Neuroscience II Pathology

Ghadeer Hayel, M.D.
Assistant Professor of Pathology
Consultant Hematopathologist
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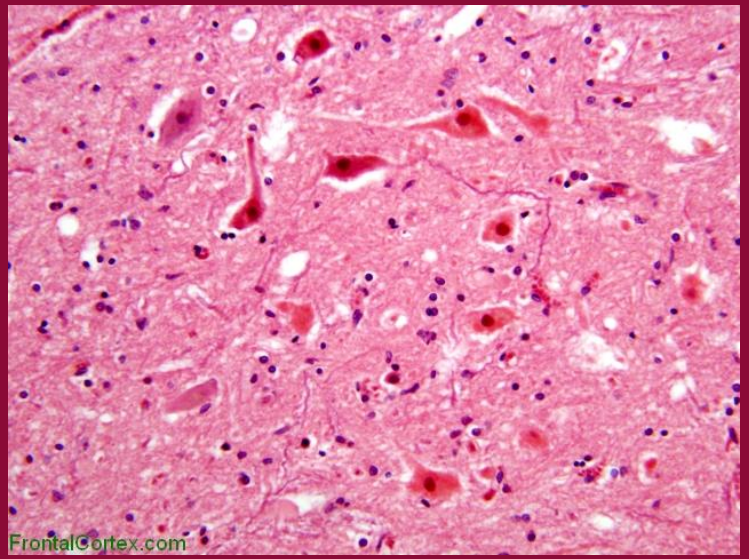
Central nervous system

Characteristic Features of Cellular Pathology in CNS

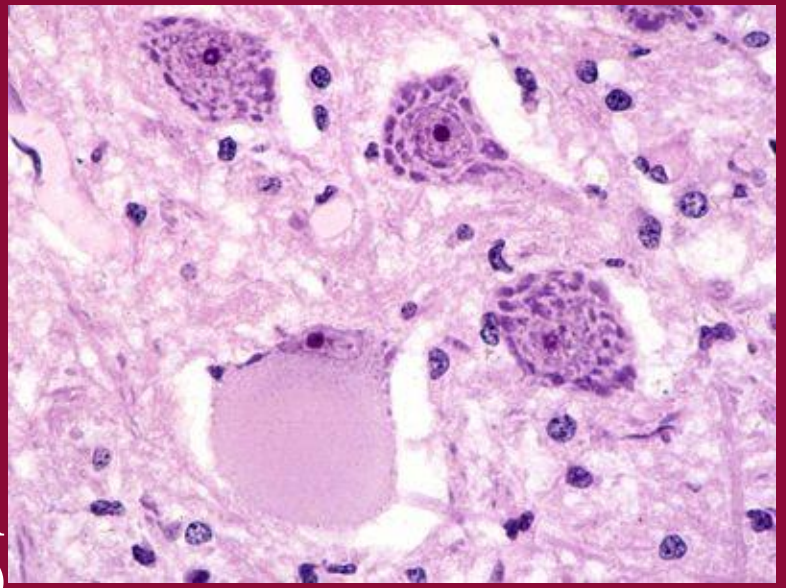
Neurons – Acute neuronal injury

- 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**"



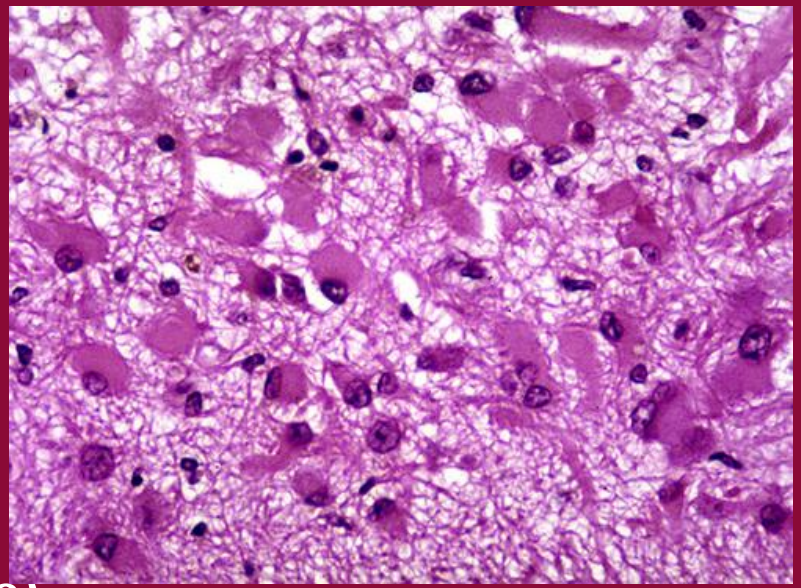
Neurons – Axonal injury/reaction

- **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)**



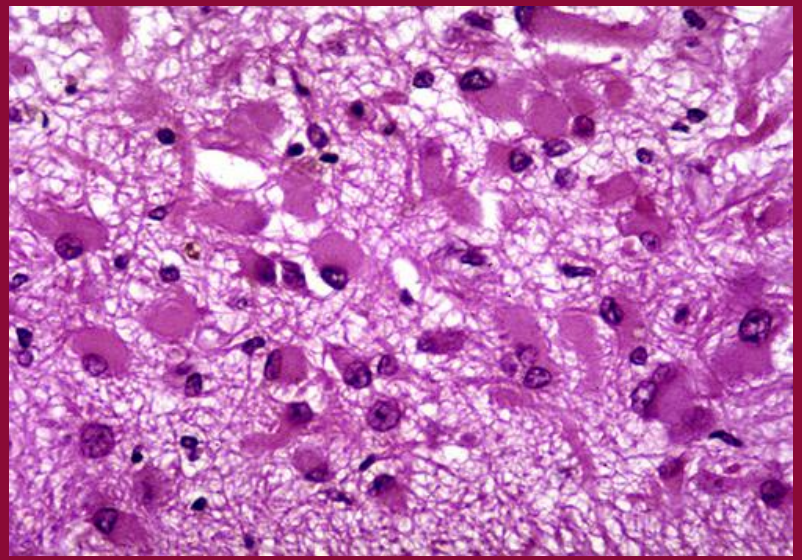
Astrocyte Injury and Repair

- 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**).



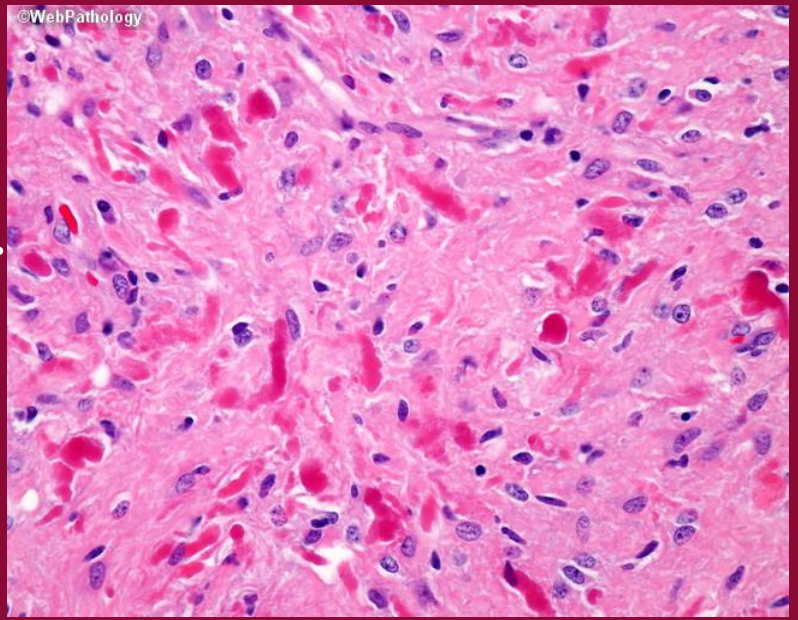
Astrocyte Injury and Repair

- 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).



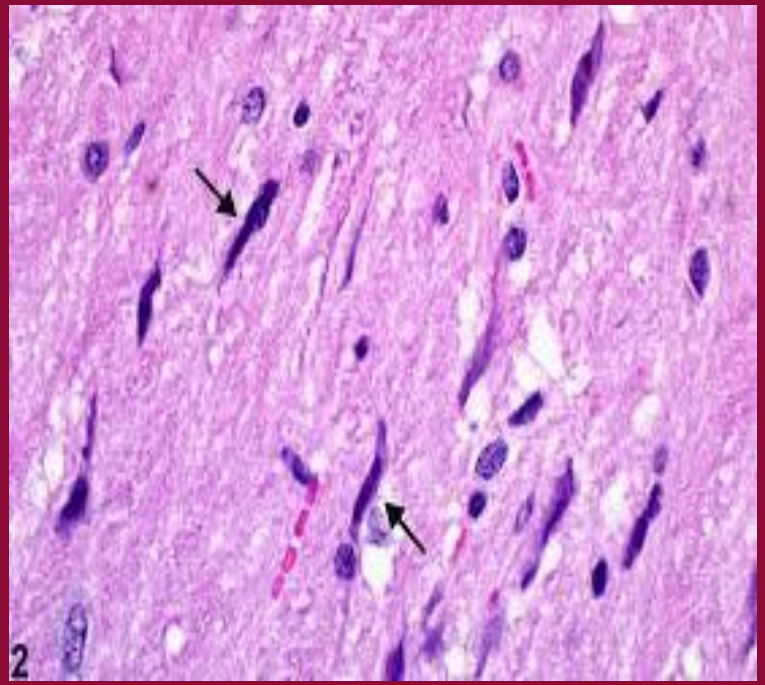
Astrocyte Injury and Repair

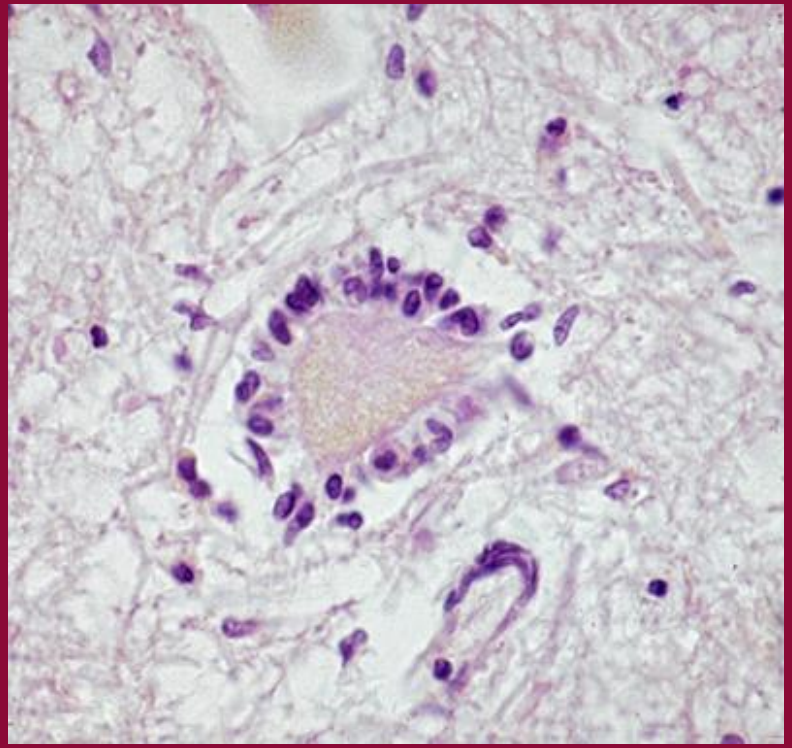
- In long-standing gliosis, the cytoplasm of reactive astrocytes shrinks in size, & cellular processes become tightly interwoven **(fibrillary astrocytes).**
- **Rosenthal fibers:** thick,elongated, brightly eosinophilic protein aggregates found in astrocytic processes in chronic gliosis & in some low-grade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

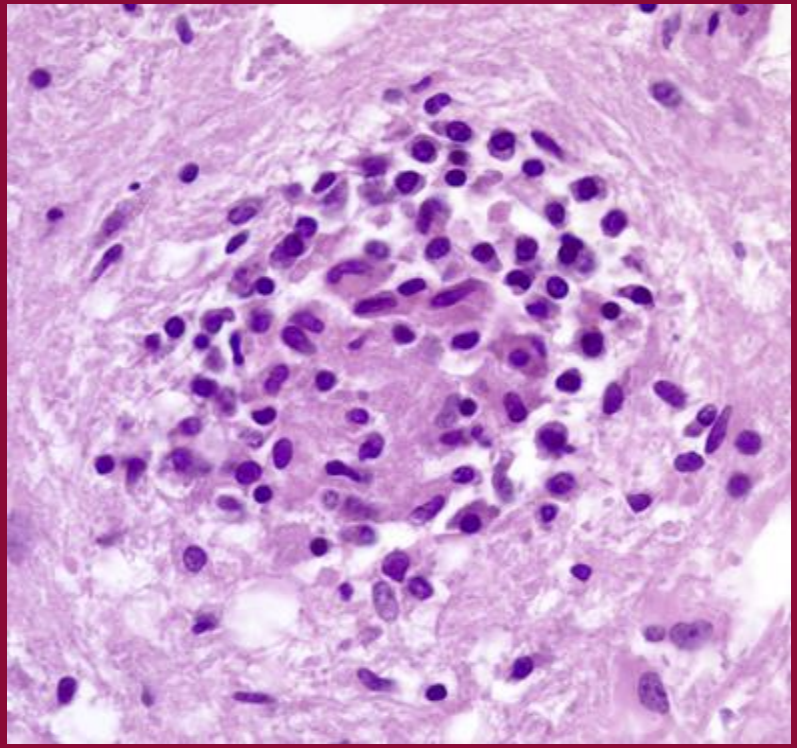


Microglial cells

- 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 & degenerative diseases of CNS (1)

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.

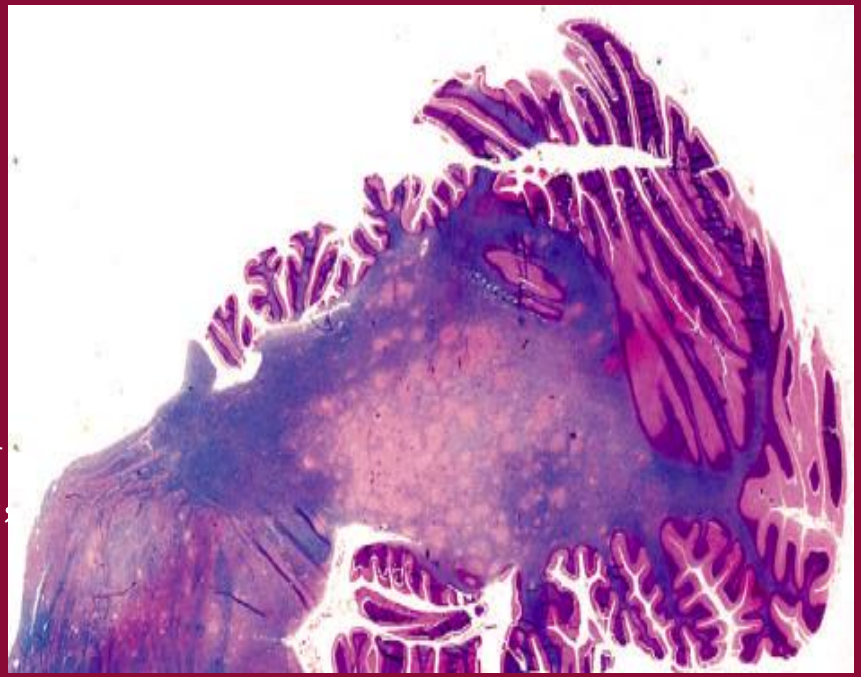
Differences b/w CNS & PNS Myelin

1) PNS myelin is made by Schwann cells, CNS 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), or (3) injury caused by drugs and other toxic agents.

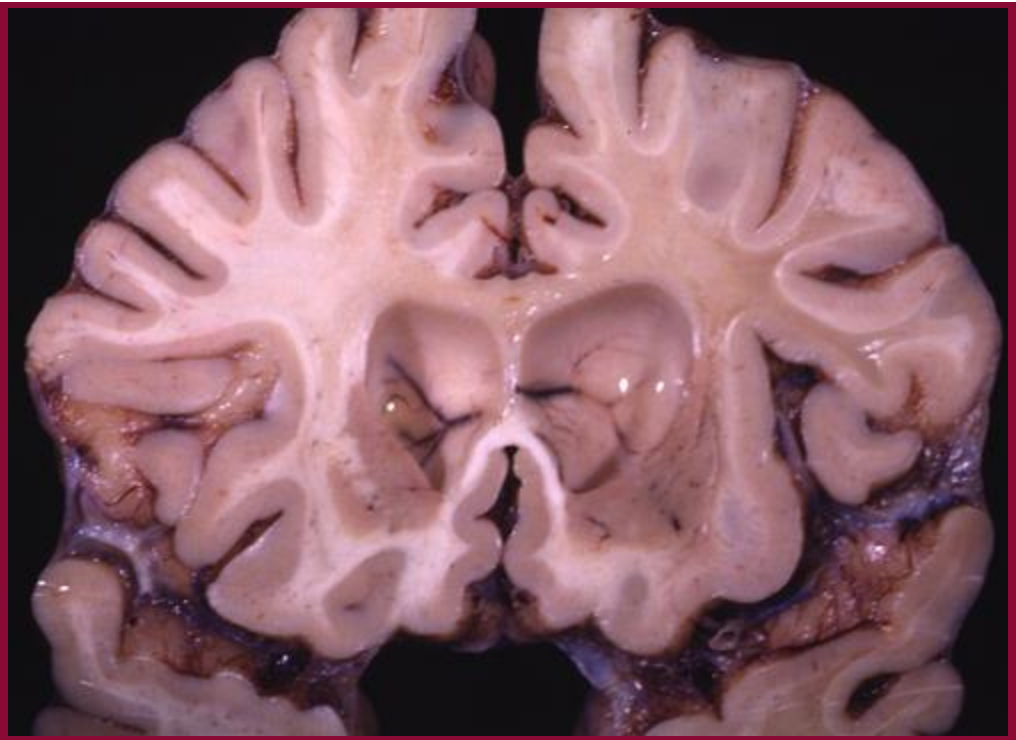


diseases of myelin are separated to two groups:

II. Leukodystrophy or dysmyelinating diseases:

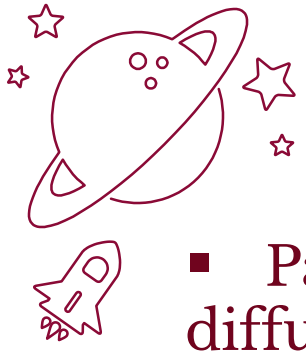
+Myelin is not formed properly or has abnormal kinetics

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



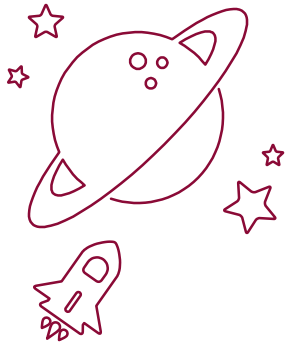
Leukodystrophies

- Inherited dysmyelinating diseases. (Most autosomal recessive).
- Mutations of the genes involved in the generation, turnover, or maintenance of myelin.
- Clinically, Each disorder of the various types has a characteristic presentation→ diagnosed by genetic or biochemical methods.
- Affected children are normal at birth but begin to miss developmental milestones during infancy & childhood



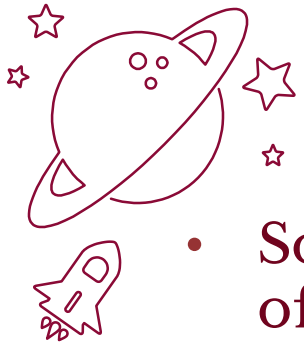
Leukodystrophies - morphology

- Pathologic change mainly in the white matter → diffusely abnormal in color (gray and translucent) and volume (decreased). Leading to deterioration in motor skills, spasticity, hypotonia, or ataxia.
- Later the brain becomes atrophic, the ventricles enlarge, & changes can be found in the gray matter.
- Compared to demyelinating diseases they have insidious presentation & progressive loss of function at younger age, & associated with symmetric changes on MRI.



