Degenerative diseases of CNS (2)

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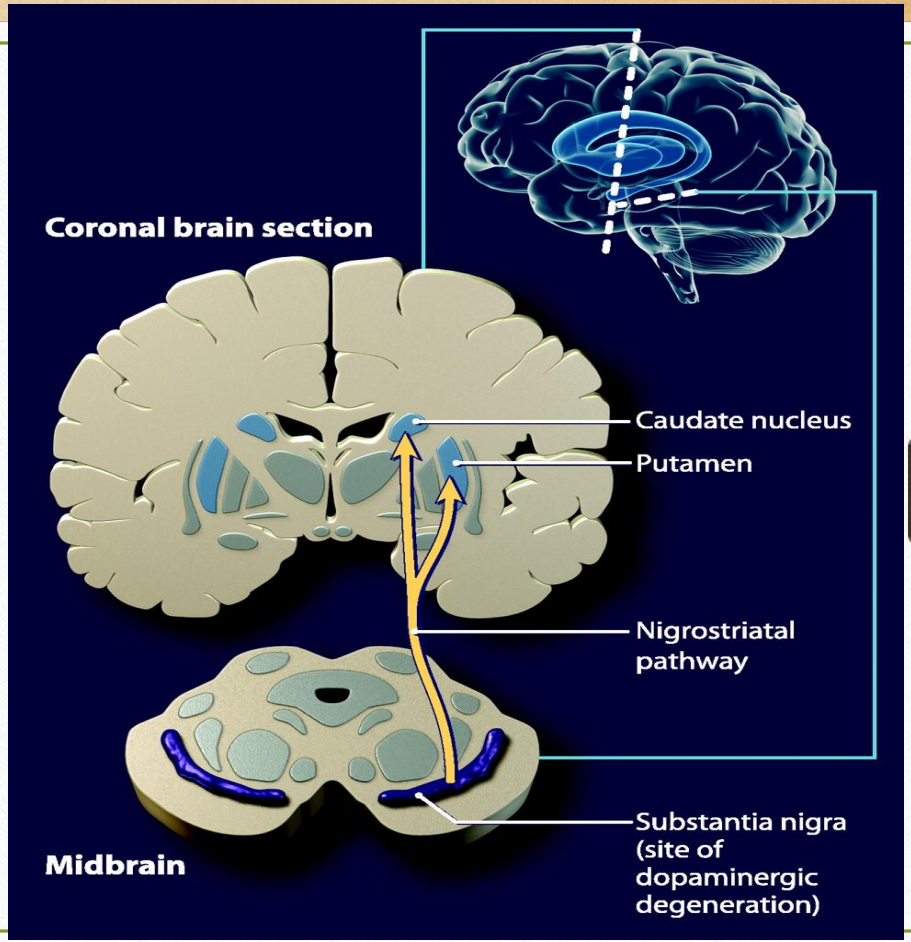
Parkinson Disease (PD)

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 a 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.

