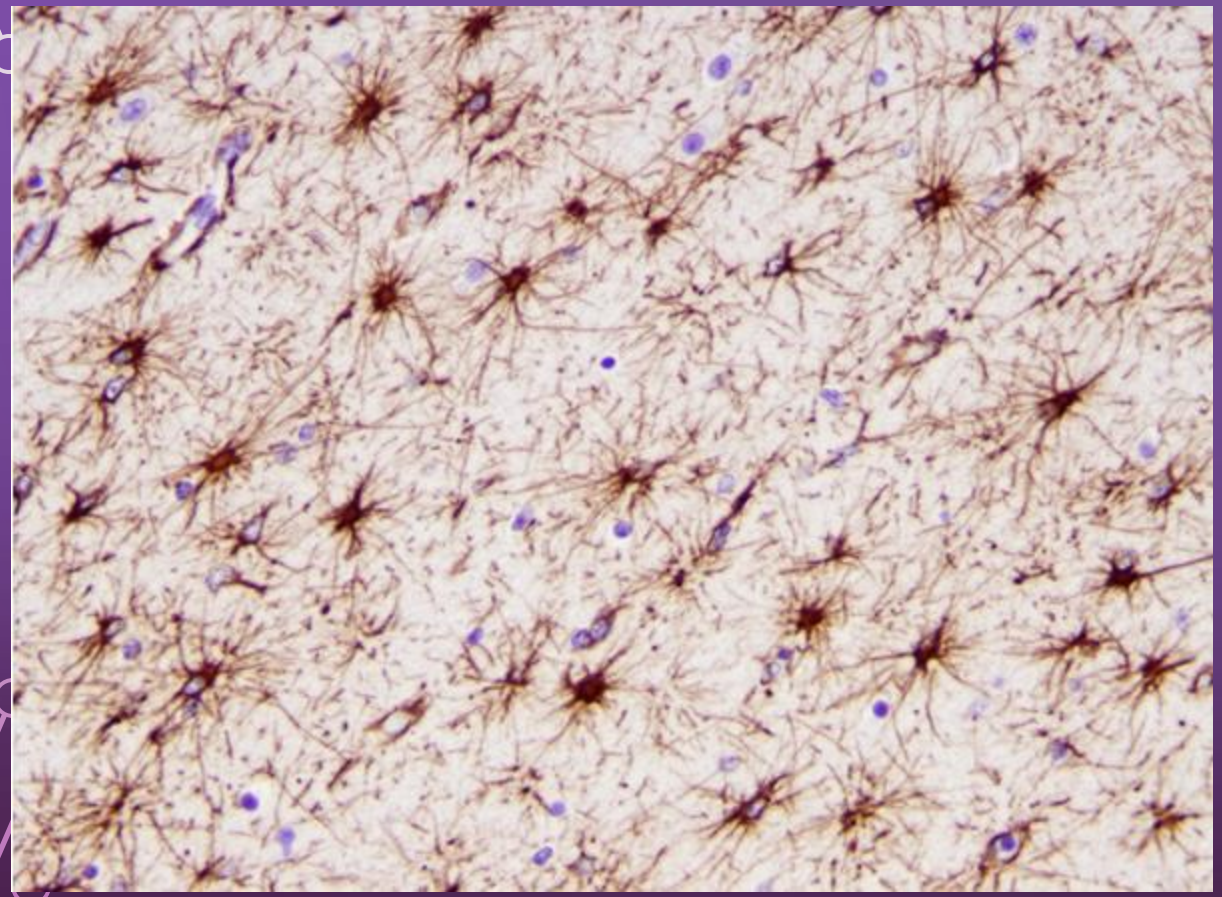
eosinophilia ← زيادة

2. SUPPORTING CELL CHANGES

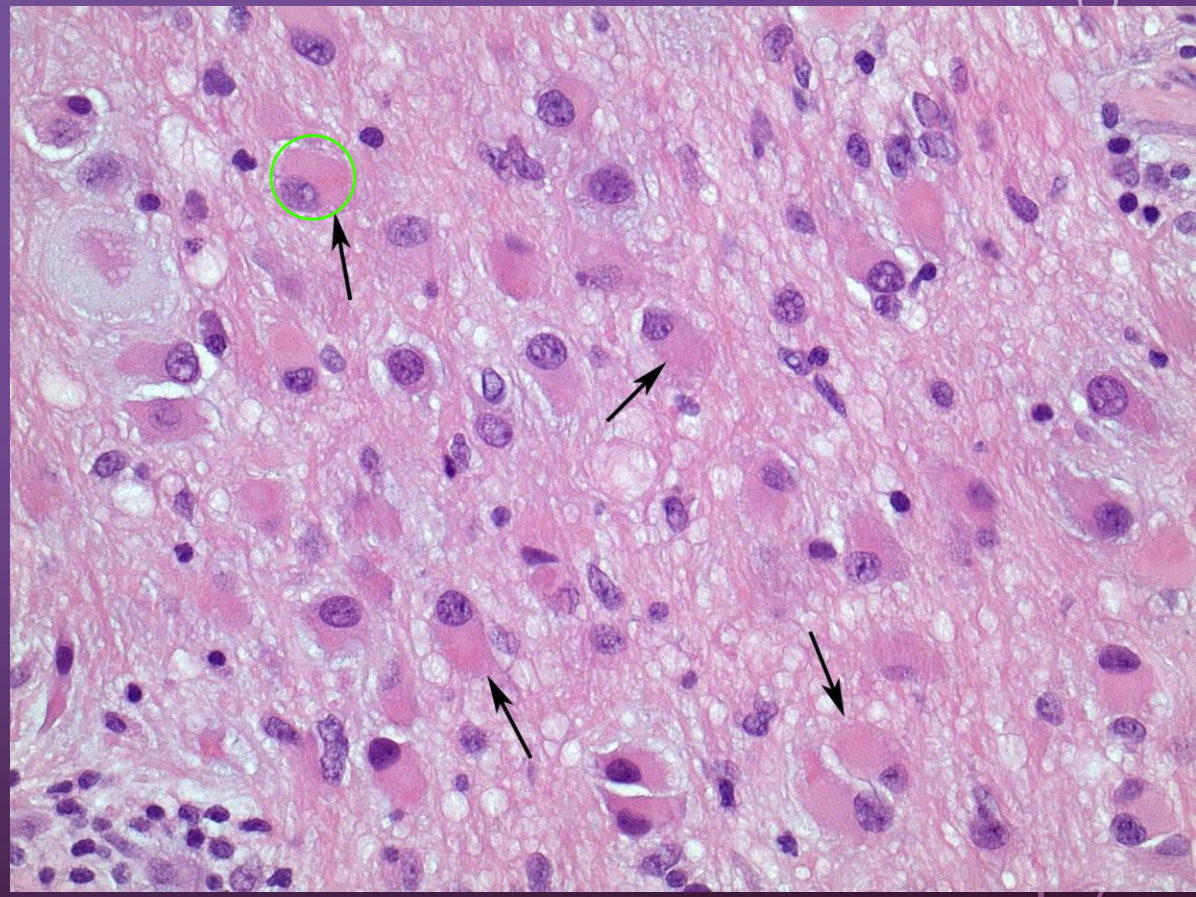
- **Astrocyte Injury**:
- After injury they undergo hypertrophy and hyperplasia (**gliosis**).
- The nucleus enlarges & the nucleolus becomes prominent. The cytoplasm expands with bright pink colour & extends multiple processes (**gemistocytic astrocyte**).