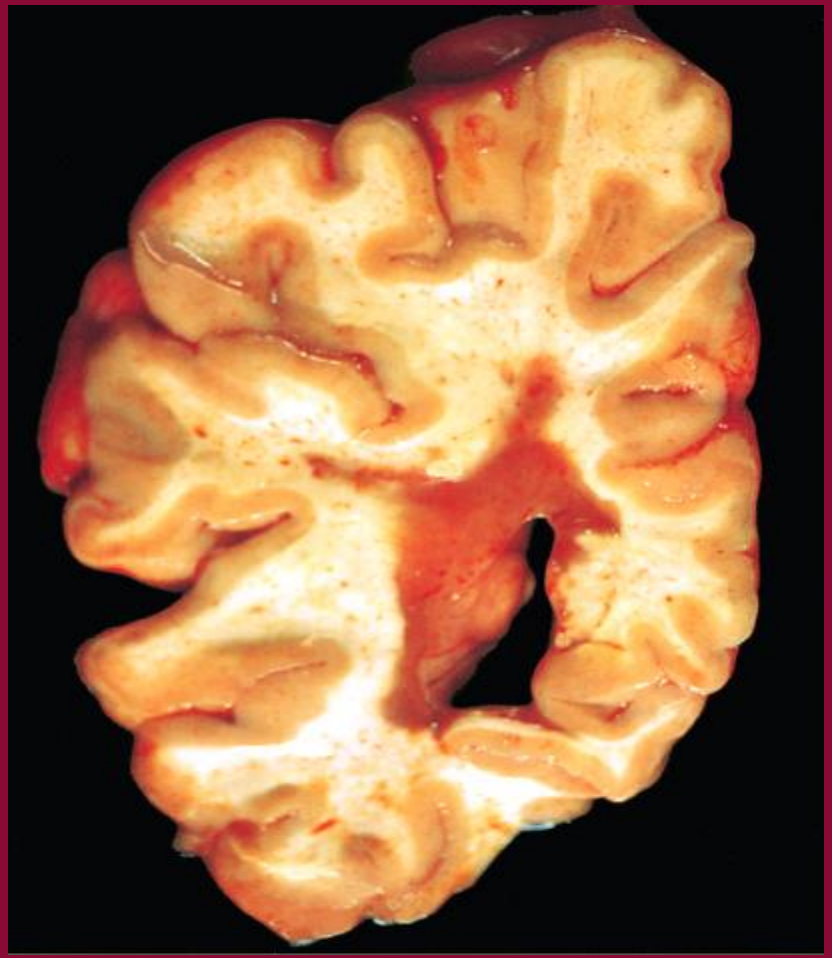
Multiple Sclerosis (MS)

- The most common demyelinating disease.
- Episodes of disease activity, separated in time which produce white matter lesions, 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.
- Course is variable, commonly multiple relapses followed by episodes of remission; typically, recovery during remissions is not complete.

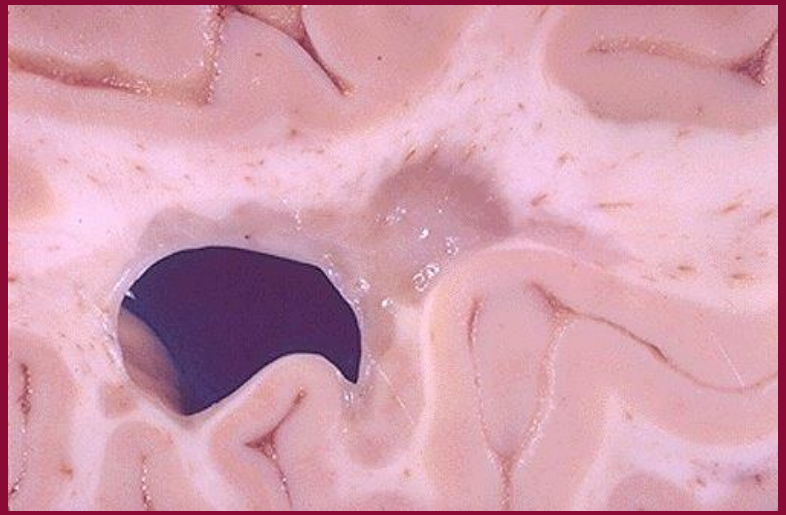


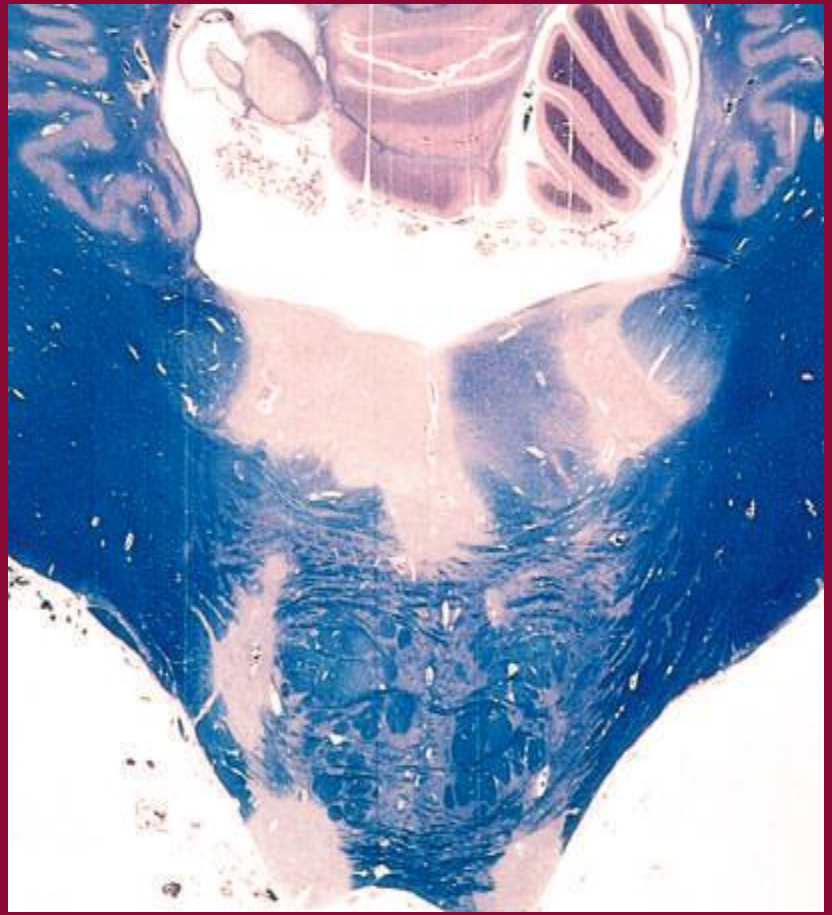
Multiple Sclerosis (MS)

- 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.



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





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.

NEURODEGENERATIVE DISEASES

- Progressive loss of neurons, affecting groups of neurons with functional interconnections.
- All Caused by the accumulation of protein aggregates,
- The clinical phenotype is determined more by the **distribution of the aggregates** than by the nature of the aggregating protein.
- Many of the protein aggregates are capable of spreading to healthy neurons.(like prions).

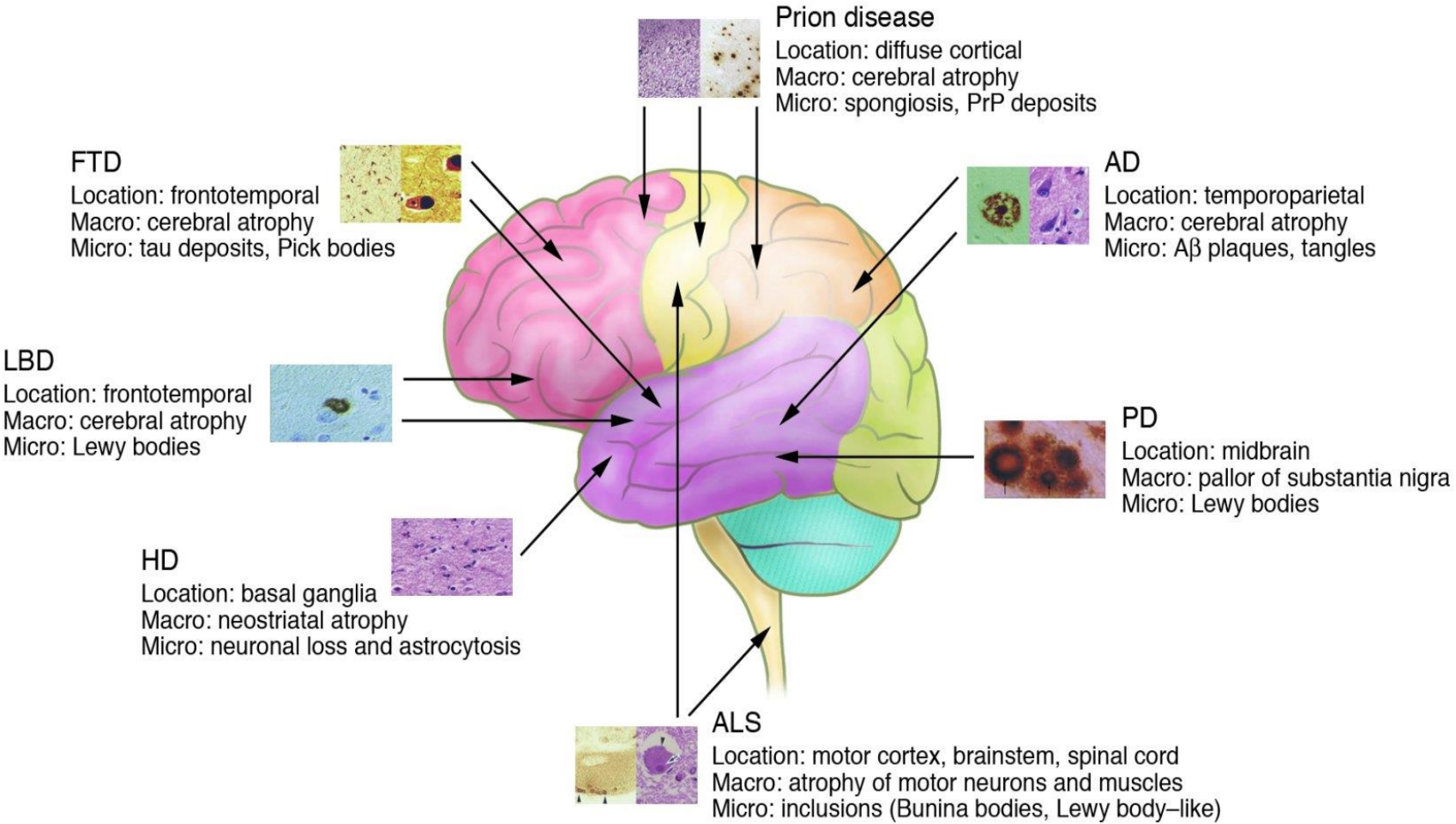
NEURODEGENERATIVE DISEASES

- What causes the aggregates:

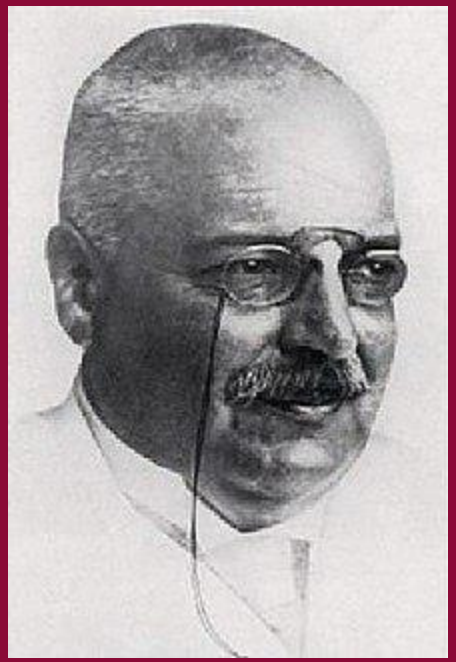
1- Mutations that (a) alter protein's conformation or (b) disrupt pathways involved in processing or clearance of the proteins.

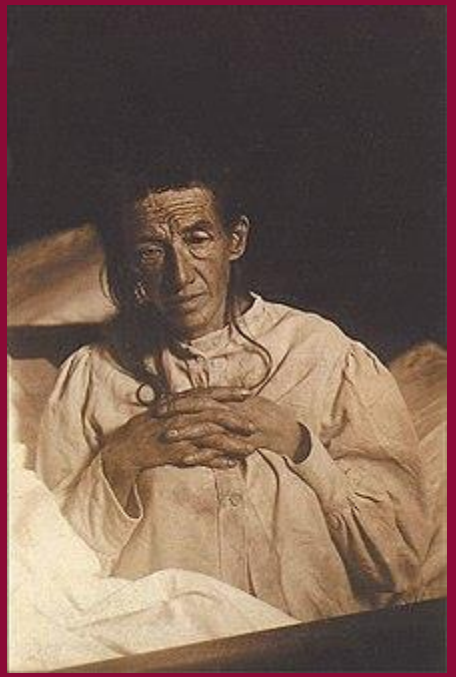
2- A subtle imbalance between protein synthesis & clearance (due to genetic, environmental, or stochastic factors) →allows gradual accumulation

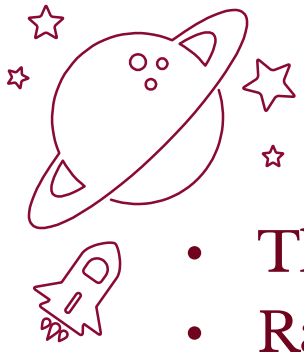
- Aggregates often are resistant to degradation by normal cellular proteases, accumulate within cells, elicit an inflammatory response, & may be directly toxic to neurons.


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)



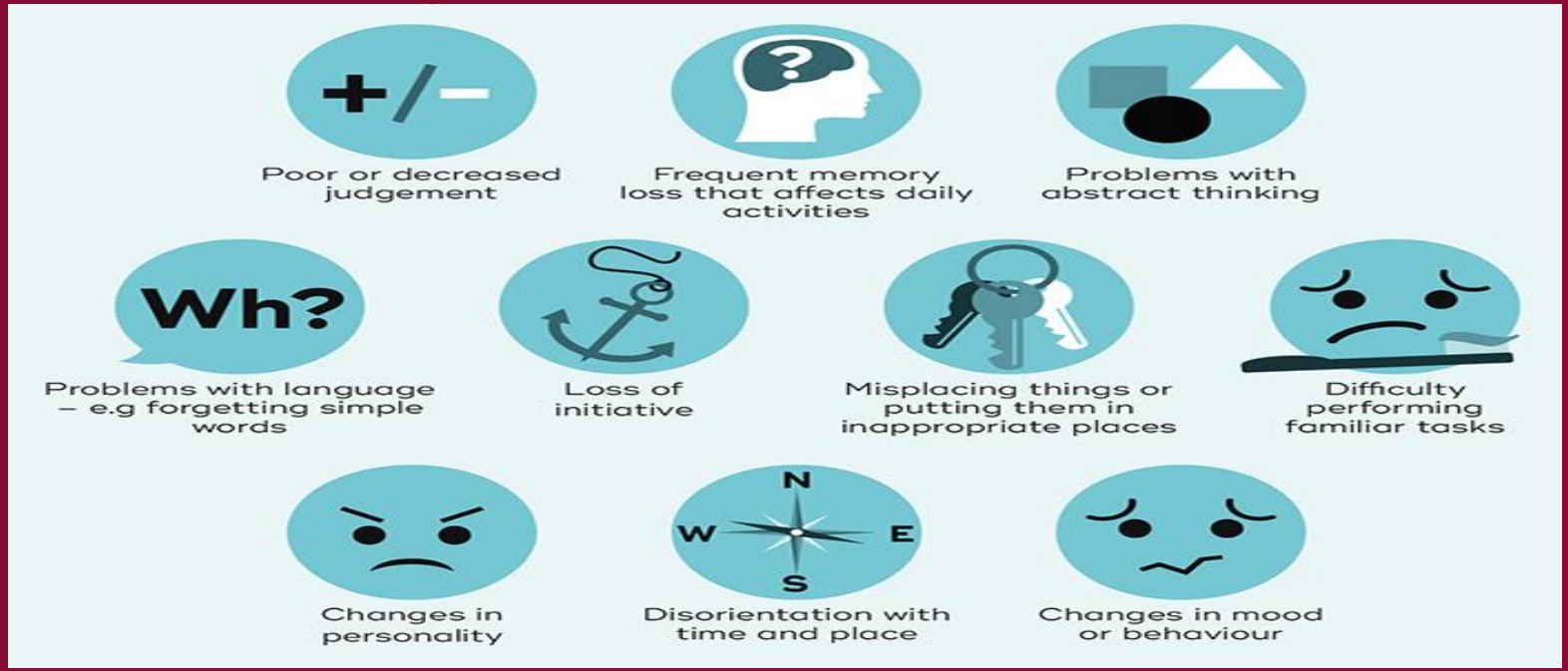




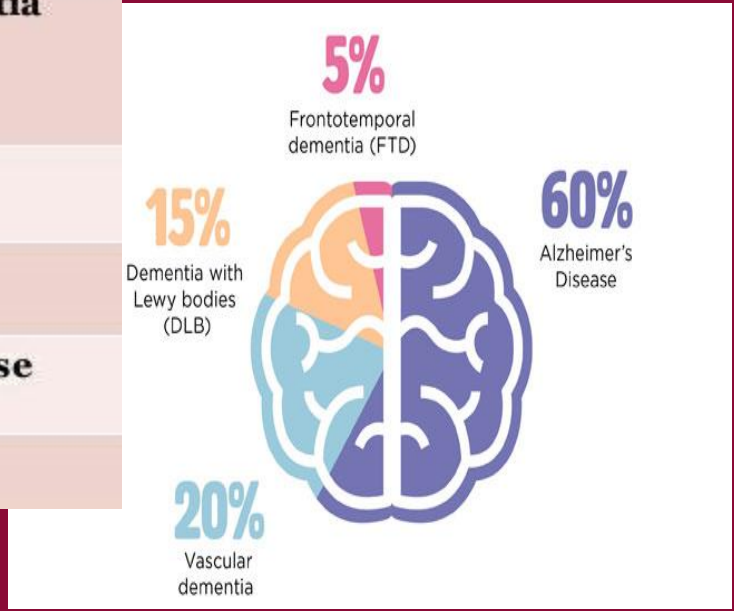
Alzheimer Disease (AD)