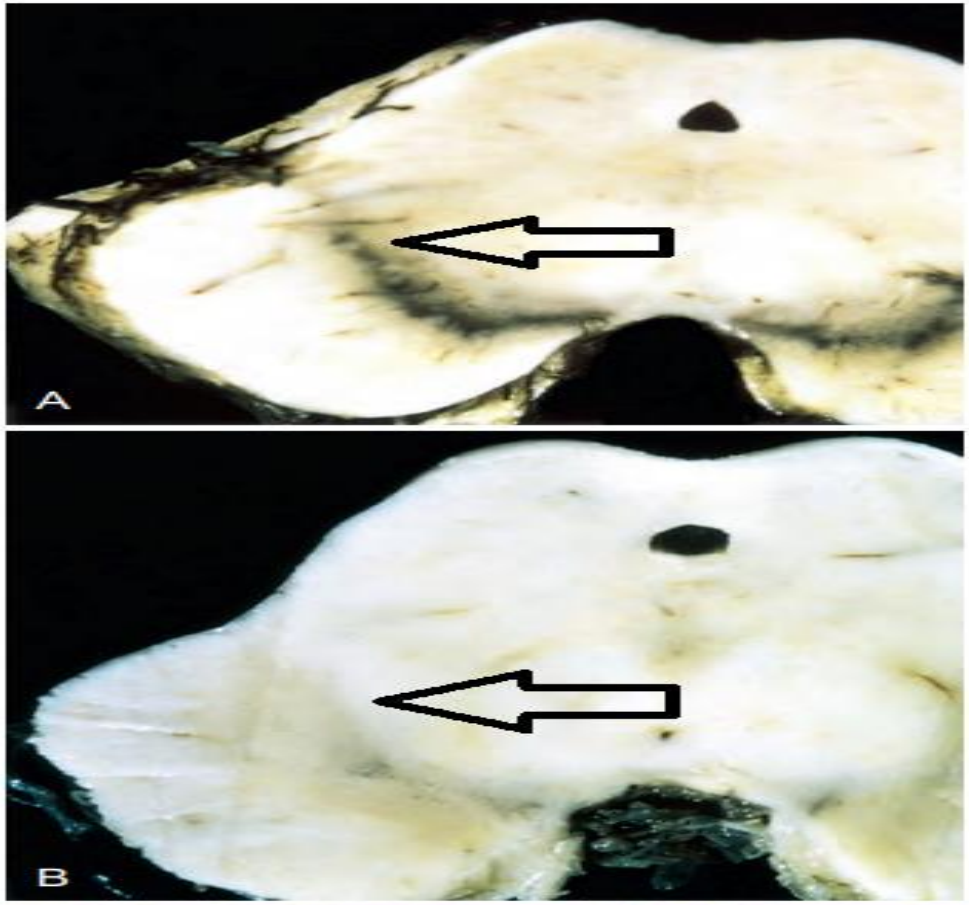
+ Abnormal protein & organelle clearance due to defects in autophagy & lysosomal degradation.

+ Dopaminergic neurons degeneration → reduction in dopamine in the striatum.