Astrocyte Injury

GFAP Stain



Normal astrocyte



Gemistocytic astrocyte

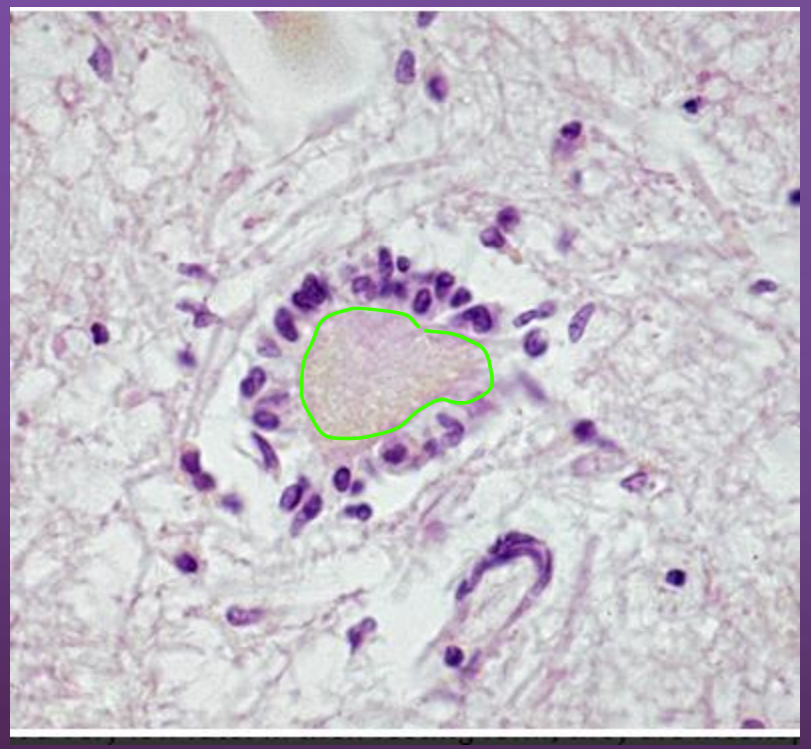
2. MICROGLIAL CELLS : Modified macrophage

- Microglia are the mesoderm-derived, resident macrophages of the CNS, they phagocytose and remove foreign or damaged material, cells, or organisms.

- So they activated by tissue injury, infection, or trauma.

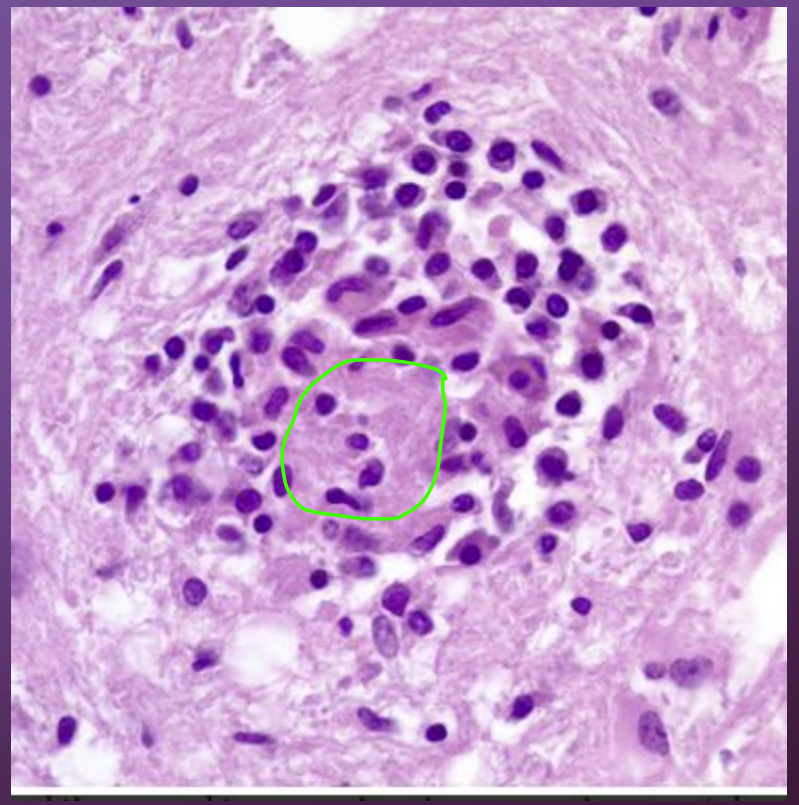
- After activation they proliferate, and extend the length of their nuclei, then either form aggregates around tissue necrosis (**microglial nodules**) A
- or form aggregates around the cell bodies of dying tissue (**Neuronophagia.**) B