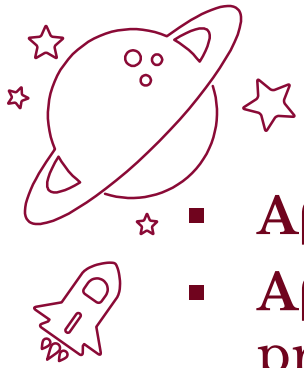
- The most common cause of **dementia** in older adults.
- Rare before 50, incidence increases with age (1% → 60 to 64, reaching 47% in 85 and older).
- Manifests with the insidious onset of impaired higher intellectual function, **memory impairment**, & altered mood and behavior.
- **Aβ** (amyloid β)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

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



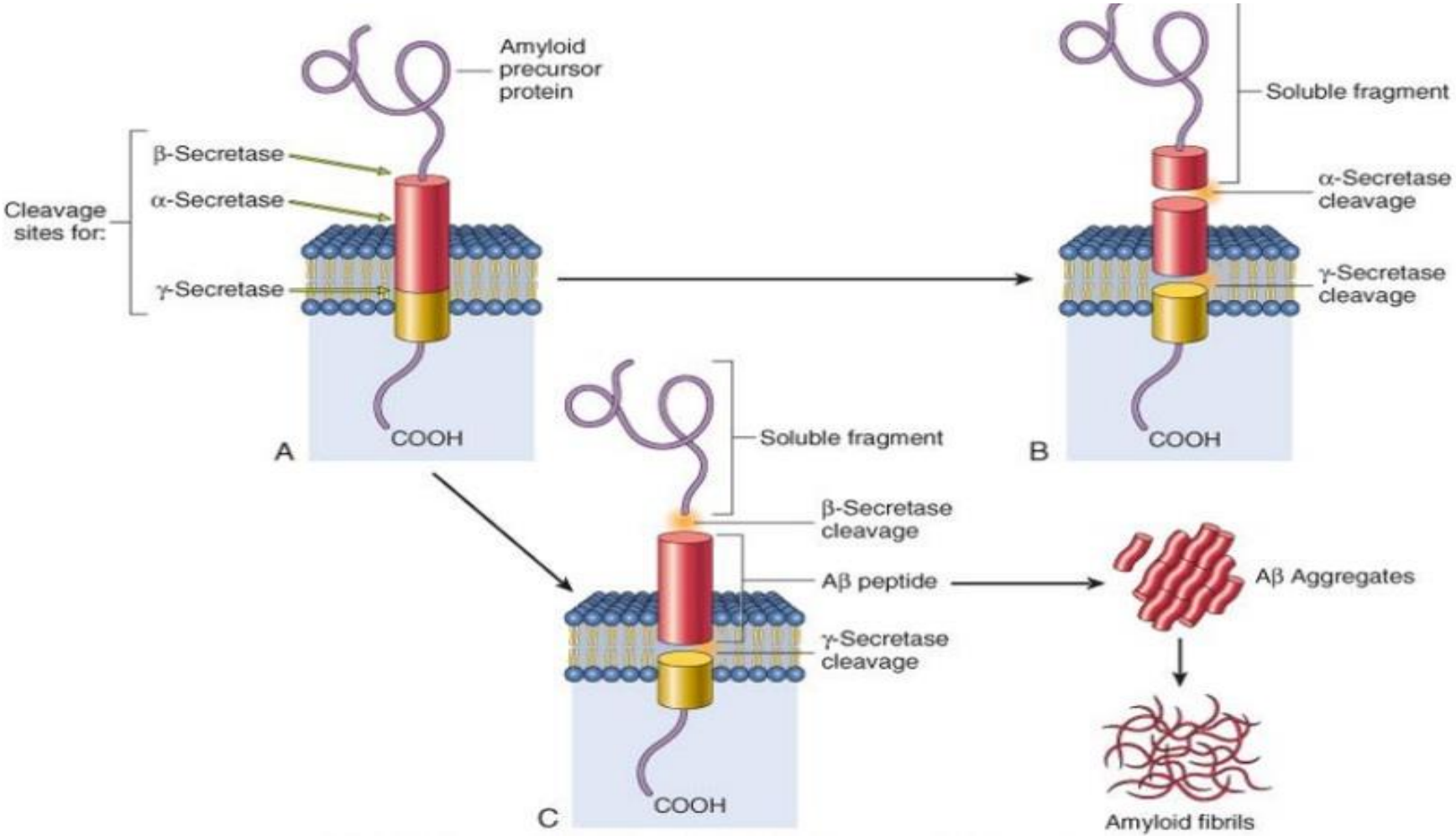
REVERSIBLE DEMENTIA[10-20%]	IRREVERSIBLE DEMENTIA[80-90%]
D= Drugs	Alzheimer
E= Endocrine disorders	Lewy Body dementia
M= Metabolic	Frontotemporal Dementia (Picks disease)
E= Emotional	Parkinson disease
N= Nutritional	Huntington's disease
T = Toxic, Tumor, Trauma	Creutzfeldt-Jakob disease
A= Alcohol	others

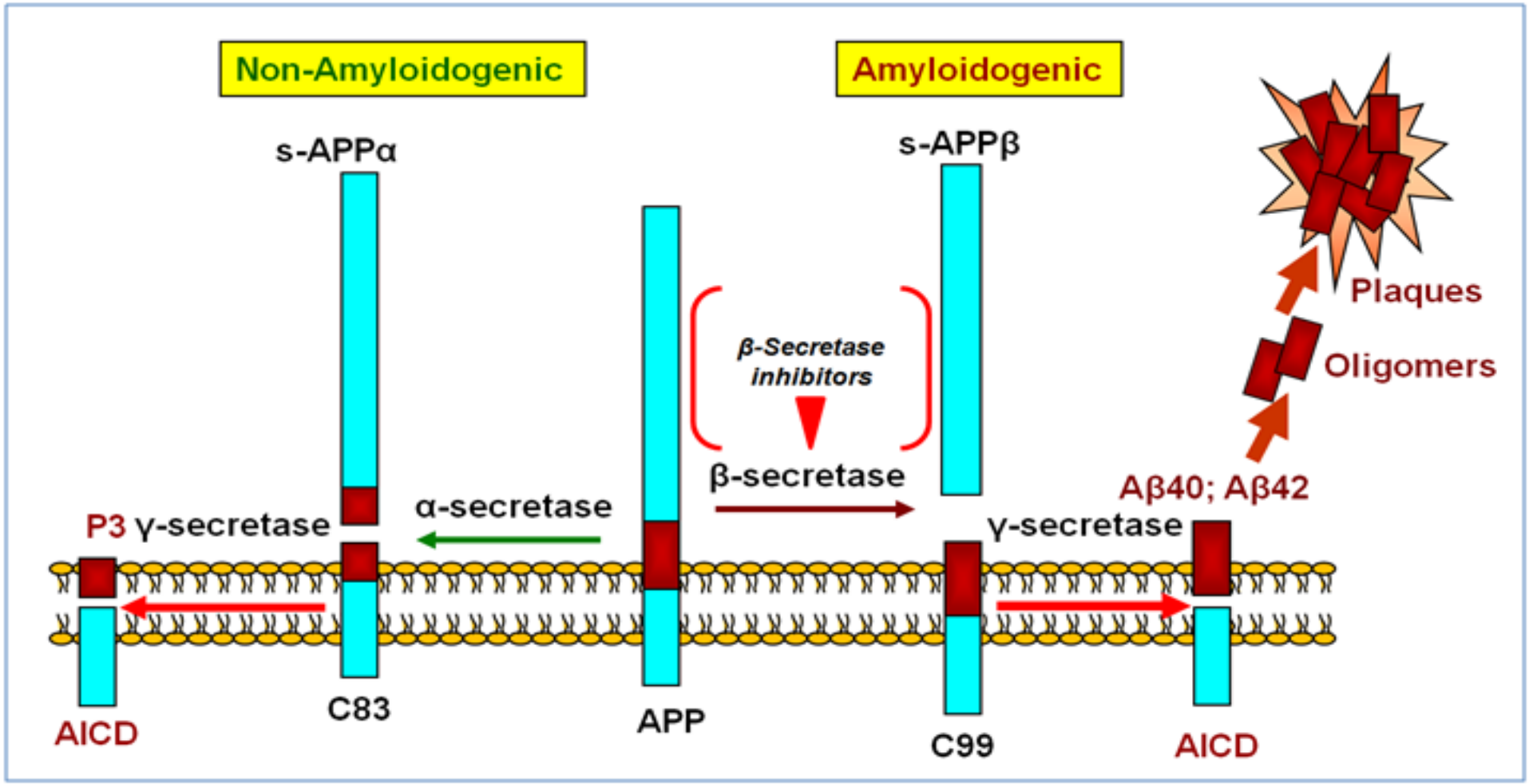




AD – Pathogenesis

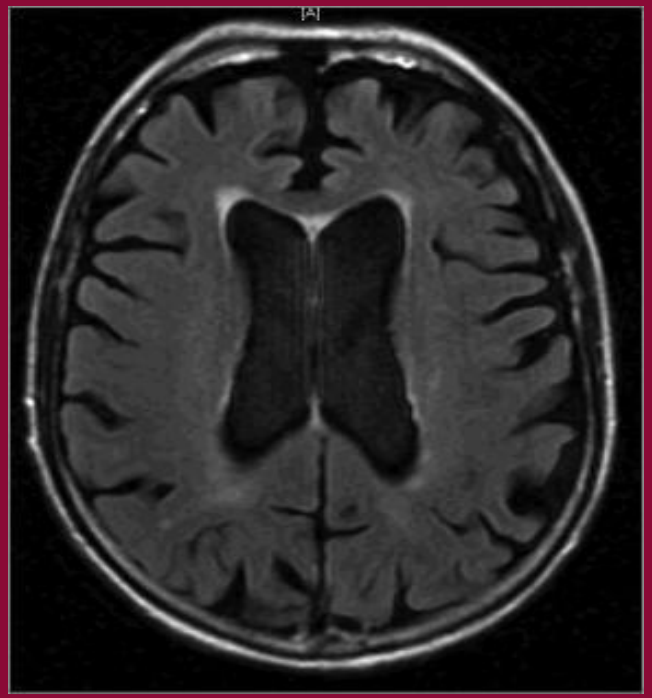
- **Aβ generation → critical initiating event to develop AD**
- **Aβ is** derived from a membrane protein; amyloid precursor protein (APP).
- APP processed in 2 ways pathways:
  (1) Starts with α-secretase (non-amyloidogenic), **no Aβ generation.**
  (2) Starts with β-secretase (amyloidoigenic), **Aβ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

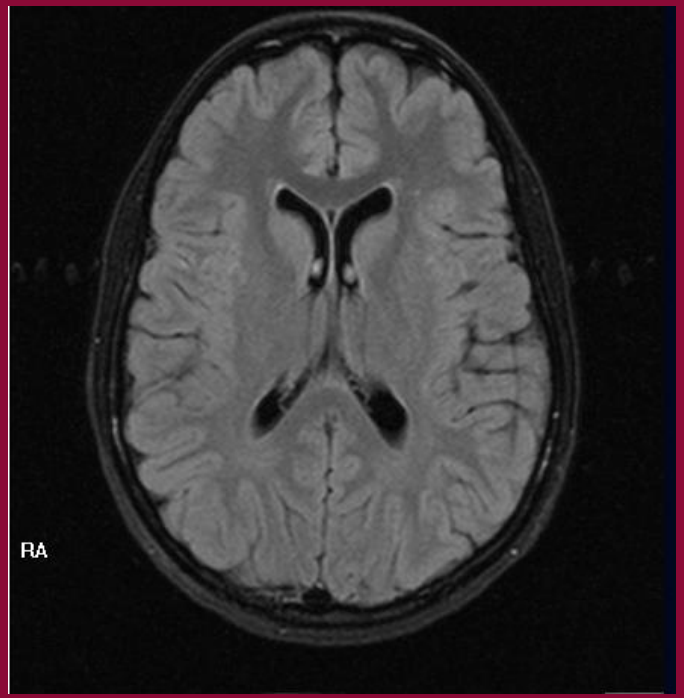

Amyloid precursor protein
Cleavage sites for:
β-Secretase
α-Secretase
γ-Secretase
COOH
A
Soluble fragment
α-Secretase cleavage
γ-Secretase cleavage
COOH
B
Soluble fragment
β-Secretase cleavage
Aβ peptide
γ-Secretase cleavage
COOH
C
Aβ Aggregates
Amyloid fibrils


Non-Amyloidogenic
Amyloidogenic
s-APPα
s-APPβ
β-Secretase inhibitors
β-secretase
α-secretase
P3 γ-secretase
γ-secretase
Aβ40; Aβ42
Plaques
Oligomers
AICD
C83
APP
C99
AICD

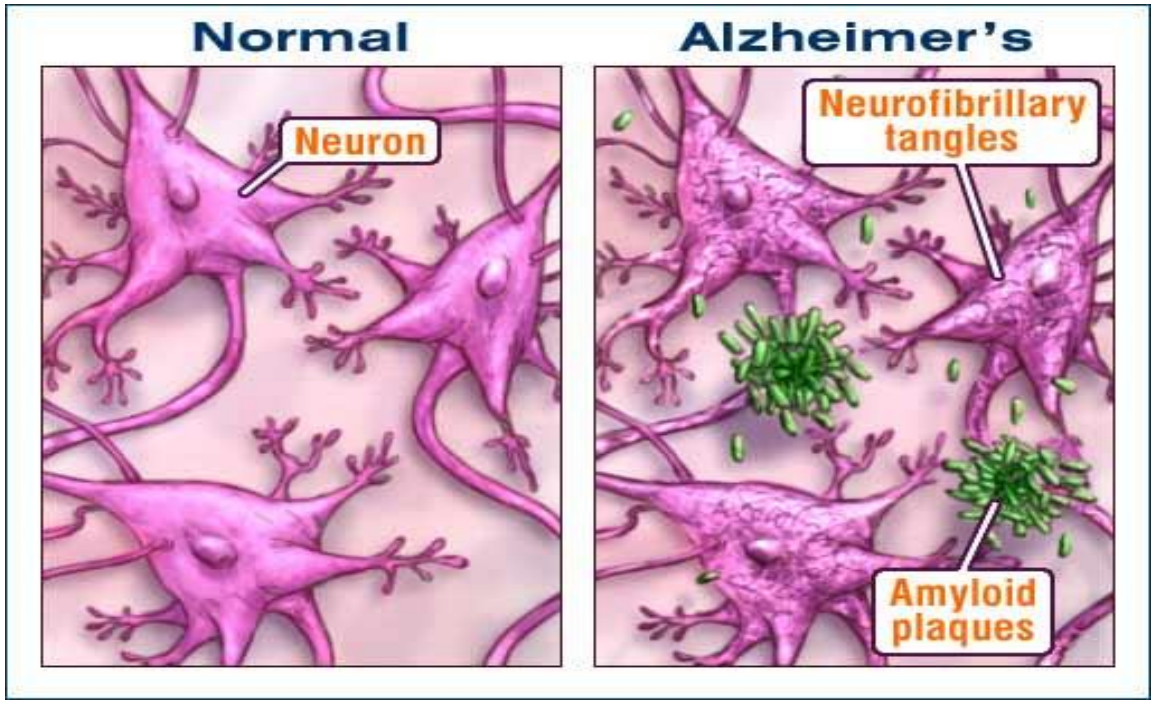
A variable degree of cortical atrophy, resulting in a widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.

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

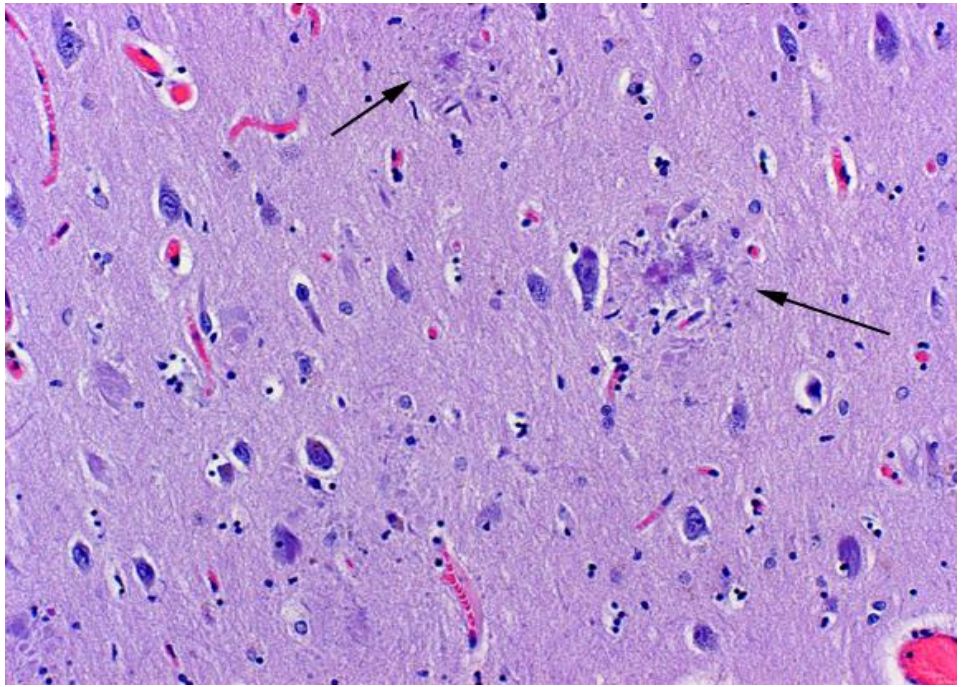


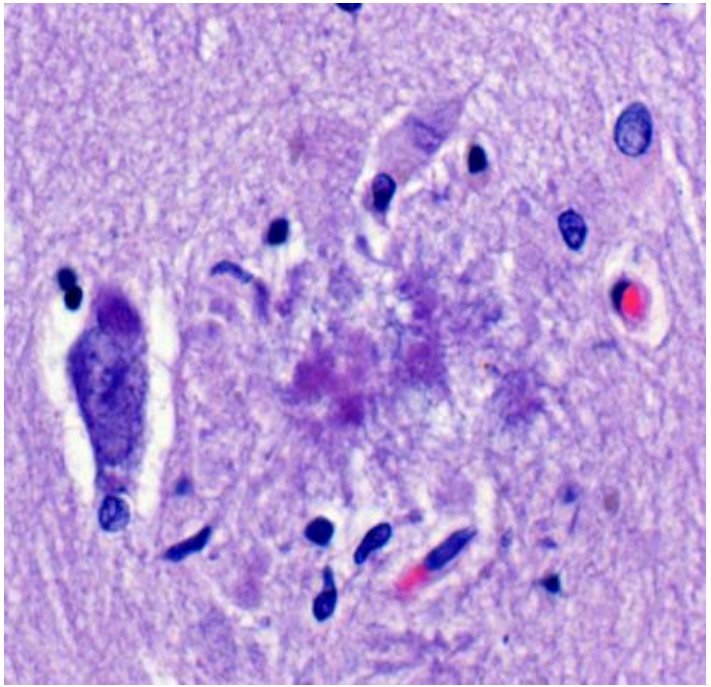


- Microscopy: Amyloid plaques (extracellular - accumulation of Aβ amyloid) and neurofibrillary tangles (intracellular - *Tau* accumulation).