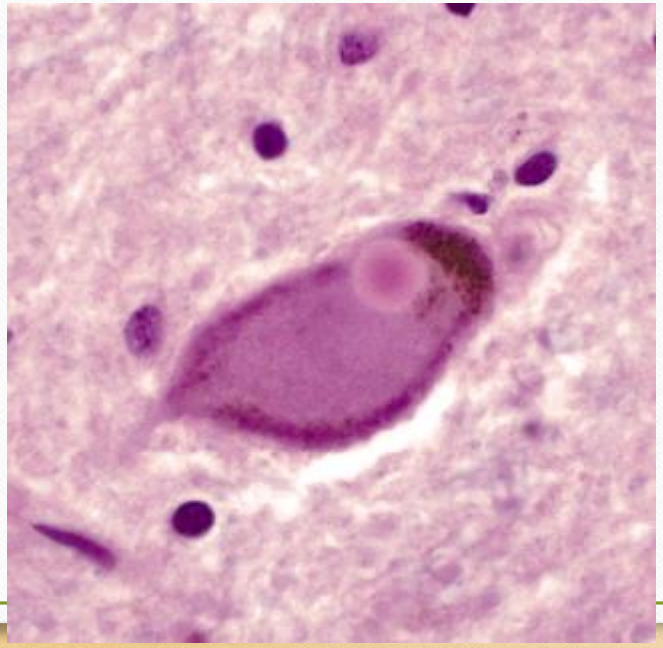
PD– Clinical

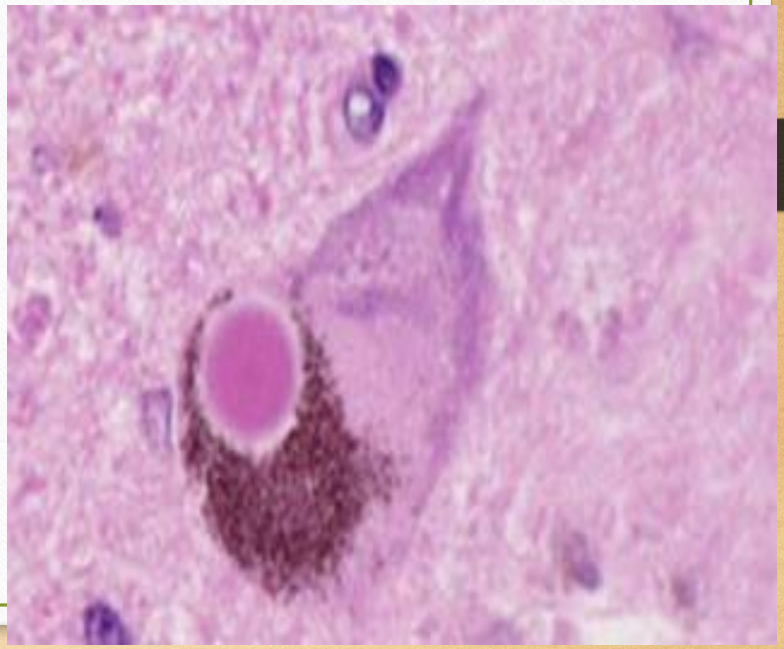
- Diagnosis is based on a triad of (tremor, rigidity, & bradykinesia), in the absence of toxic injury or other etiology.
- Usually progresses over 10 to 15 years, eventually producing severe motor slowing → near immobility.
- Death usually is the result of aspiration pneumonia or trauma from falls caused 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.