MICROGLIAL ACTIVATION



Neuronophagia

cell Body



microglial nodules

Necrosis

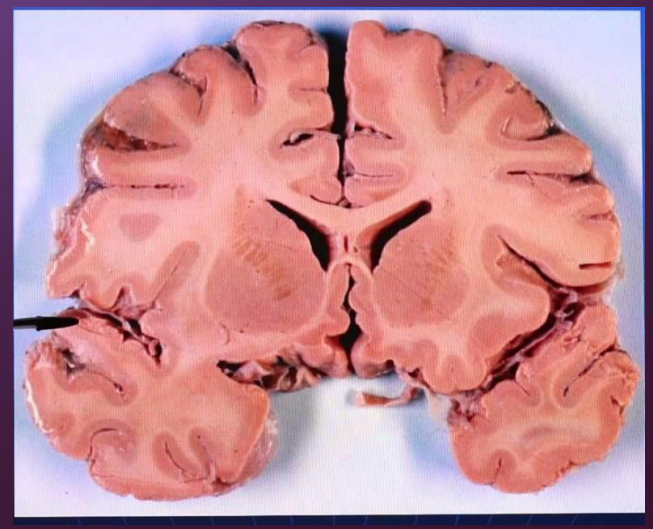
DEMYELINATING DISEASES OF CNS

- No myelin ….. What's myelin?
- Myelin sheath is a fatty product formed from specific neuroglial cells that provides numerous vital supporting functions as well as increases the rate of conduction of action potentials for some central and peripheral nervous system neurons.

- Myelin is formed via oligodendrocytes [CNS] and Schwann cells [PNS] in the central and peripheral nervous systems, respectively.

- myelinated vs non- myelinated fibers???

- the myelinated fibers have the collective name of white matter, and the non myelinated fibers are collectively known as gray matter as they look white and gray respectively on gross inspection of the brain in sagittal cross-section



DISEASES OF MYELIN ARE SEPARATED INTO TWO GROUPS:

1

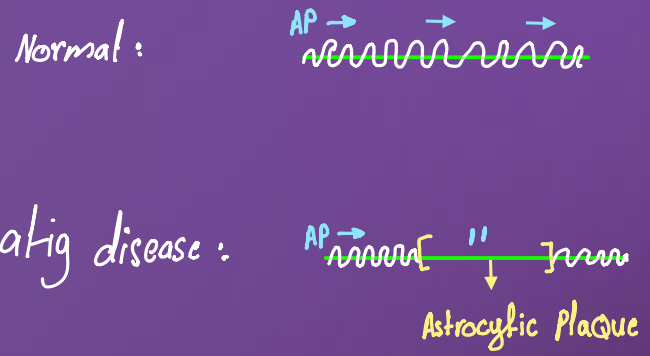
Demyelinating diseases vs 2 **Dysmyelinating disease**

no synthesis.

loss of myelin with relative preservation of axons

failure to form myelin normally

DEMYELINATING DISEASES



- In demyelinating diseases groups of oligodendrocytes and their myelin segments degenerate and are replaced by astrocytic plaques.
- This loss of myelin results in an interruption of the propagation of the AP.
- The axons that become demyelinized survive temporarily, and some may even regenerate

Demyelinating diseases of the CNS can be classified according to their pathogenesis

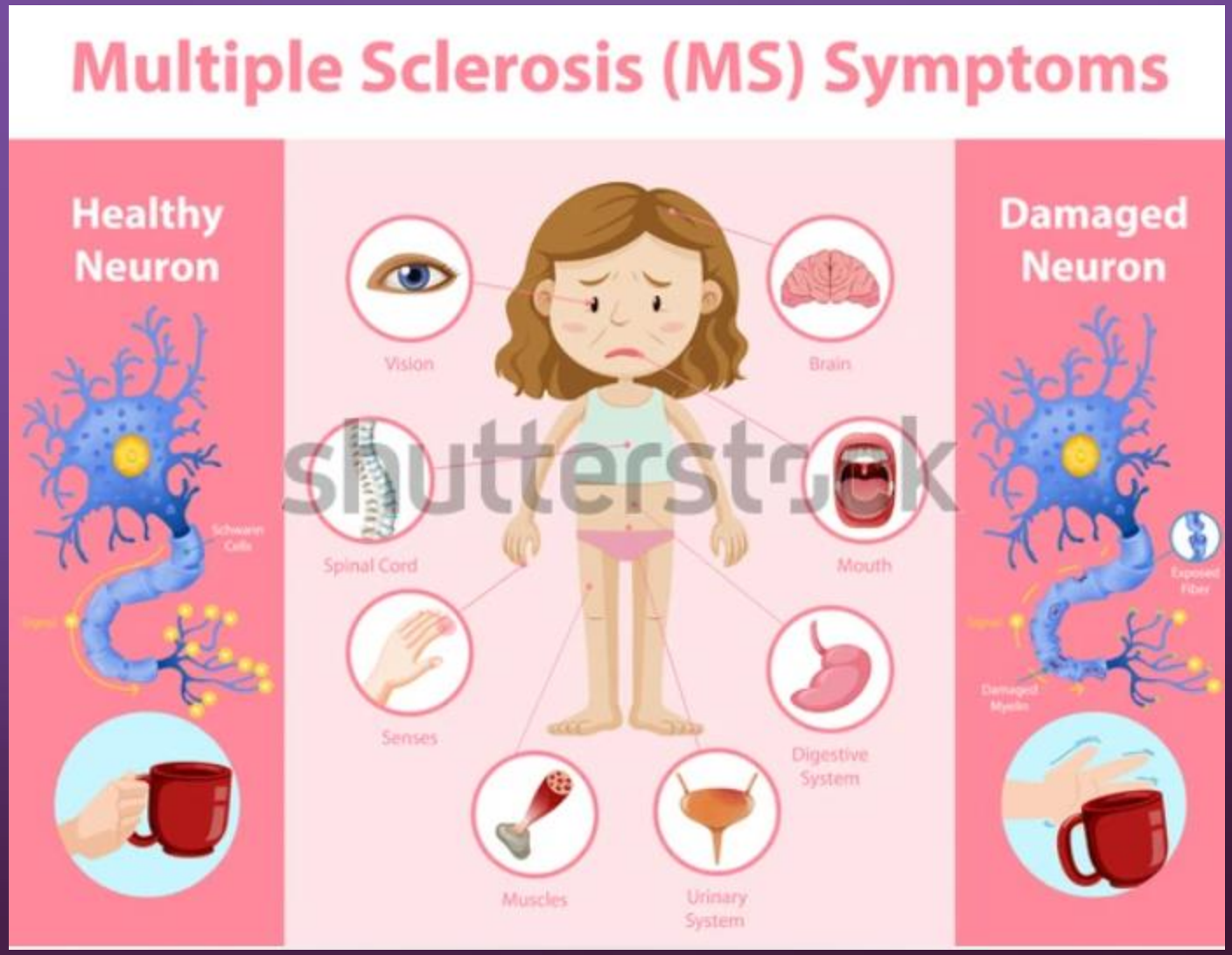
- Demyelination due to inflammatory processes: MS Multiple Sclerosis
- viral demyelination: progressive multifocal leucoencephalopathy (PML) caused by the papovavirus, JC virus John Cunningham
- demyelination caused by acquired metabolic derangements: chronic alcoholism and malnourishment
- hypoxic–ischaemic forms of demyelination.
- Demyelination caused by focal compression*. ex: tumor, ↑ ICP, vesseles (vein. ↓ Art) compress Nerve