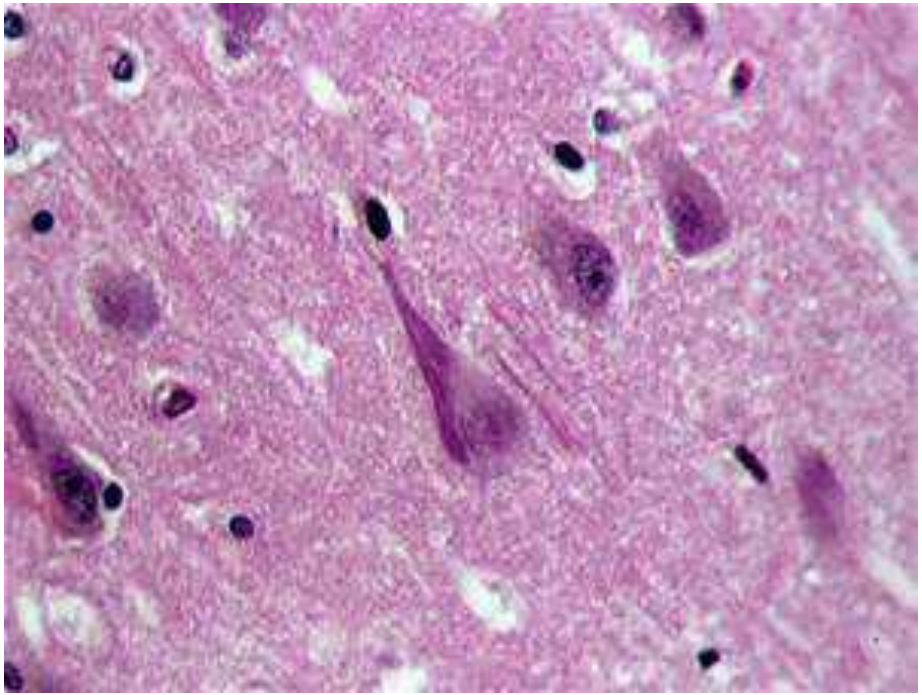
Neuritic plaques are focal, spherical collections of dilated, tortuous, processes of dystrophic neurites around a central amyloid (Aβ) core. Aβ deposition without neurites termed **diffuse plaques.**

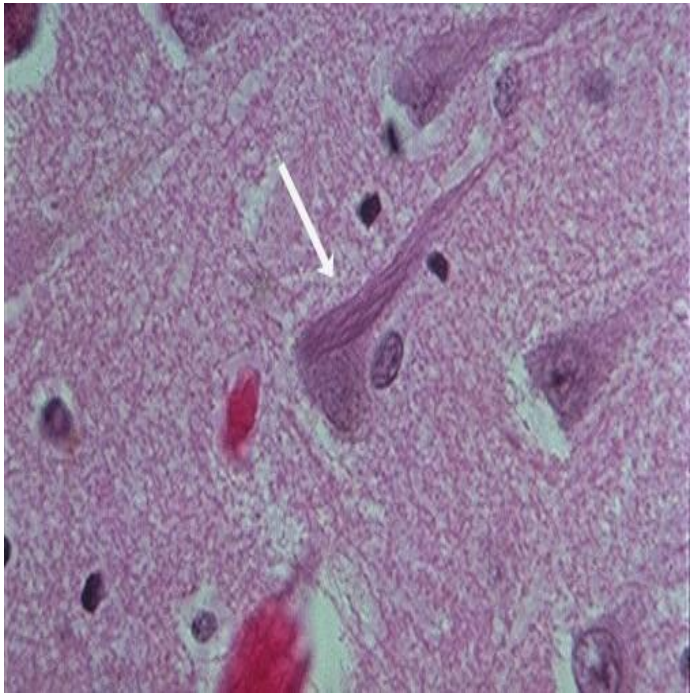




Neurofibrillary tangles: Tau containing bundles of filaments in neurons cytoplasm (encircle the nucleus), <**flame** shapes>

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



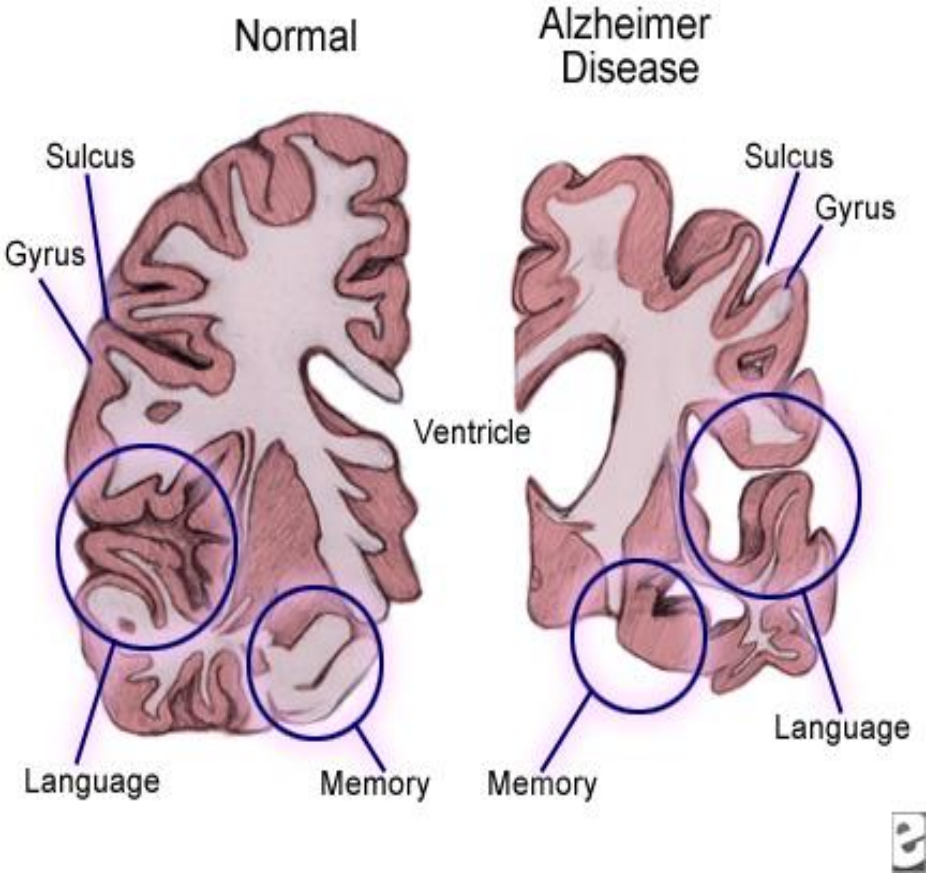


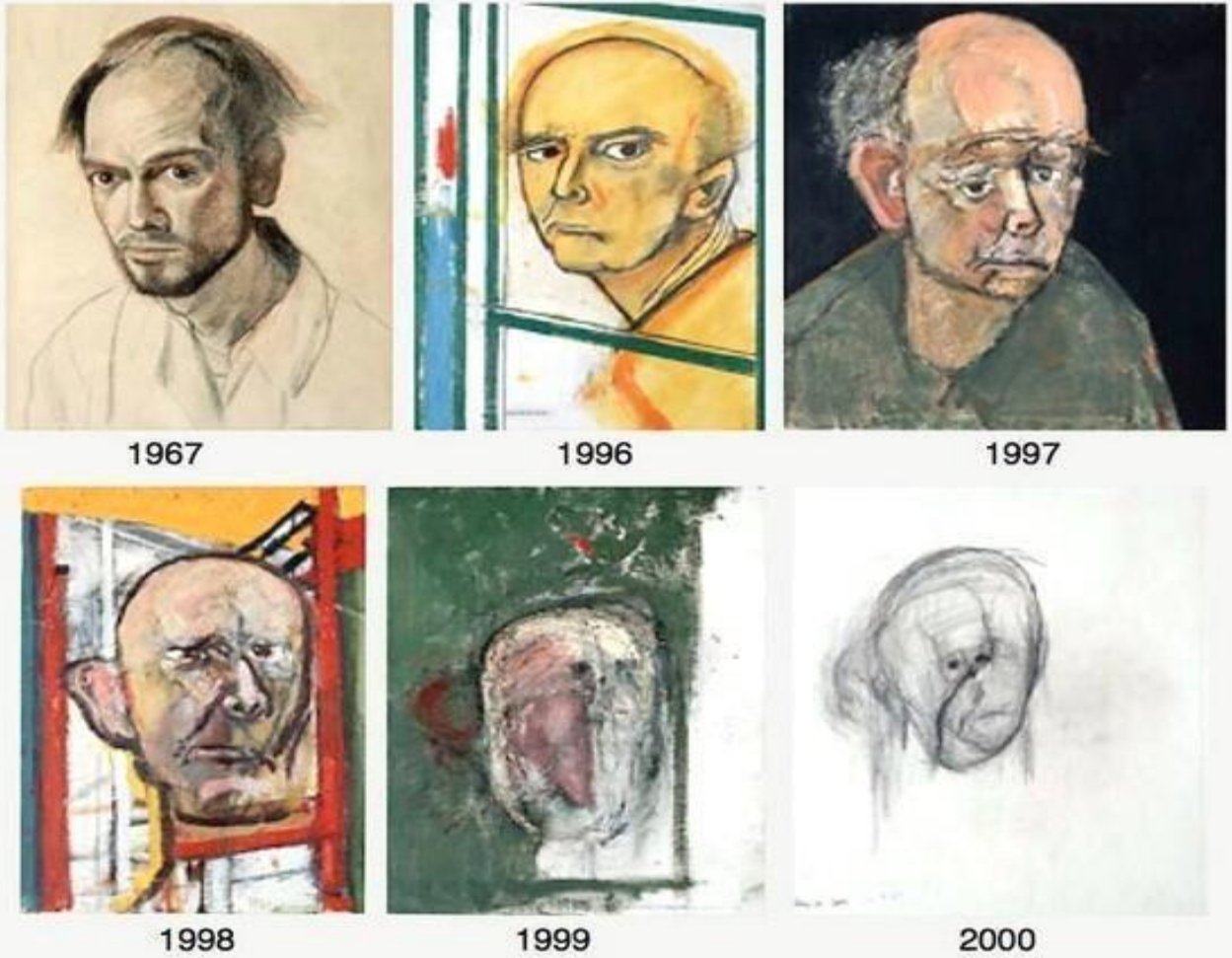
Clinically: Insidious onset of impaired higher intellectual function & memory & altered mood & behavior.

Over time, disorientation & aphasia.

In final stages they are disabled, mute & immobile.

Death → intercurrent pneumonia or other infections.



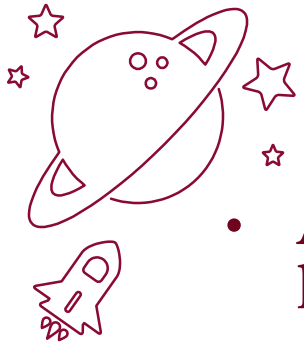


"can the arts ever illuminate a condition that by its very nature resists all understanding?"

William Utermohlen's self-portraits, the first, made in 1967, the rest from 1996 the year following his diagnosis of Alzheimer's disease, to 2000, charting his decline.

Demyelinating & degenerative diseases of CNS

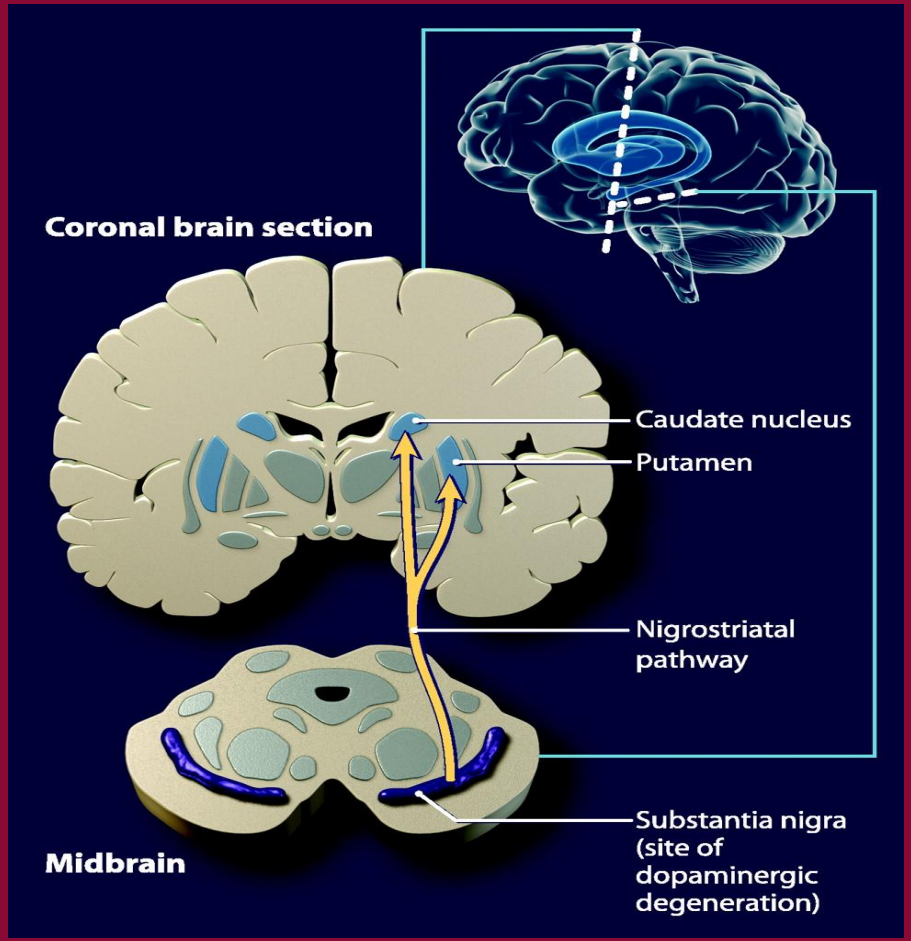
Parkinson Disease (PD)



Parkinson Disease

- A neurodegenerative disease marked by a prominent hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the **substantia nigra.**
- Has characteristic neuronal inclusions containing α-synuclein. **(Lewy bodies)**
- **Parkinsonism**: a clinical syndrome characterized by diminished facial expression (masked facies), stooped posture, slowness of voluntary movement, festinating gait (progressively shortened, accelerated steps), rigidity, & a "pill-rolling“ tremor.

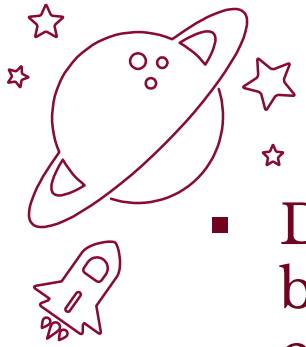
Parkinsonism is seen in a range of diseases that damage dopaminergic neurons, which project from the substantia nigra to the striatum (nigrostriatal pathway) and are involved in control of motor activity.



PD– Pathogenesis

- PD is associated with protein (α-synuclein) aggregation, mitochondrial abnormalities, & neuronal loss in the substantia nigra & elsewhere in the brain:

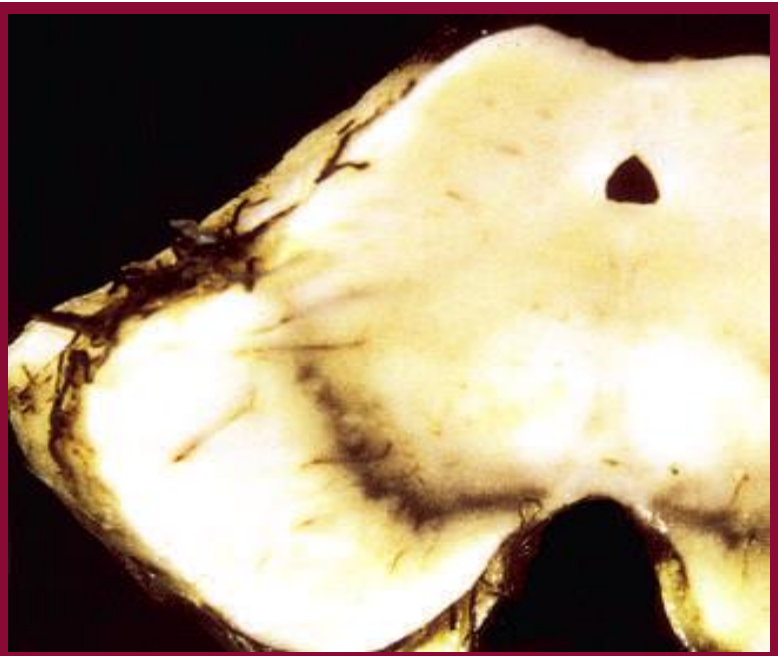
+ Synuclein aggregates are normally cleared by autophagy.
+ Abnormal protein & organelle clearance due to defects in autophagy & lysosomal degradation.
+ Dopaminergic neurons degeneration → reduction in dopamine in the striatum.

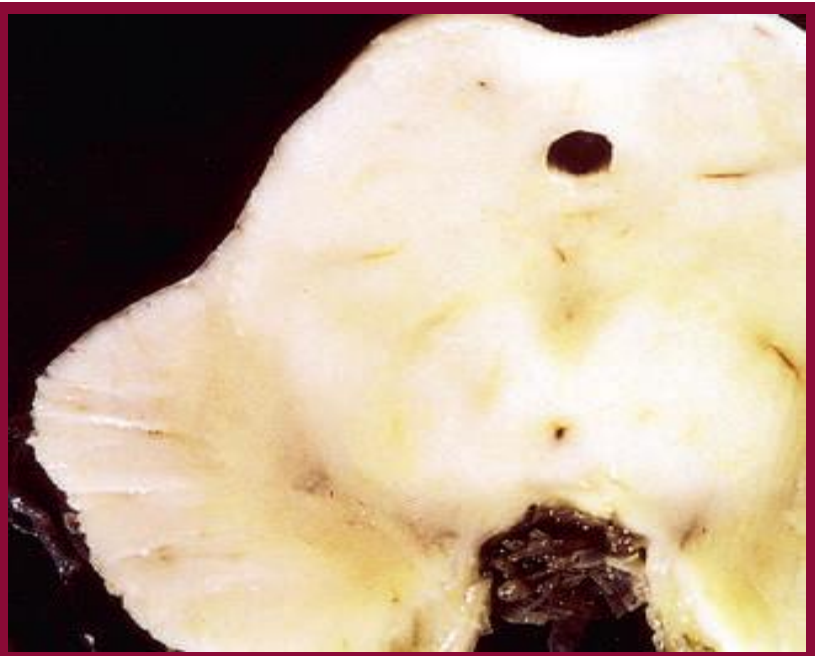


PD– Clinical

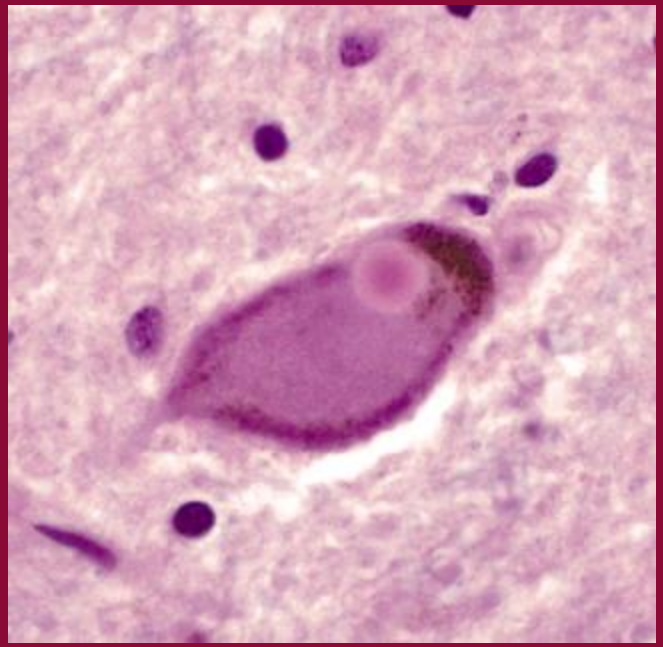
- Diagnosis is based on a triad of (tremor, rigidity, & bradykinesia), in the absence of toxic injury or other etiology.
- Usually progresses over 10 to 15 years, eventually producing severe motor slowing → near immobility.
- Death usually is the result of aspiration pneumonia or trauma from falls caused by postural instability.
- Movement symptoms initially respond to L-dihydroxyphenylalanine (L-DOPA), but it does not slow disease progression. Over time, L-DOPA becomes less effective.

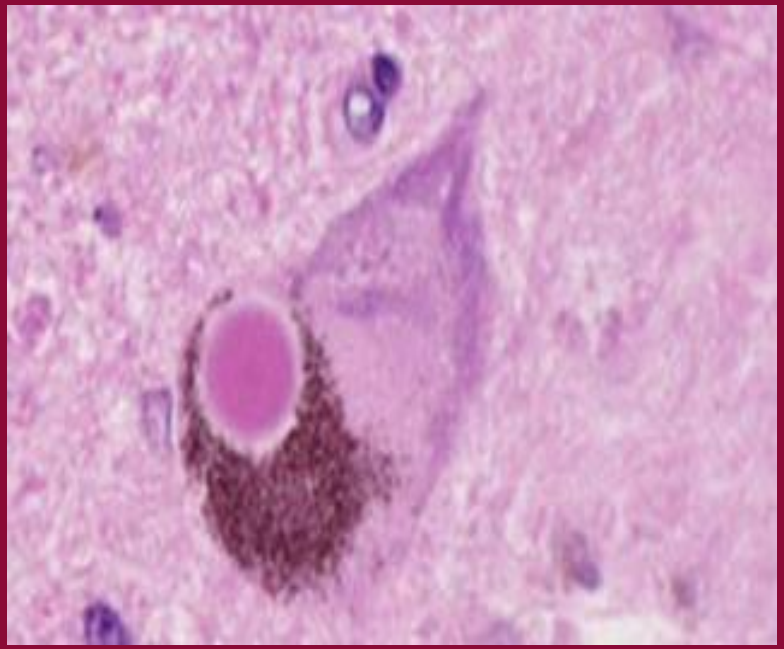
At autopsy is pallor of the substantia nigra and locus ceruleus, due loss of pigmented catecholaminergic neurons.



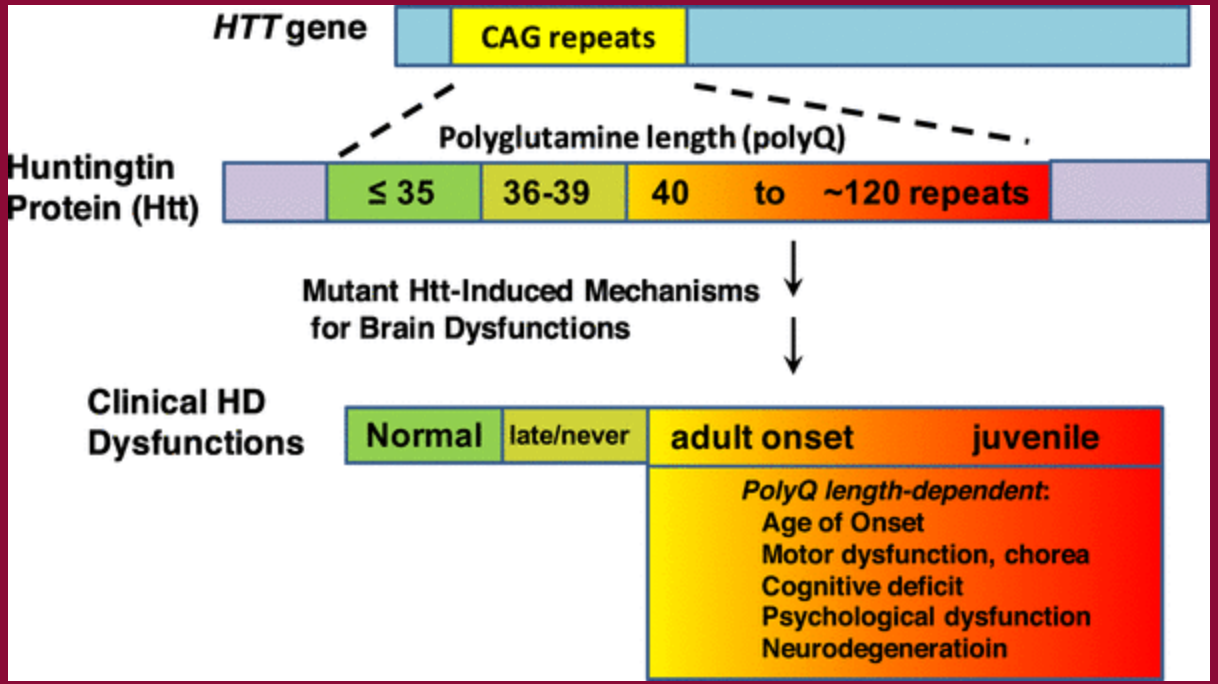


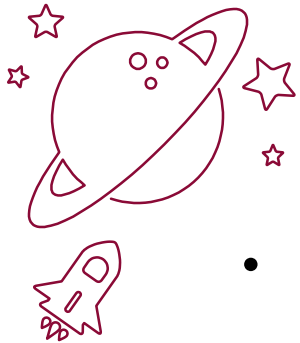
Areas of neuronal loss show gliosis. Lewy bodies found in those neurons that remain; single or multiple, cytoplasmic, eosinophilic, round inclusions (dense core with pale halo)





Huntington Disease (HD)





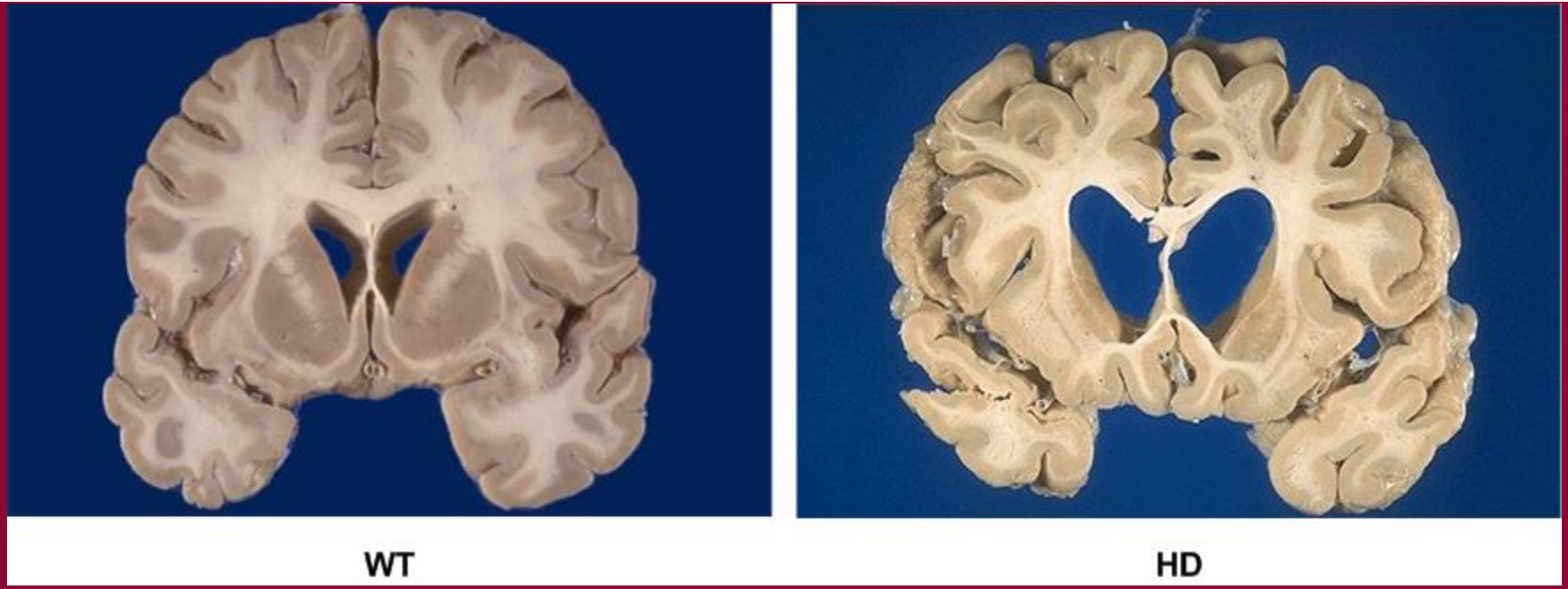
Huntington Disease-HD

- An autosomal dominant disease of progressive movement disorders & dementia caused by degeneration of the striatal neurons (caudate and putamen).
- Characterized by involuntary jerky movements (dystonic sometimes) of all parts of the body→ **Chorea.**
- Relentlessly progressive, resulting in death after an average 15 years.
- No sporadic form.

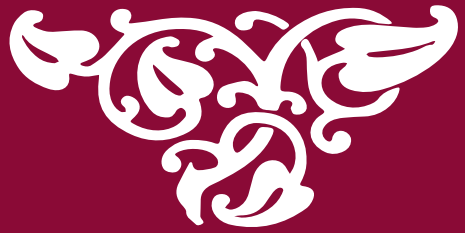
HD – Pathogenesis

- HD is caused by CAG **trinucleotide repeat expansions** in a gene on ch. 4 encodes the protein **Huntingtin**.
- Normal alleles contain 6 to 35 copies of the repeat; in HD the number of repeats is increased.
- A strong genotype-phenotype correlation → larger numbers of repeats resulting in earlier-onset disease. (average 40-50)
- Repeats occur during spermatogenesis → paternal transmission is associated with earlier onset in the next generation → **anticipation**.
- Mutant protein aggregates are potentially injurious.

The brain is small and shows striking atrophy of the caudate nucleus and, sometimes, the putamen. The lateral and third ventricles are dilated.

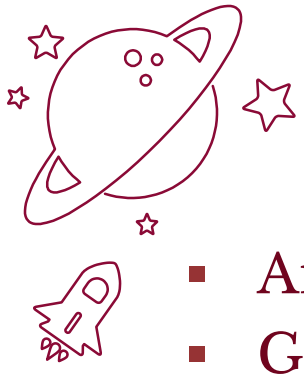


Spinocerebellar Degenerations



Spinocerebellar Degenerations

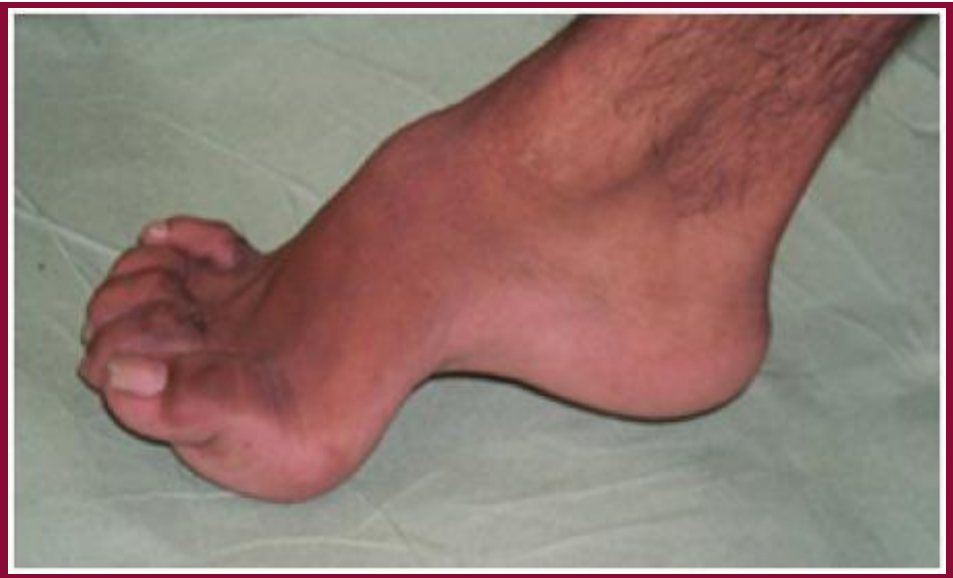
- A heterogeneous group of diseases that involve the cerebellum & components of the nervous system.
- Distinguished from one another based on causative mutations, patterns of inheritance, age at onset, and signs and symptoms.
- Degeneration of neurons, often without distinctive histopathologic changes, only with mild gliosis.
- There is a series autosomal dominant (AD) disorders → Spinocerebellar ataxias (SCAs) and the two most common autosomal recessive(AR)ones; Friedreich Ataxia & Ataxia-Telangiectasia

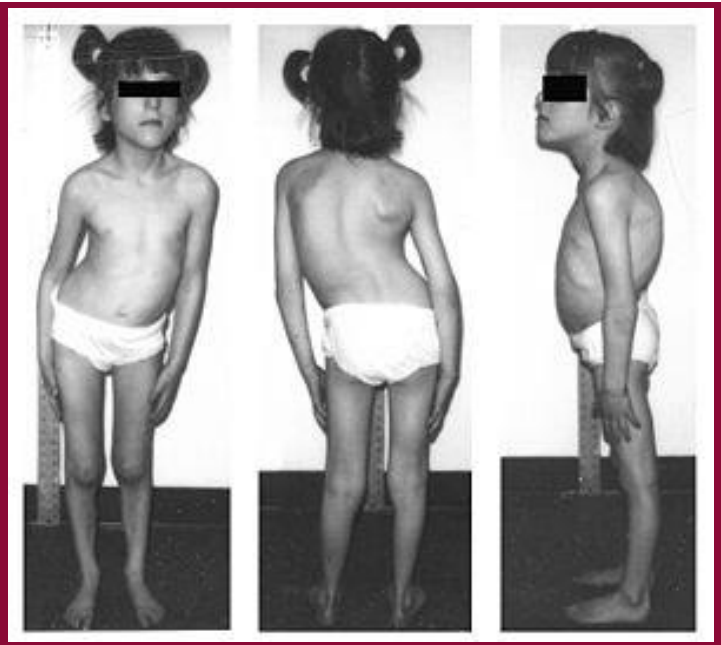


Friedreich ataxia

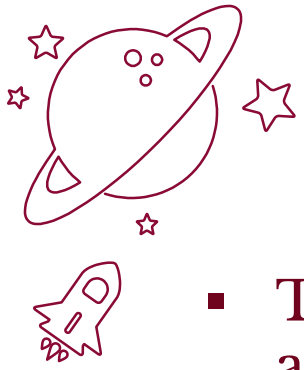
- An AR disorder that manifests in the first decade of life.
- Gait ataxia, followed by hand clumsiness & dysarthria.
- Caused by a GAA trinucleotide repeat expansion in the gene encoding **frataxin**, a protein that regulates cellular iron levels,(in mitochondria).
- The repeat expansion results in decreased protein levels through transcriptional silencing. Decreased frataxin leads to mitochondrial dysfunction as well as increased oxidative damage

Most patients develop pes cavus and kyphoscoliosis, & there is a high incidence of cardiac disease and diabetes.