2. DYSMYLEINATING DISEASE (LEUKODYSTROPHY)

أولا شهرة.

- Leukodystrophy generally refers to a genetic disorder that affects white matter.
- Can result from a wide range of genetic defects involving formation, maintenance and breakdown of myelin.

The most common cause of nontrauma related neurologic disability in young adults

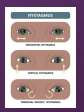


MULTIPLE SCLEROSIS (MS)

- Chronic, inflammatory demyelinating disease that may involve any part of the central nervous system
- Most common immune mediated demyelinating disorder of the central nervous system, directed against components of the myelin sheath.
- Course is variable, commonly multiple relapses followed by episodes of remission; typically, recovery during remissions is not complete.

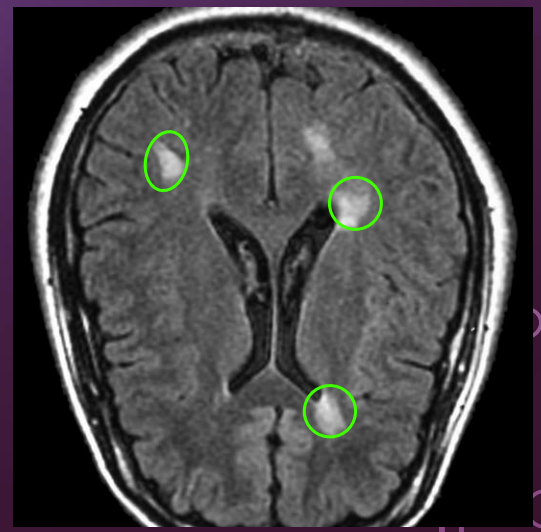
CLINICAL PRESENTATION

- Patients present with one or more distinct episodes of CNS dysfunction so the presenting symptoms depend on site:

- Most common sites for MS plaques:
  - optic nerve involvement produces Unilateral visual impairment, optic neuritis .
  - Brainstem involvement produces cranial nerve signs; ataxia & nystagmus.  
  - spinal cord lesion give rise to motor & sensory impairment.
  - Uhthoff phenomenon: heat and exercise worsen symptoms

DIAGNOSIS

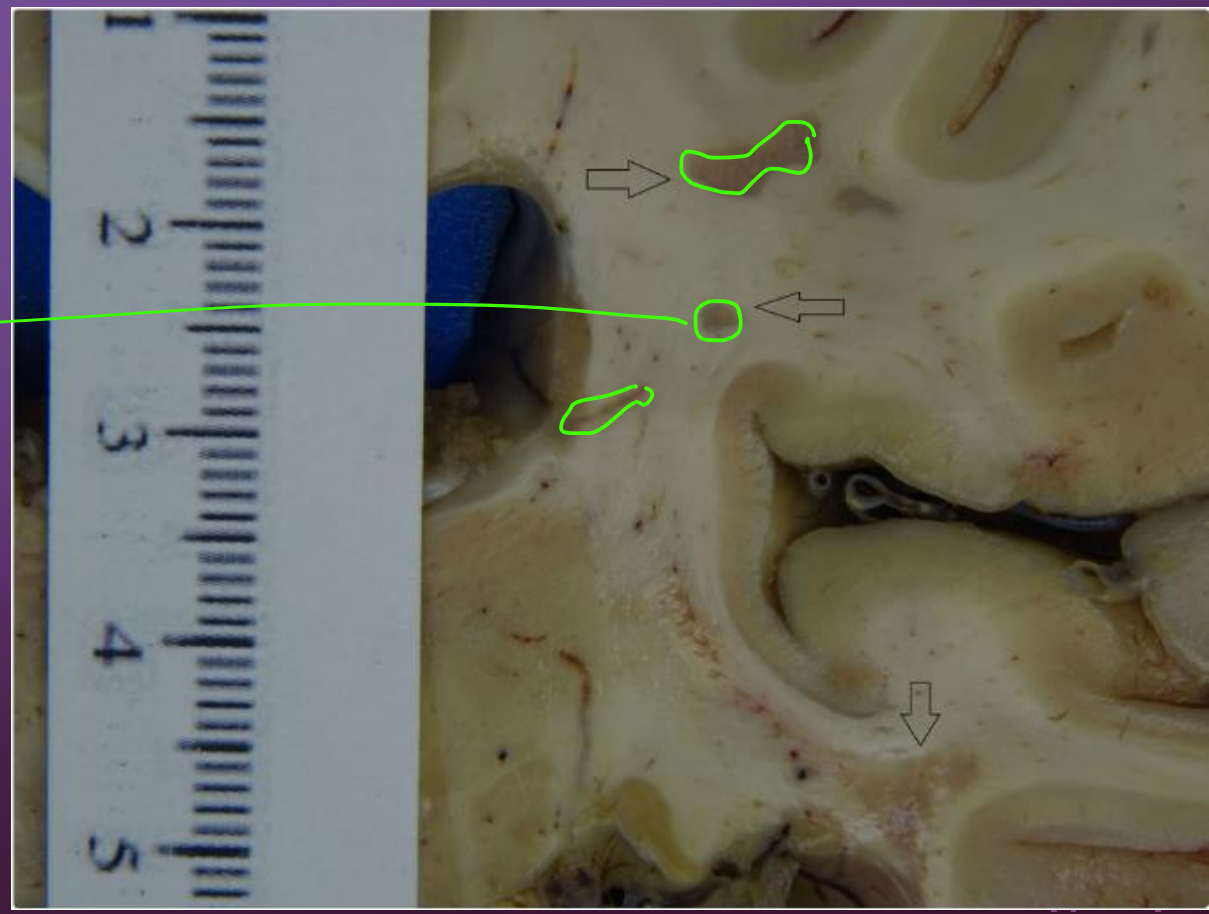
- MS is a clinical diagnosis, combining clinical history, physical exam findings with imaging :
- LAB : presence of oligoclonal IgG bands in the cerebrospinal fluid (CSF)*.
- Imaging:



- Treatment: [High dose glucocorticoids], [Monoclonal antibodies]

GROSS APPEARANCE

plaques tend to be rounded, tan-gray and variably sized with a sharp demarcation from the surrounding brain tissue



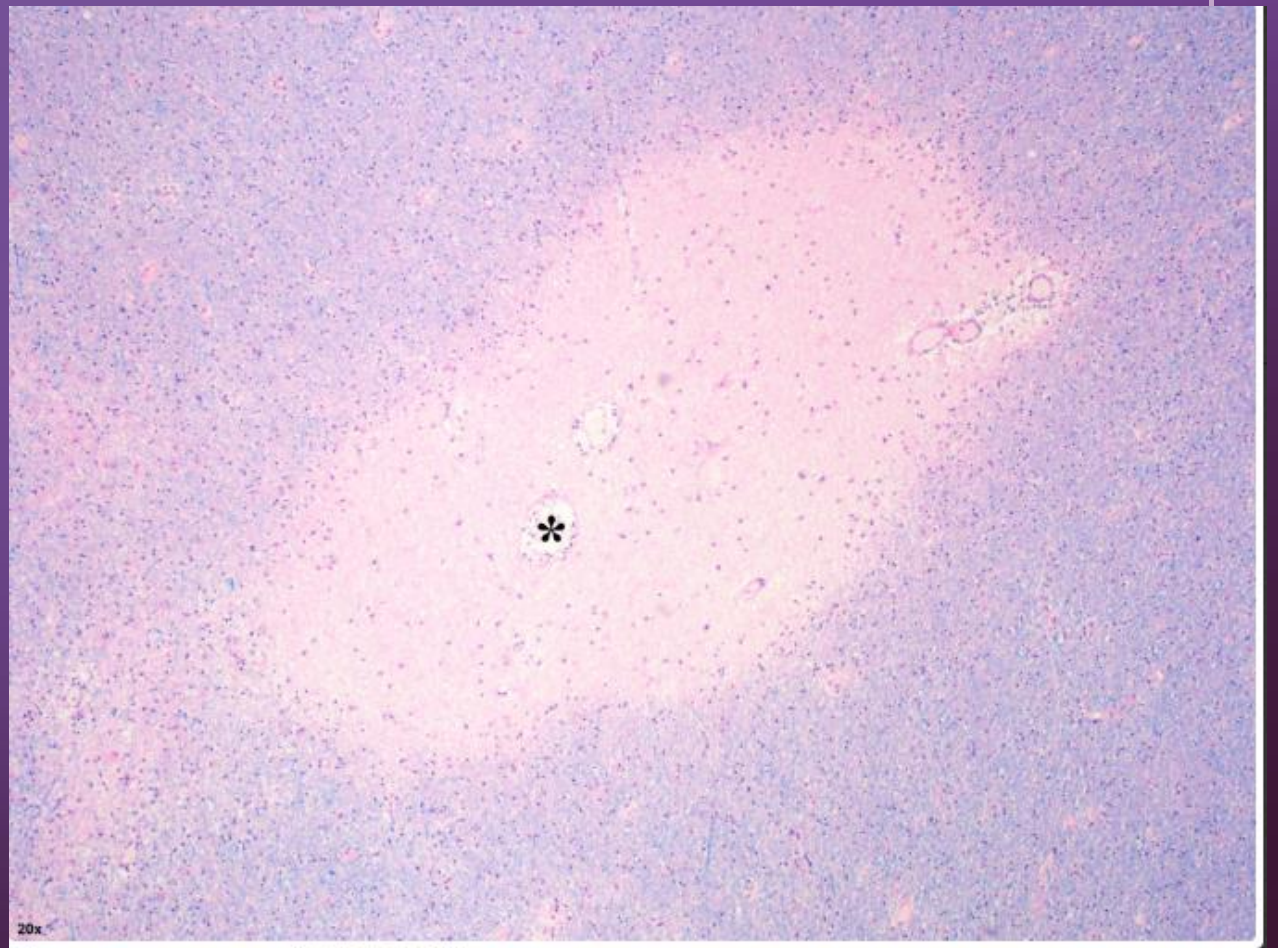
MICROSCOPIC FEATURES

Active plaque	Inactive plaque
Inflammation present	No inflammation
Macrophages كثيرة	Macrophages غائبة
Myelin breakdown مستمر	
Lymphocytic cuffs	Gliosis

*Active plaques (ongoing myelin breakdown): contain abundant macrophages with perivascular cuffs of Lymphocytes.