Amyotrophic Lateral Sclerosis (ALS)



Amyotrophic Lateral Sclerosis (ALS)

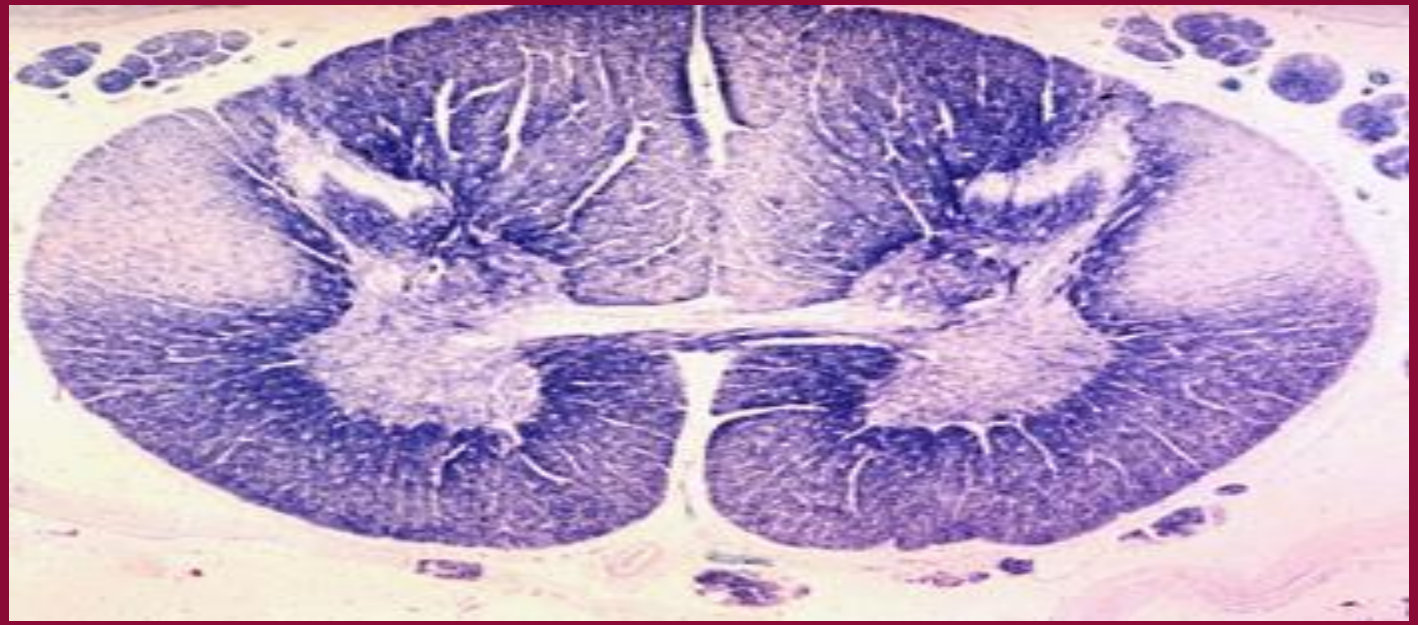
- The most common neurodegenerative disease affecting the motor system.
- A-Myo-trophic-lateral (corticospinal tracts –lateral column in spinal cord (SC))-sclerosis.
- A progressive disorder of loss of upper motor neurons in the cerebral cortex (Betz cells) and lower motor neurons in the SC and brainstem.
- Male slightly more than females, 5th decade & later.
- Sporadic 80% more common than familial.

ALS – pathogenesis

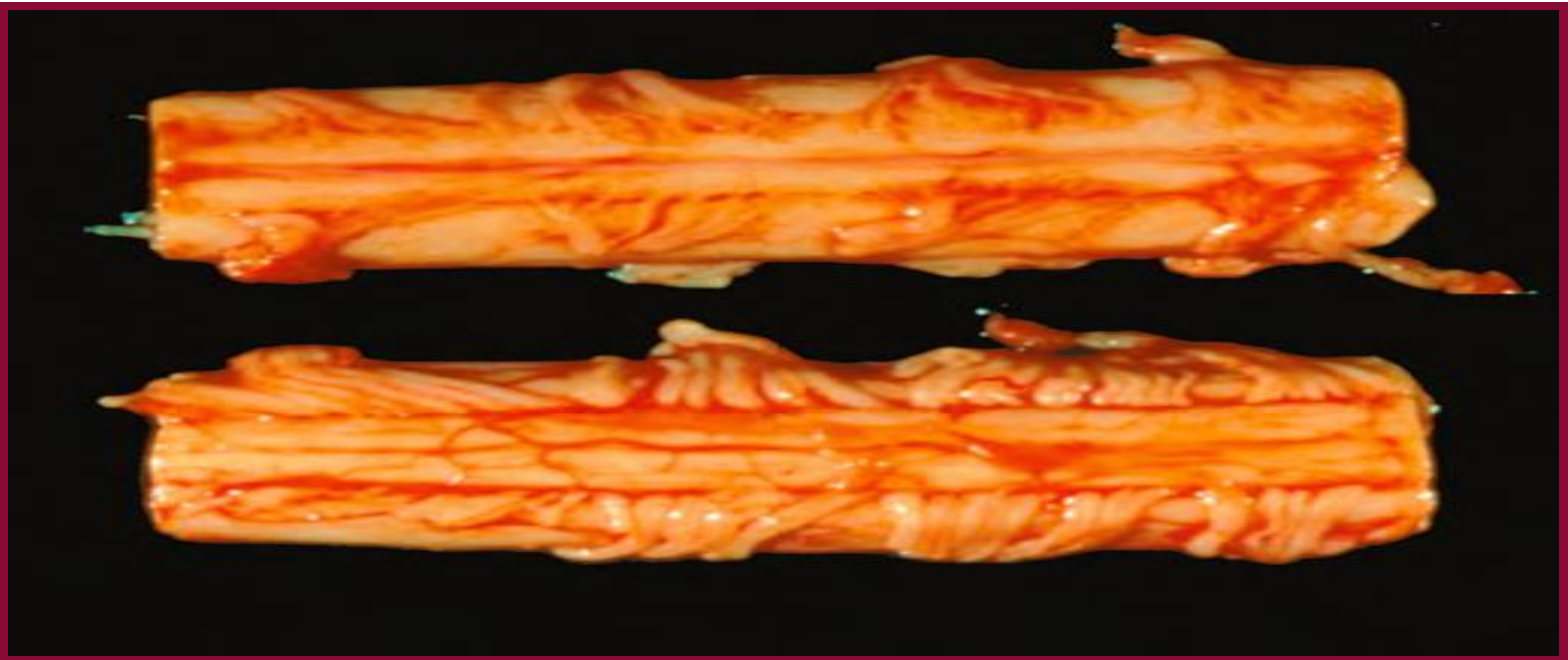
- Mutations in the superoxide dismutase gene, *SOD1*, on chr. 21 were the first identified genetic cause of ALS.
- Abnormal misfolded forms of the SOD1 protein are generated→ trigger 'unfolded protein response' in cells → apoptosis.

I. Death of **upper motor** neurons, causes degeneration of the descending corticospinal tracts.
II. Death of anterior horn cells (**lower motor** neurons) with loss of innervation causes atrophy of skeletal muscles.

Loss of the upper motor neurons leads to degeneration of the corticospinal tracts, resulting in volume loss and absence of myelinated fibers.



Segment of spinal cord viewed from anterior (upper) and posterior (lower) surfaces showing attenuation of anterior (motor) roots compared with posterior (sensory) roots.



ALS – Clinical

- Early symptoms include **asymmetric weakness of the hands (**dropping objects & difficulty performing fine motor tasks).
- Later, muscle strength & bulk diminish & involuntary contractions of individual motor units (**fasciculations)** occur.
- Eventual **respiratory muscles involvement** cause recurrent pulmonary infection, which is the usual cause of death.

Acquired metabolic diseases

- Because of its high metabolic demands, the brain is vulnerable to nutritional diseases & alterations in metabolic state.
- Metabolic disarray may disrupt the brain function but without detectable morphological changes.
- Severe hypoglycemia may result to necrosis while hyperglycemia can lead to confusion, stupor and eventually coma.
- Certain vitamin deficiency affect the brain.

Thiamine deficiency (Vitamine B1)

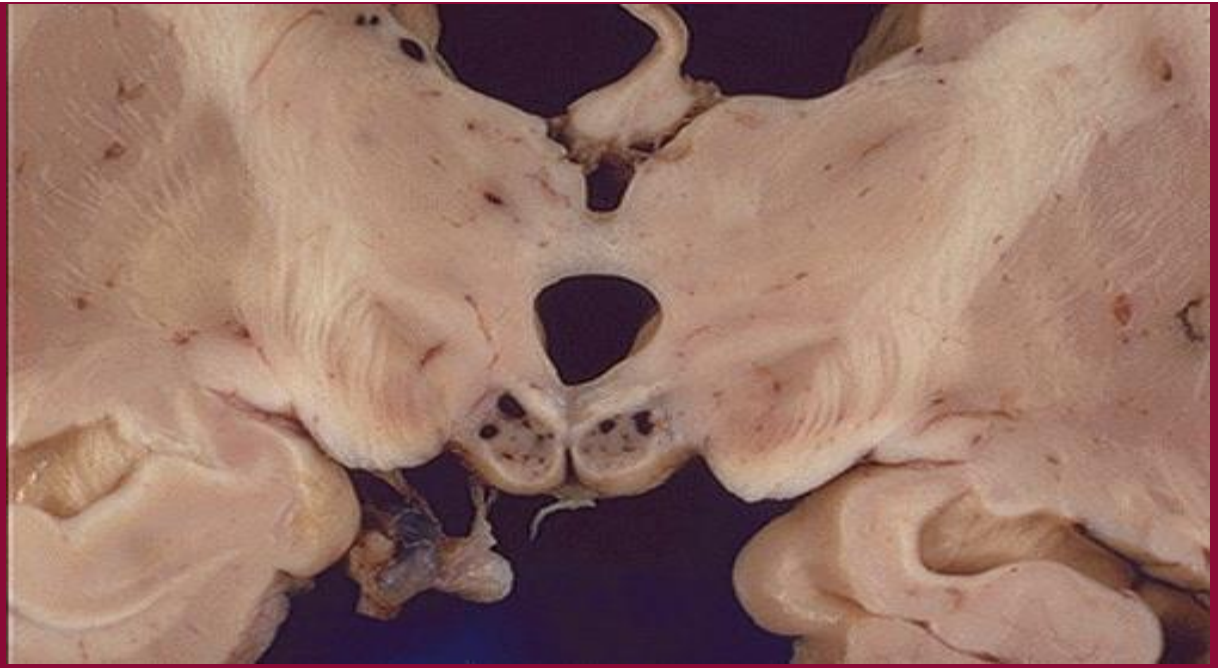
Wernicke encephalopathy

- Acute appearance of a combination of psychotic symptoms and ophthalmoplegia.
- Reversible when treated with thiamine.
- If this is unrecognized and untreated → irreversible syndrome →

Korsakoff syndrome

- Disturbances of short term memory & confabulation.
- Both are common in chronic alcoholism.
- Also thiamine deficiency from gastric disorders (carcinoma, chronic gastritis, or persistent vomiting)

Wernicke encephalopathy is characterized by foci of hemorrhage and necrosis in the mamillary bodies and the walls of the third and fourth ventricles.

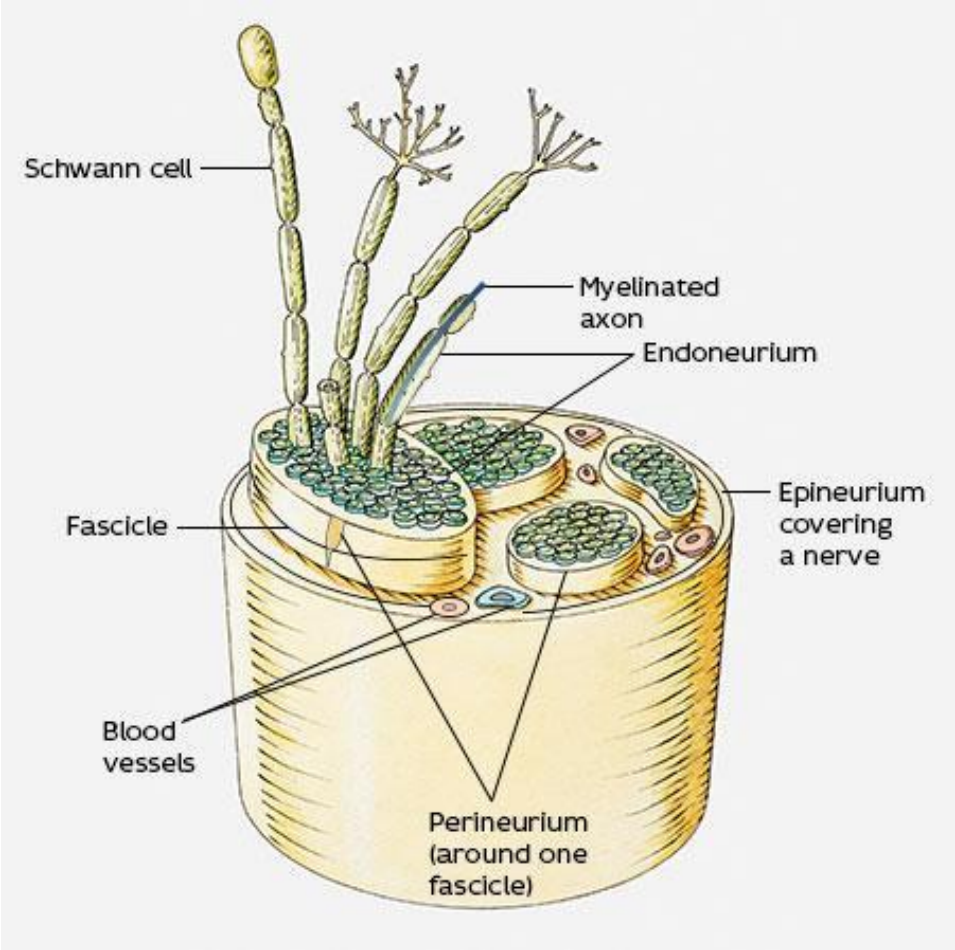


Vitamine B12 deficiency

Subacute combined degeneration of the spinal cord.

- Degeneration of both ascending & descending spinal tracts, caused by a defect in myelin formation.
- Symptoms (over a few weeks) initially bilaterally symmetrical numbness, tingling, & slight ataxia in the lower extremities, may progress to include spastic weakness of the lower extremities → later paraplegia.
- With vitamin replacement, clinical improvement occurs; however, once complete paraplegia has developed, recovery is poor.

Peripheral Nervous system Pathology



Axons are bundled
together by three major connective tissue components: + the *epineurium*: encloses the entire nerve.
+ the *perineurium*:
a multilayered concentric connective tissue sheath
that groups subsets of axons into fascicles.
+*endoneurium*: surrounds individual nerve fibers

Peripheral neuropathies are subclassified as:

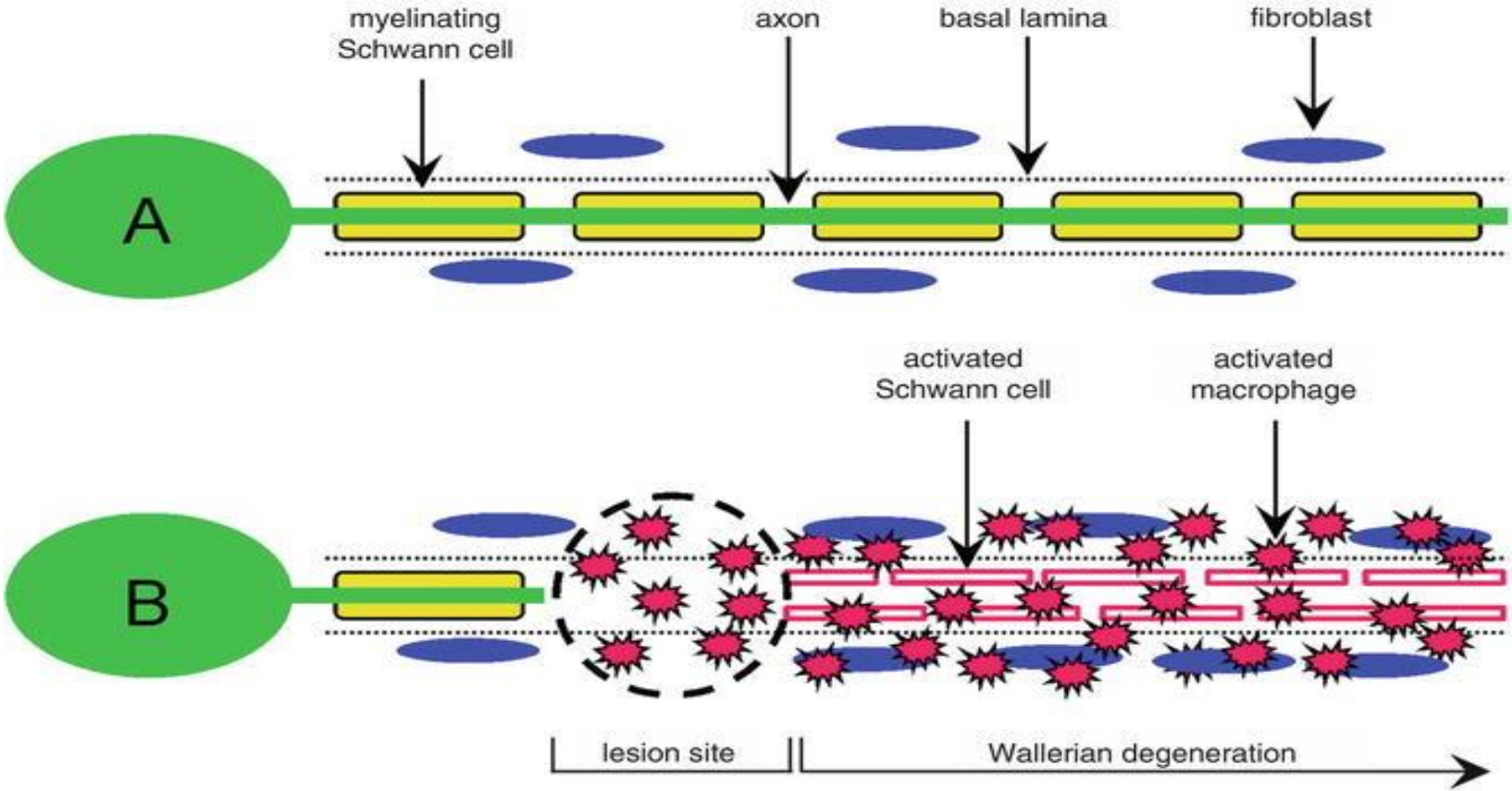
Axonal neuropathies:

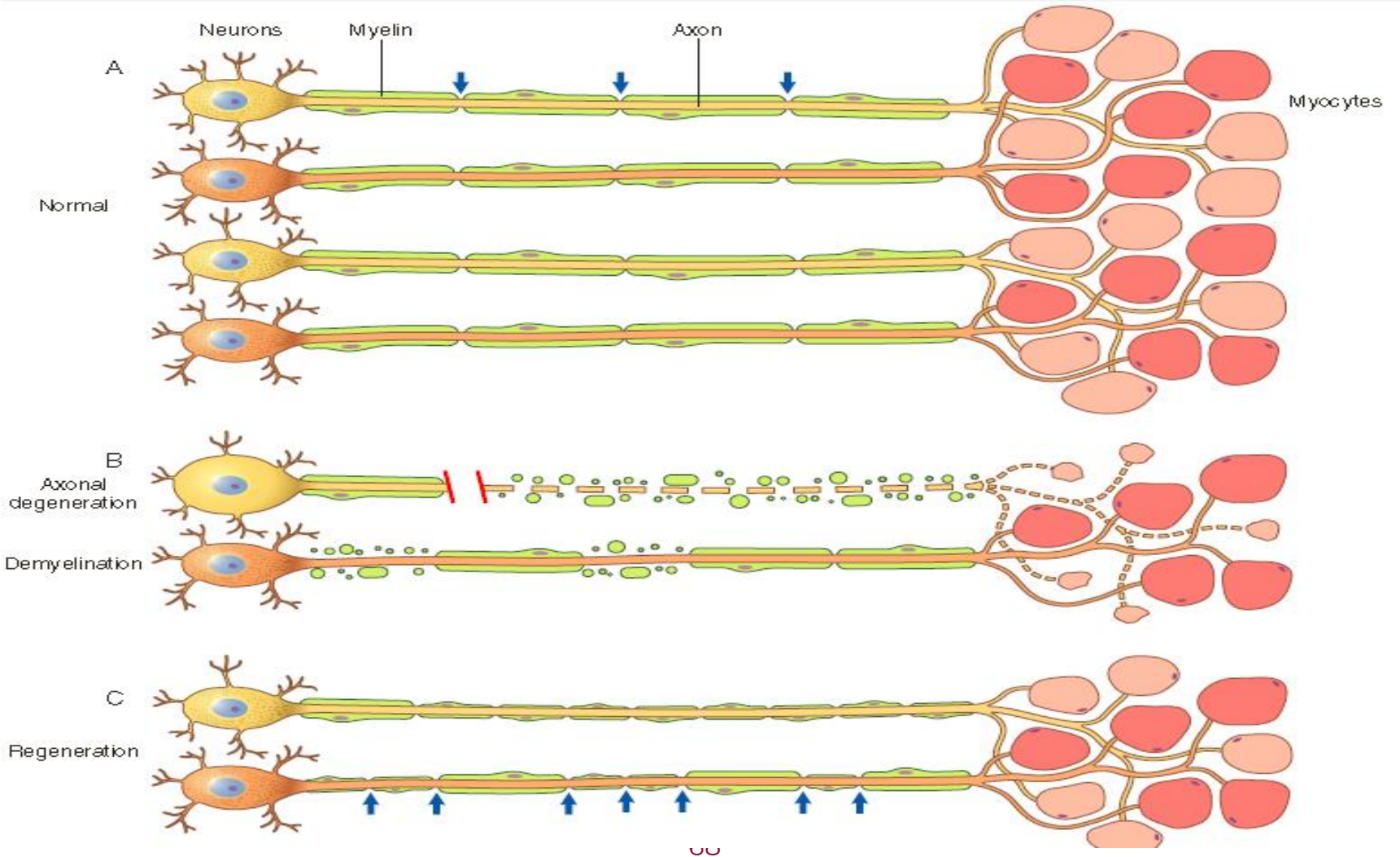
Caused by insults that directly injure the axon. The entire **distal** portion of an affected axon degenerates. Secondary myelin loss can happen . **(Wallerian degeneration**)

Demyelinating neuropathies

Damage to Schwann cells or myelin with relative axonal sparing.

Typically occurs discontinuously → **segmental demyelination**


myelinating
Schwann cell
axon
basal lamina
fibroblast
A
activated
Schwann cell
activated
macrophage
B
lesion site
Wallerian degeneration


Neurons
Myelin
Axon
A
Normal
Myocytes
B
Axonal degeneration
Demyelination
C
Regeneration

Axonal neuropathies

- Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon, where the proximal stump of the axon sprouts and elongate.

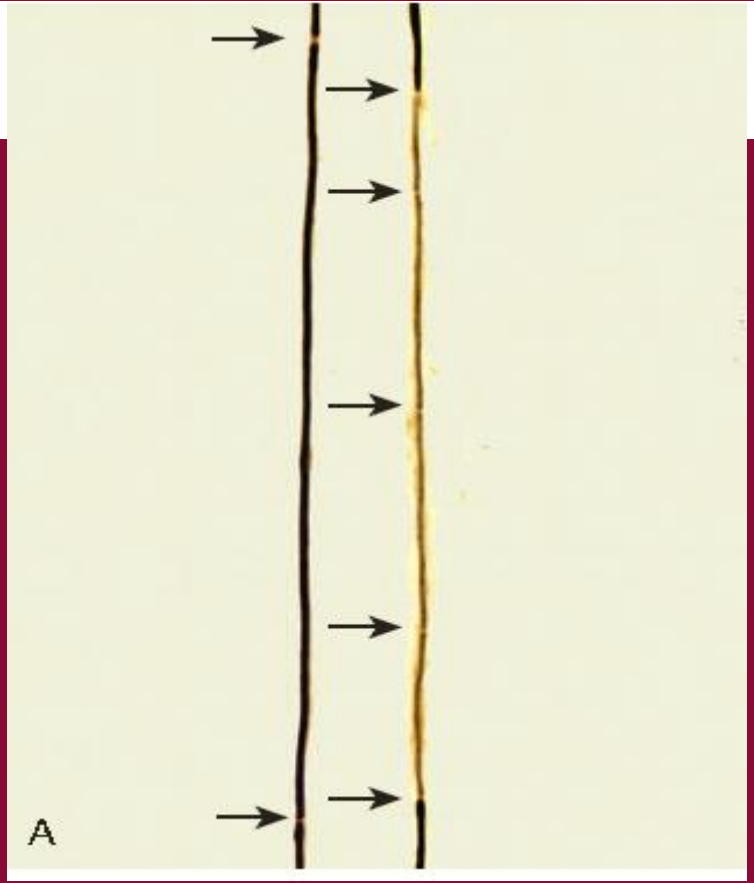
- The morphologic hallmark of axonal neuropathies is a decrease in the density of axons, which in electrophysiologic studies correlates with a decrease in the signal strength or amplitude of nerve impulses.

Demyelinating neuropathies

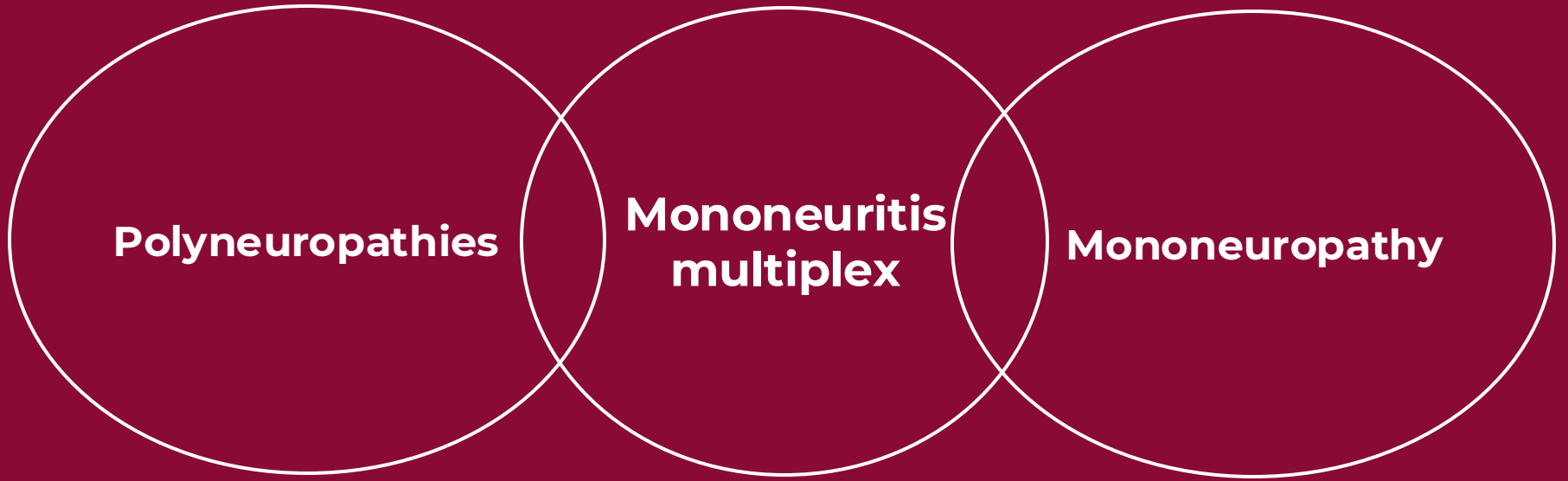
- Segmental demyelination: affecting individual internodes along the length of an axon (while saving others) in a random pattern.
- Resulting in slow nerve conduction velocities but preserved amplitude, with relatively normal density of axons.

Demyelinating neuropathies

- Denuded axon provides a stimulus for remyelination & cells within the endoneurium differentiating to replace injured Schwann cells.
- Regeneration gives thinly myelinated internodes of uneven length (shorter).



Peripheral neuropathies anatomic patterns.



Polyneuropathies

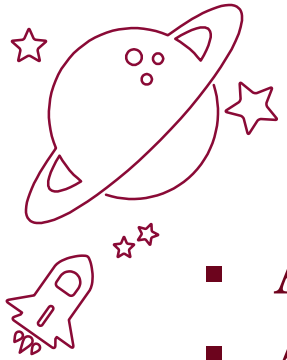
- A symmetrical multiple nerves involvement, length-dependent fashion.
- Axonal loss is more pronounced in the distal segments of the longest nerves.
- Patients present with loss of sensation and paresthesias that start in the toes and spread upward. “stocking-and-glove” distribution.
- This pattern is often encountered with toxic and metabolic damage. (Diabetes mellitus)

Simple & multiplex Mononeuritis

- **Mononeuritis multiplex**: the damage randomly affects individual nerves, resulting (eg. A right radial nerve palsy & wrist drop, & at a separate point in time, a left foot drop. Often caused by vasculitis.

- **A simple mononeuropathy:** only involves a single nerve & is most commonly the result of traumatic injury, entrapment (e.g., carpal tunnel syndrome), or certain infections such as Lyme disease.

Etiologic Category	Causative Disorders/Agents
Nutritional and metabolic	Diabetes mellitus Uremia Vitamin deficiencies—thiamine, vitamin B6, vitamin B12
Toxic	Drugs, including vinblastine, vincristine, paclitaxel, colchicine, and isoniazid Toxins—alcohol, lead, aluminum, arsenic, mercury, acrylamide
Vasculopathic	Vasculitis Amyloidosis
Inflammatory	Autoimmune diseases Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy (CIDP)
Infections	Herpes zoster Leprosy HIV infection Lyme disease
Inherited	Charcot-Marie-Tooth neuropathy, type I, type II, and X-linked Hereditary neuropathy with liability to pressure palsy
Others	Paraneoplastic, some leukodystrophies

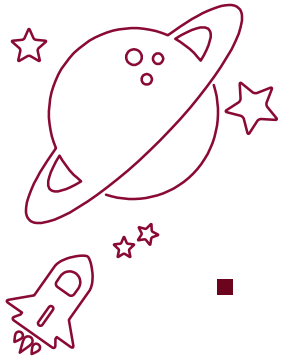


Guillain-Barré Syndrome

- Acute Inflammatory Demyelinating Polyneuropathy.
- A rapidly progressive acute demyelinating disorder characterized clinically by weakness beginning in the distal limb→ rapidly advances to proximal muscle function → “ascending paralysis”
- One of the most common life-threatening diseases of PNS, can lead to death from failure of respiratory muscles in days.

GBS – pathogenesis & morphology

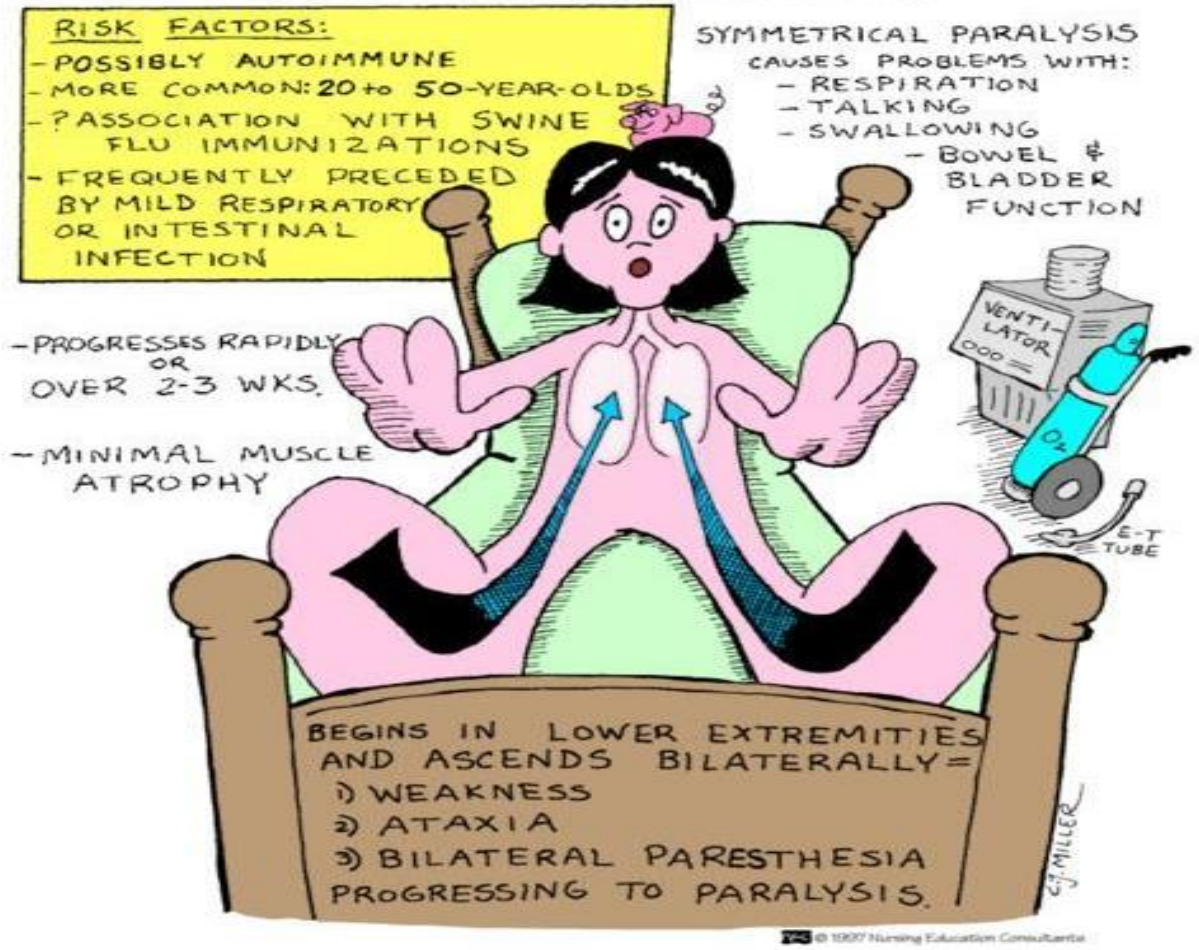
- Triggered by an infection or vaccination → breaks down self-tolerance → an autoimmune response.
- Usually acute, influenza-like illness from which the affected individual has recovered by the time the neuropathy becomes symptomatic.
- Infections with Campylobacter jejuni, CMV, Epstein-Barr virus, & Mycoplasma pneumoniae are ass with GBS
- Histological findings include Segmental demyelination & inflammation of peripheral nerves, (perivenular and endoneurial mononuclear cell infiltrates rich in macrophages).

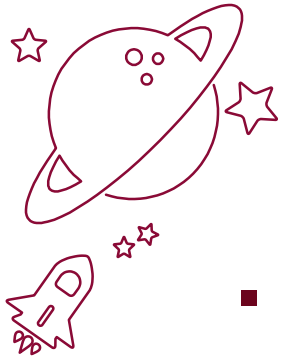


GBS- clinical

- CSF protein levels are elevated due to inflammation and altered permeability of the microcirculation within the spinal roots.
- Treatments include plasmapheresis (to remove offending antibodies), intravenous immunoglobulin, and supportive care, such as ventilatory support.
- Patients who survive the initial acute phase of the disease usually recover with time.

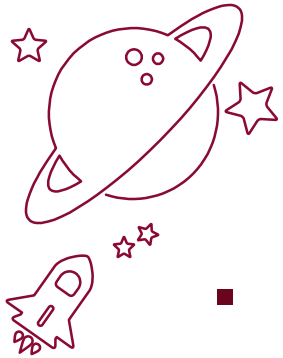
GUILLAIN-BARRE' SYNDROME





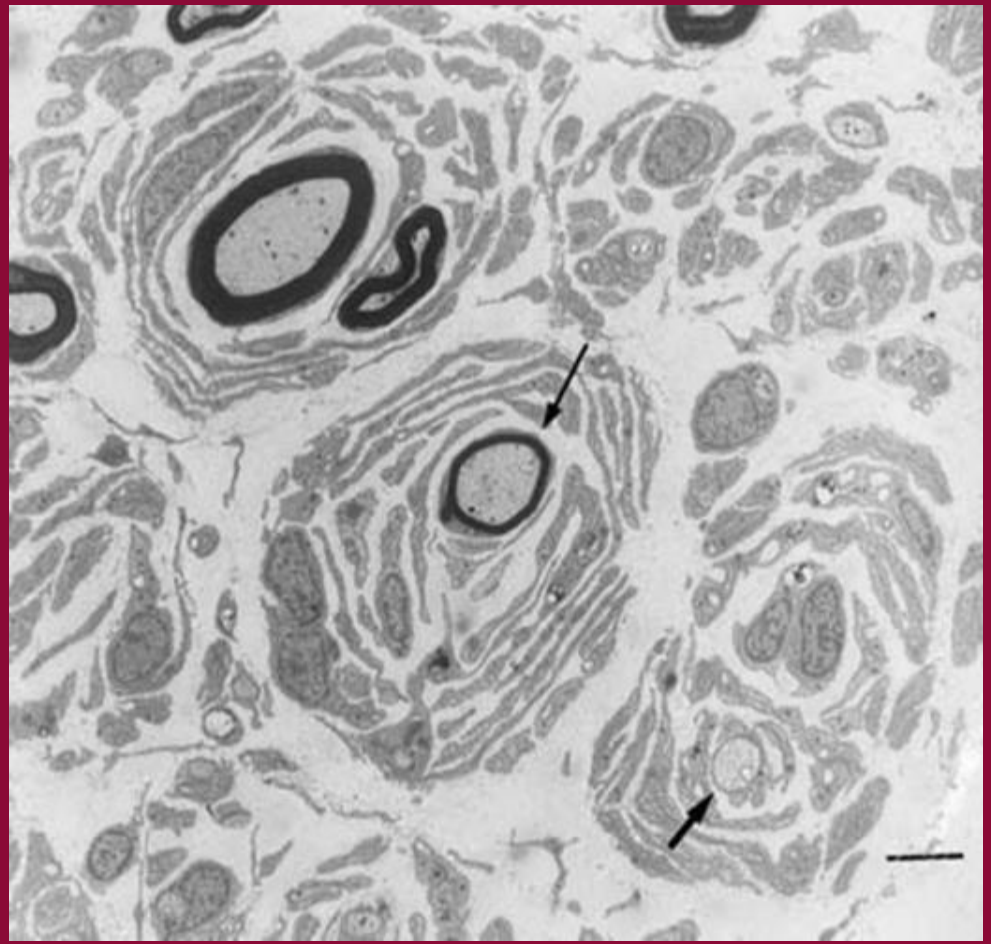
Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP)

- The most common chronic acquired inflammatory peripheral neuropathy.
- Characterized by symmetrical mixed sensorimotor polyneuropathy that persists for 2 months (at least) or more.
- Abnormalities include weakness, difficulty in walking, numbness, and pain or tingling sensations.
- CIDP is immune mediated also, but in contrast to GBS, CIDP follows a chronic relapsing-remitting, or progressive course.