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

No Attack



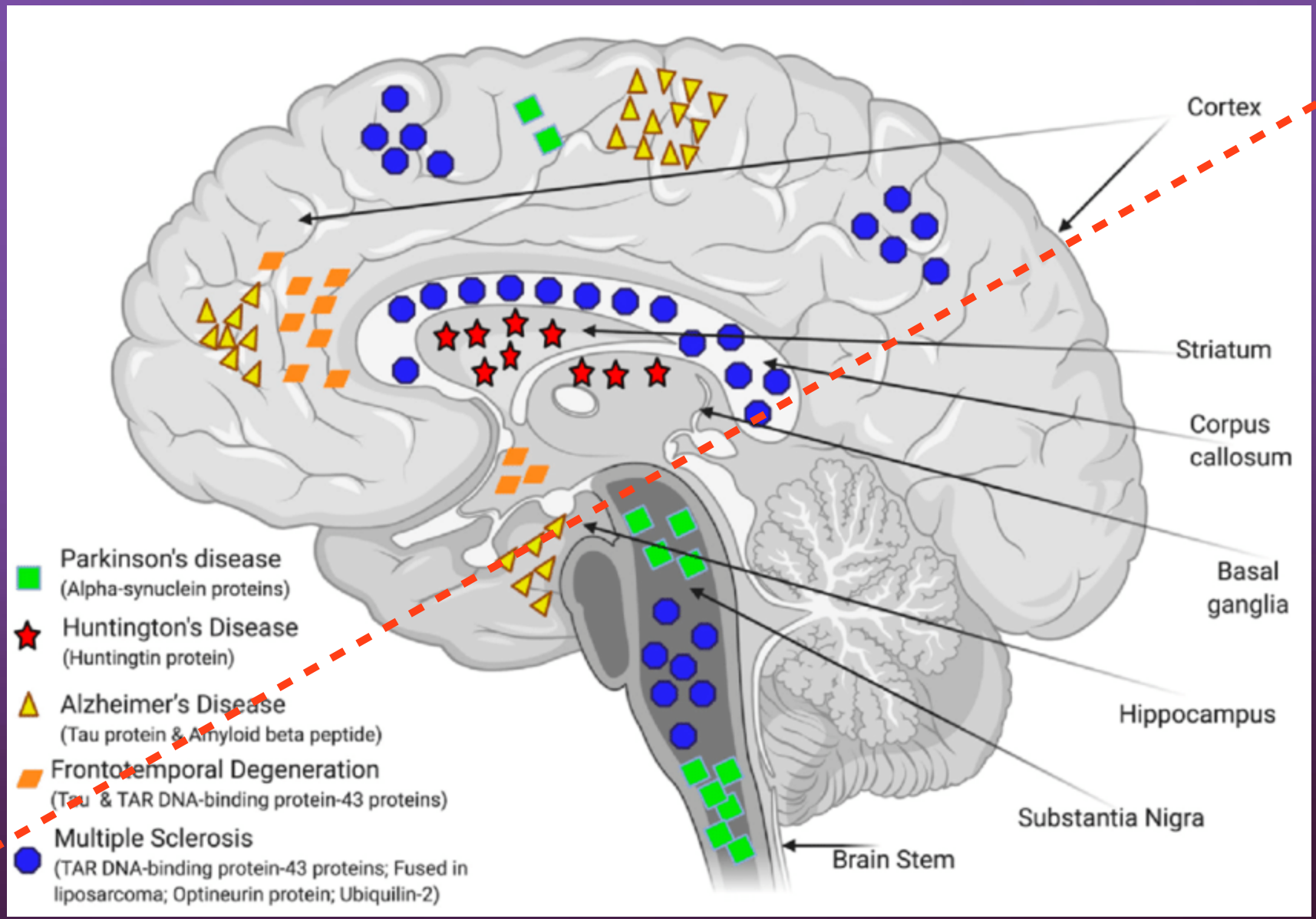
H&E / LFB stained section with a well demarcated area of demyelination centered around a vein (*).

NEURODEGENERATIVE DISEASES

- Progressive loss of neurons, affecting groups of neurons with functional interconnections. (even if not immediately adjacent.)
- Caused by the accumulation of protein aggregates, often are resistant to degradation by normal cellular proteases
- The clinical phenotype is determined more by the distribution of the aggregates than by the nature of the aggregating protein.

[distribution > nature]

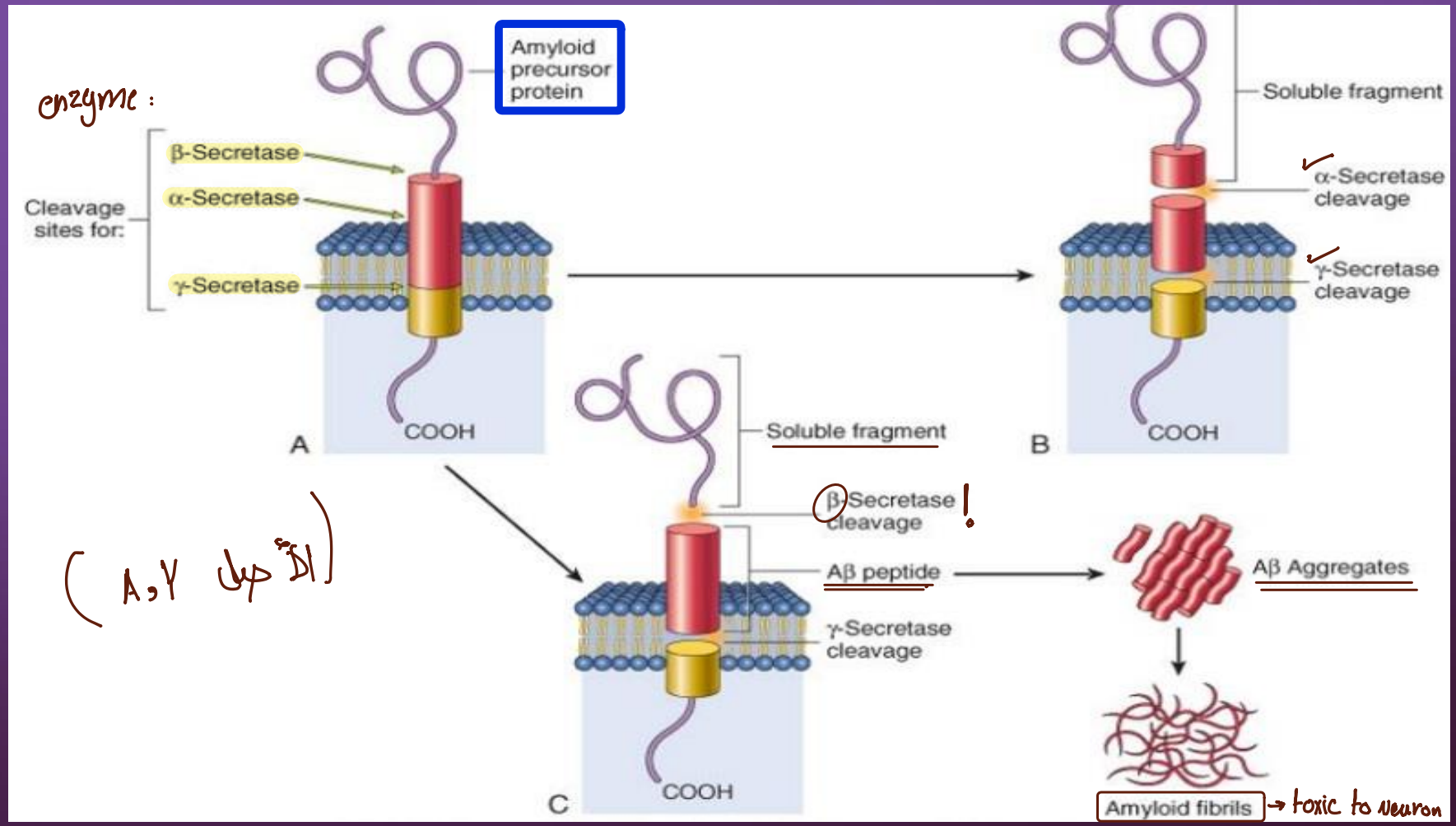
غير مطلوب


Cortex
Striatum
Corpus callosum
Basal ganglia
Hippocampus
Substantia Nigra
Brain Stem
Parkinson's disease
(Alpha-synuclein proteins)
Huntington's Disease
(Huntingtin protein)
Alzheimer's Disease
(Tau protein & Amyloid beta peptide)
Frontotemporal Degeneration
(Tau & TAR DNA-binding protein-43 proteins)
Multiple Sclerosis
(TAR DNA-binding protein-43 proteins; Fused in liposarcoma; Optineurin protein; Ubiquilin-2)

ALZHEIMER DISEASE (AD)

- Alzheimer's Disease (AD) is a neurodegenerative disease and is the most common cause of dementia in old people.
- 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).

PATHOGENESIS OF AD



- Aβ is a 36 to 43 amino acid peptide, which is part of **Amyloid Precursor Protein (APP).**

- APP is a transmembrane protein, made by neurons and other brain cells.

- The Aβ amyloid residue is derived from cleavage of APP by the enzymes **β-** and **γ-secretase.**

- Defective clearance of Aβ results in its accumulation as amyloid fibrils.

- **Aβ is toxic to neurons** it causes damages synapses, and kills neurons

NEUROFIBRILLARY TANGLES : TAU

- **Neurofibrillary tangles made from** insoluble polymers of **over-phosphorylated microtubule associated protein tau.**

- These deposits interfere with cellular functions by displacing organelles, they impair the axonal transport thus affecting the nutrition of axon terminals and dendrites.

SO THE TWO MAIN LESIONS IN AD:

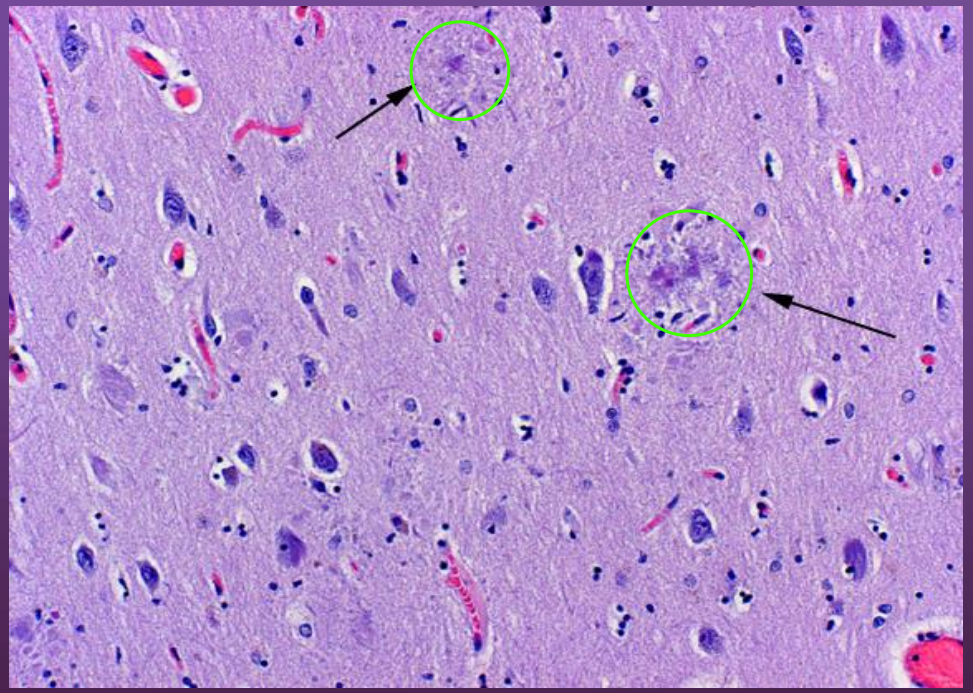
- **Senile plaques (SPs)** (also called Alzheimer's plaques) which contain Aβ.
- **Neurofibrillary tangles (NFTs)**, which contain over-phosphorylated tau.

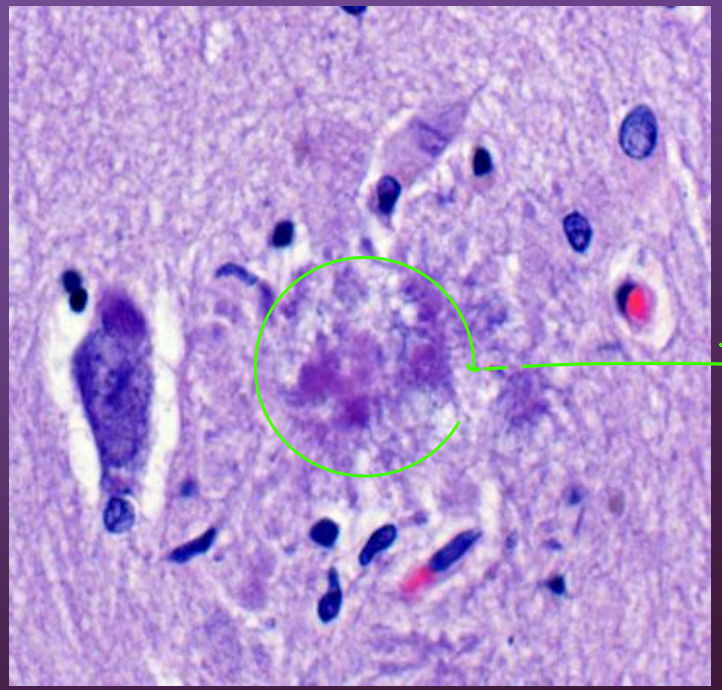
Gross features

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.