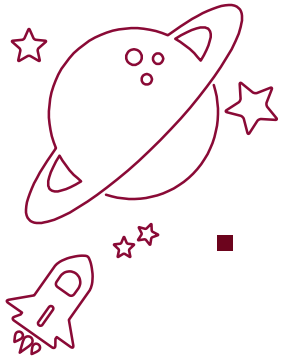


Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP)

- The peripheral nerves show segments of demyelination and remyelination.
- Tx : Plasmapheresis and administration of immunosuppressive agents. Some patients recover completely, but more often recurrent bouts of symptomatic disease lead to permanent loss of nerve function.
- The time course and the response to steroids distinguish chronic inflammatory demyelinating polyradiculoneuropathy from Guillain-Barré syndrome.



In long-standing cases, repeated activation and proliferation of Schwann cells result in the concentric arrangement of multiple Schwann cells around individual axons to produce multilayered structures → **onion bulbs**.



Diabetic Peripheral Neuropathy

- **Diabetes is the most common cause of peripheral neuropathy → developing with long-standing disease.**
- Includes several forms (can occur singly or together)

1. *Autonomic neuropathy* is characterized by changes in bowel, bladder, cardiac, or sexual function.

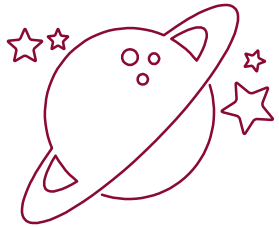
2. *Lumbosacral radiculopathy* manifests with asymmetric pain that can progress to lower extremity weakness & muscle atrophy.

3. *Distal symmetric sensorimotor polyneuropathy* is the most common form of diabetic neuropathy.

Diabetic Peripheral Neuropathy

- Sensory axons are more severely affected than motor axons → a presentation dominated by paresthesias & numbness.
- This form results from the length-dependent degeneration of peripheral nerves & often exhibits features of both axonal & myelin injuries.
- Pathogenesis is complex; hyperglycemia → accumulation of advanced glycosylation end products(AGEs), increased levels of reactive oxygen species, microvascular injuries, & changes in axonal metabolism.
- The best therapy: Strict glycemic control.

PERIPHERAL NERVE SHEATH TUMORS

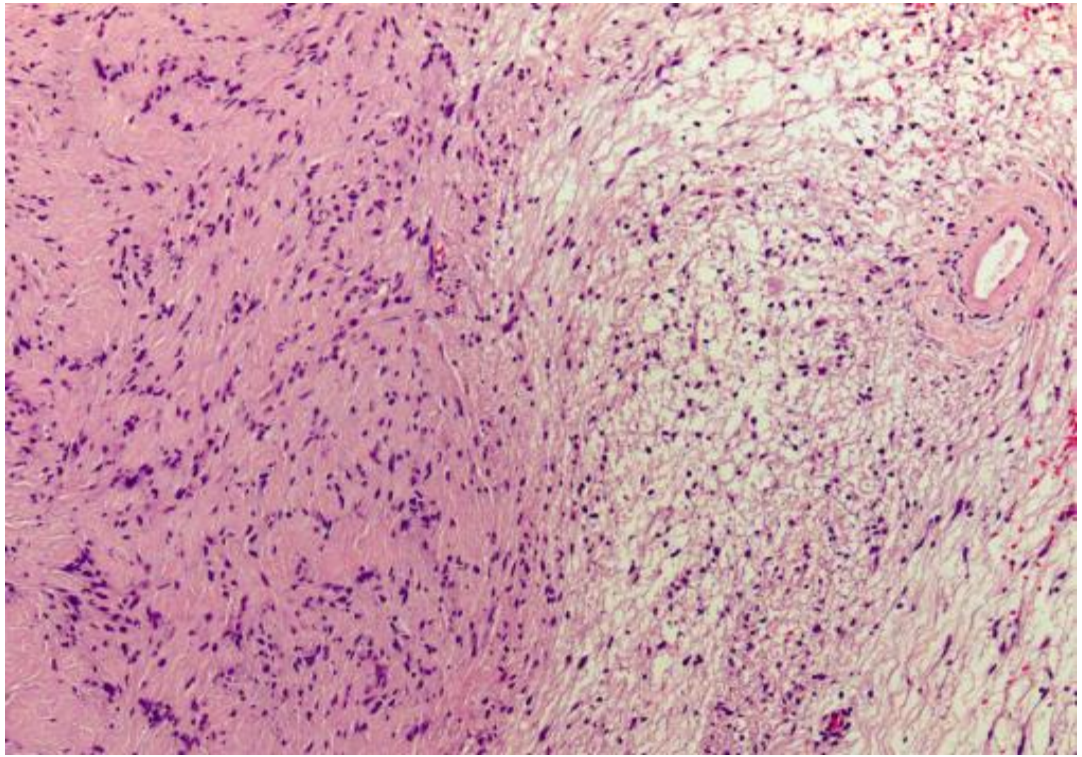


Schwannomas

- Benign encapsulated tumors that may occur in soft tissues, internal organs, or spinal nerve roots.
- The most commonly affected CN is the vestibular portion of the eighth nerve.
- Symptoms related to nerve root compression, which includes hearing loss here.
- Most are sporadic, ~10% are associated with familial neurofibromatosis type 2 (NF2)

Schwannomas - Morphology

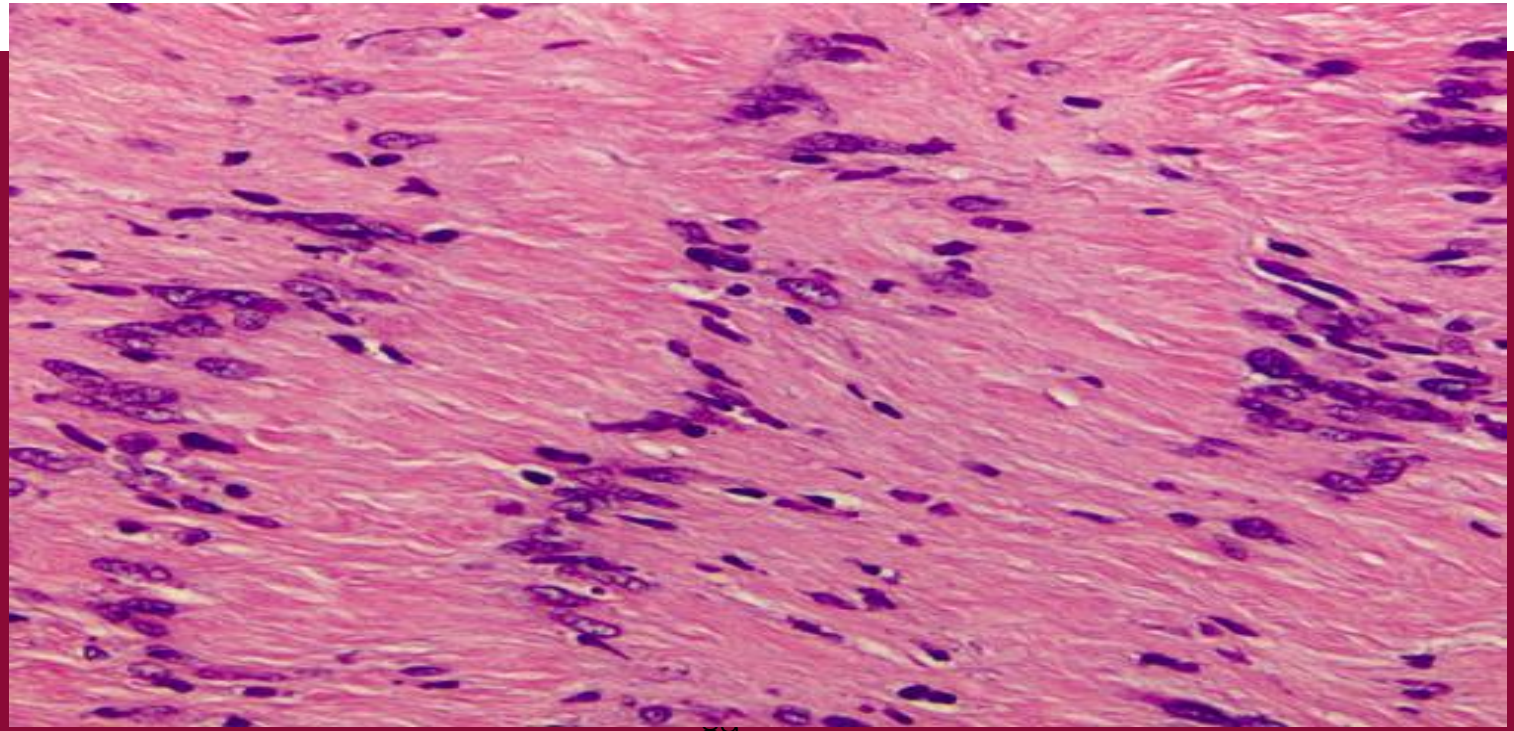
- Grossly: Circumscribed masses abutting an adjacent nerve.
- Microscopically: an admixture of dense & loose areas referred to as Antoni A and B, respectively.



Schwannomas - Morphology

- Antoni A: dense areas, bland spindle cells arranged into intersecting fascicles, often align to produce nuclear palisading →
- Verocay bodies: alternating bands of nuclear & anuclear areas.
- Antoni B: loose areas, the spindle cells are spread apart by a prominent myxoid extracellular matrix. Thick-walled hyalinized vessels often are present
- Axons are largely excluded from the tumor.
- Hemorrhage or cystic changes.

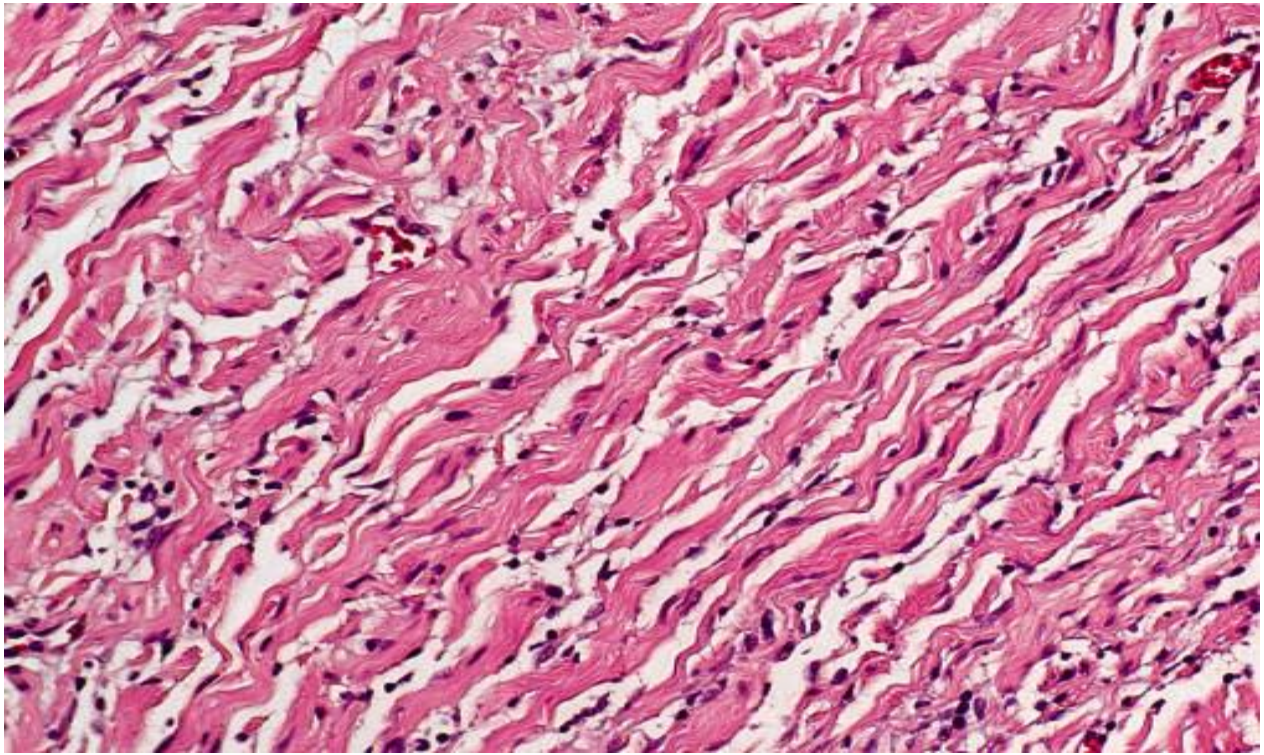
Tumor cells aligned in palisading rows → Verocay bodies:



Neurofibromas

- Neurofibromas are not encapsulated benign PNS tumor.
- Can be localized cutaneous tumors, Diffuse or Plexiform,
- In contrast to schwannomas, the neoplastic Schwann cells in neurofibroma are admixed with other cell types, mast cells, fibroblast like cells, & perineurial-like cells.
- The background stroma often contains loose wavy collagen bundles.
- Malignant Peripheral Nerve Sheath Tumors can arise from them or de novo (50% of MPNST have NF1)

Neurofibromas



Familial Neurofibromatosis

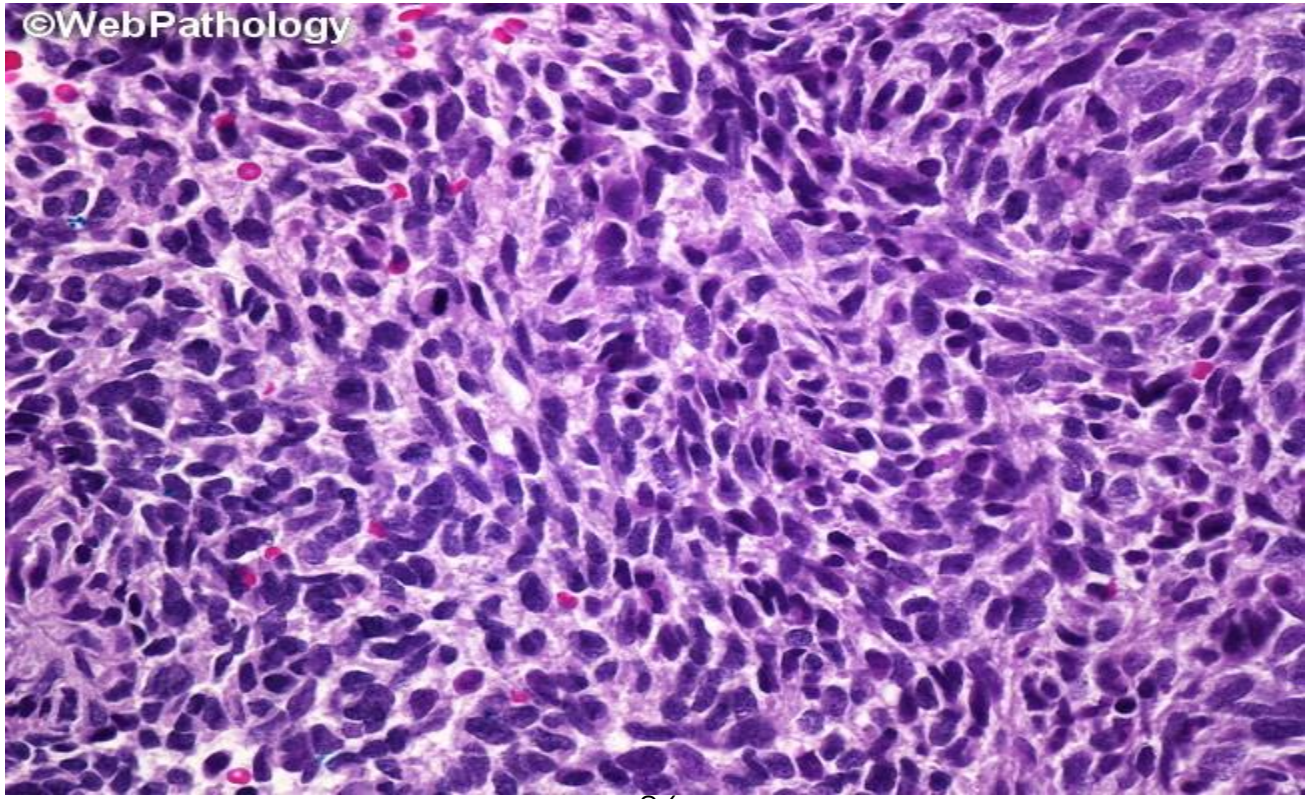
- Type 1 (1:3000)
- AD, Chr. 17
- Neurofibromas, malignant peripheral nerve sheath tumors, optic gliomas.
- pigmented nodules in iris *(Lisch nodules)*.
- pigmented skin lesions (freckling & café-au-lait spots)

- Type 2(1:40,000)
- AD, Chr. 22
- risk of developing multiple schwannomas, meningiomas, & ependymomas.
- Hearing loss, vertigo
- Multiple CN neuropathies.

Malignant Peripheral Nerve Sheath Tumors

- Neoplasms seen in adults.
- They may arise from transformation of a neurofibroma, (usually of the plexiform type).
- About one-half of such tumors arise in patients with NF1, (3-10%) of all patients with NF1 develop MPNST.
- Histologically, highly cellular and exhibit features of overt malignancy; anaplasia, necrosis, infiltrative growth pattern, pleomorphism, and high proliferative activity (mitoses).

MPNST



Questions?

“The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge.”