Microscopic features

Neuritic plaques are focal, spherical collections of dilated, tortuous, processes of dystrophic neurites around a central amyloid (aβ) core

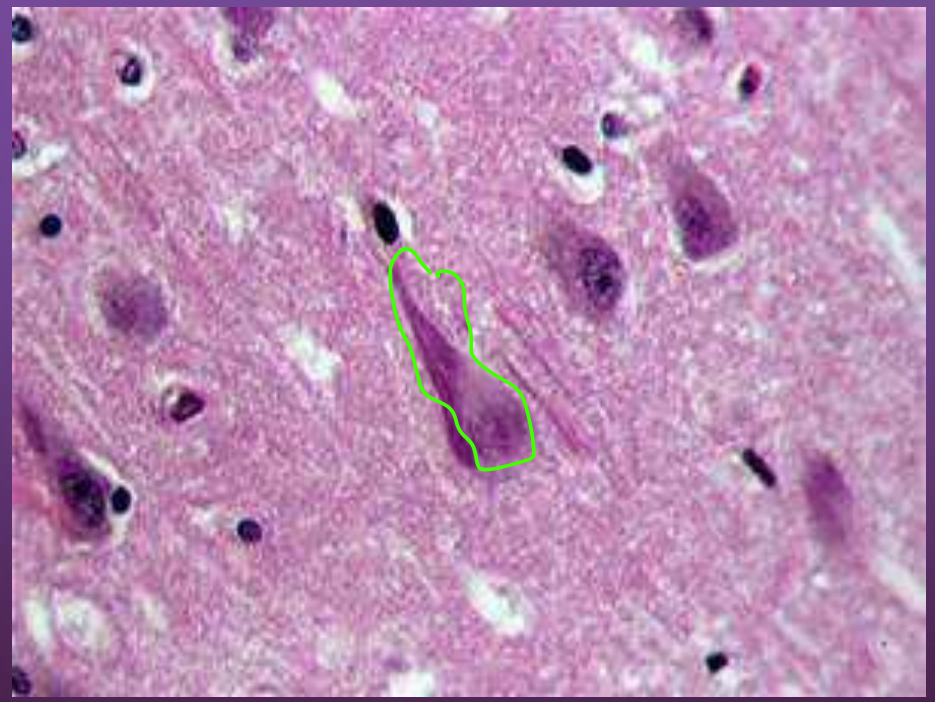


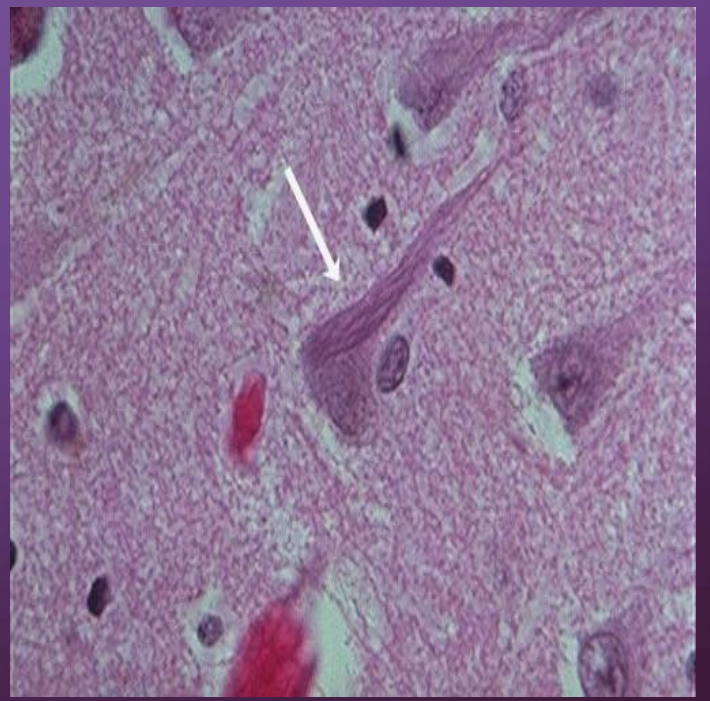


Flame shape

tau

Neurofibrillary tangles: tau containing bundles of filaments in neurons cytoplasm :flame shapes.





CLINICAL PRESENTATION AND PROGNOSIS

- insidious onset of impaired higher intellectual function.
- memory impairment.
- altered mood and behavior.

- As their disease progresses, patients with AD come to require assistance with basic activities of daily living.

- The time from diagnosis to death varies from as little as 3 years to as long as 10 or more years

Category	Topic	Key Features / Characteristics
Normal Histology & Support	Neurons	Conduct electrical impulses; consist of cell body, dendrites, and axon.
	Glial Cells	Oligodendrocytes: Myelin formation. Astrocytes: Metabolic support; undergo Gliosis (hypertrophy/hyperplasia) after injury. Microglia: Resident macrophages; perform Neuronophagia or form nodules upon activation.
Acute Injury	Neuronal Injury	"Red neurons": Shrinkage, pyknosis, loss of Nissl substance, and intense eosinophilia (within 12-24 hrs).
Myelin Diseases	Demyelinating	Loss of normally formed myelin with preservation of axons (e.g., Multiple Sclerosis).
	Dysmyelinating	Failure to form or maintain myelin due to genetic defects (Leukodystrophy).
Major Disease: MS	Multiple Sclerosis	Chronic, immune-mediated inflammatory disease. Diagnosis: MRI & Oligoclonal IgG bands in CSF. Pathology: Active plaques (macrophages/ lymphocytes) vs. Inactive plaques (gliosis).
Neurodegenerative	General Concept	Progressive loss of neurons due to accumulation of protein aggregates.
Major Disease: AD	Alzheimer Disease	Most common cause of dementia in elderly. Pathogenesis: Accumulation of Aβ (amyloid β) and Tau proteins.
	AD Lesions	Senile Plaques: Extracellular Aβ cores. Neurofibrillary Tangles (NFTs): Intracellular hyper-phosphorylated Tau (flame-shaped).
	Gross Findings	Cortical atrophy with widening of cerebral sulci (frontal, temporal, parietal).