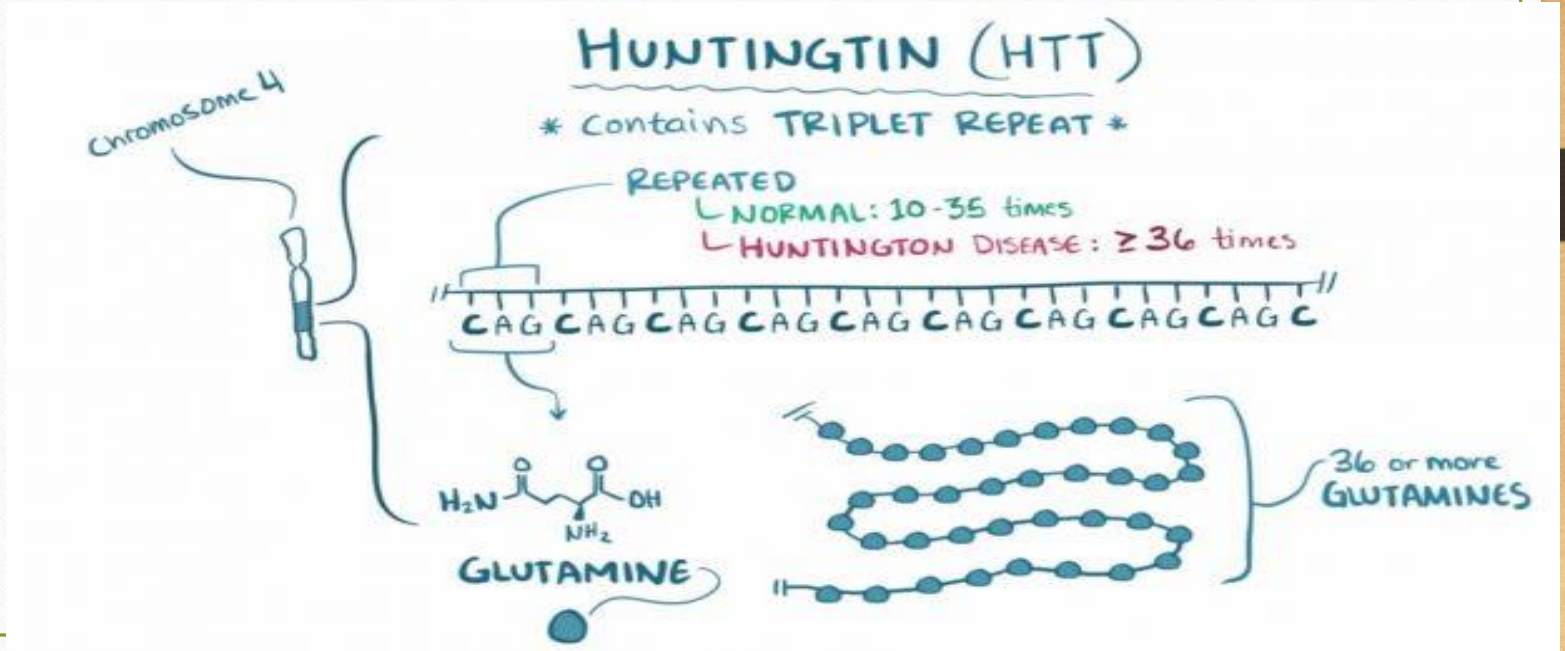


Areas of neuronal loss show gliosis. Lewy bodies found in those neurons that remain; single or multiple, cytoplasmic, eosinophilic, round inclusions (dense core with pale halo)





Huntington Disease (HD)



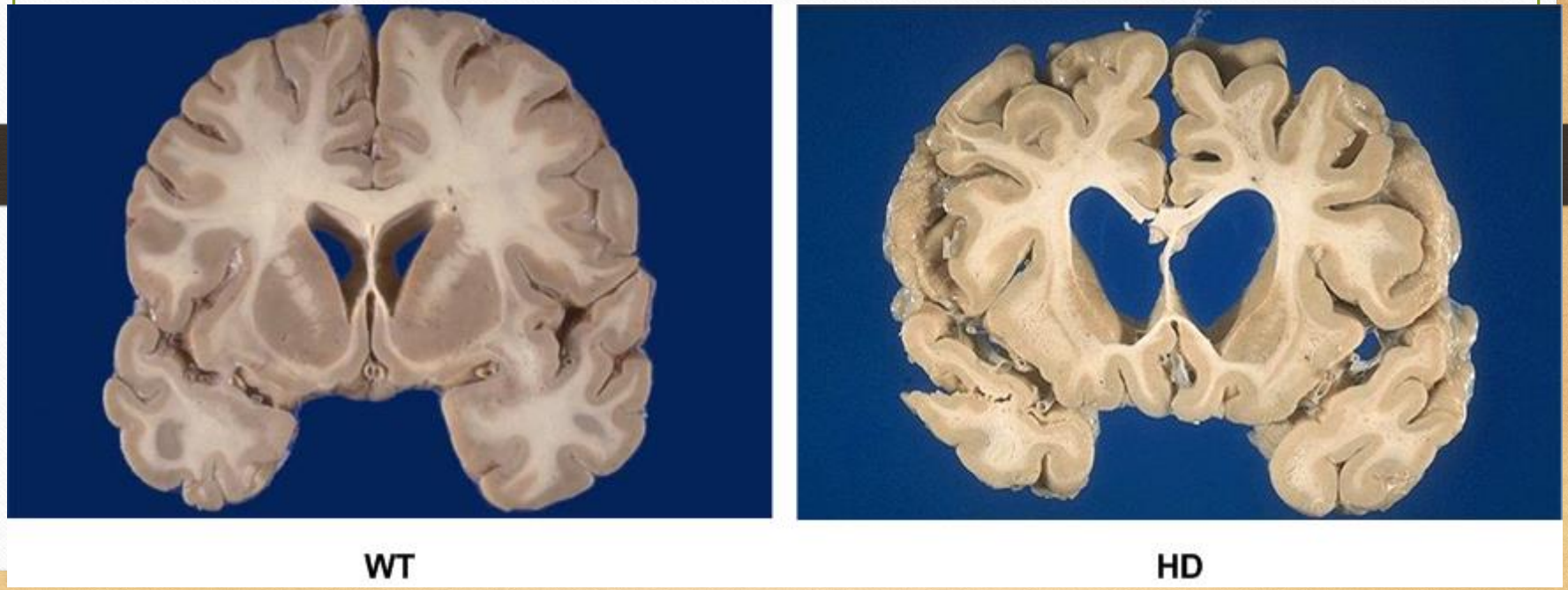
Huntington Disease-HD

- 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.



Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic Lateral Sclerosis (ALS)

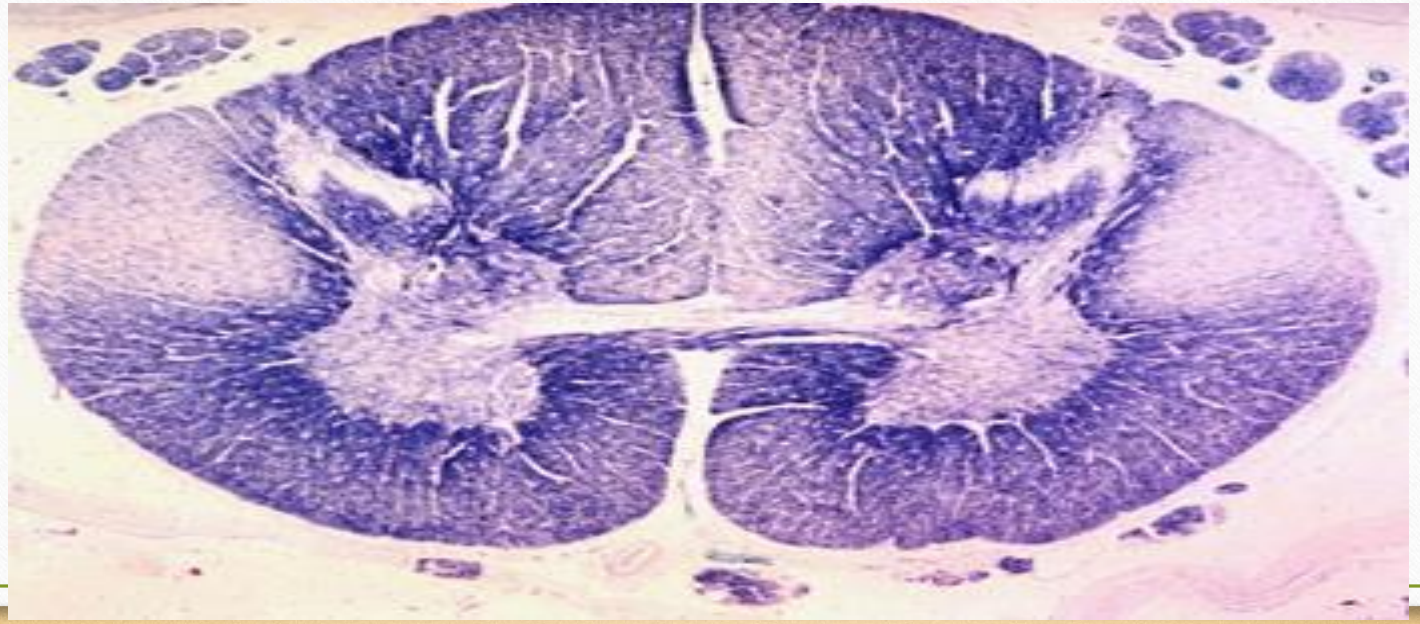
- The most common neurodegenerative disease affecting the motor system.
- A-Myo-trophic-lateral (corticospinal tracts –lateral column in spinal cord (SC))-sclerosis.
- A progressive disorder of loss of upper motor neurons in the cerebral cortex (Betz cells) and lower motor neurons in the SC and brainstem.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

ALS – pathogenesis

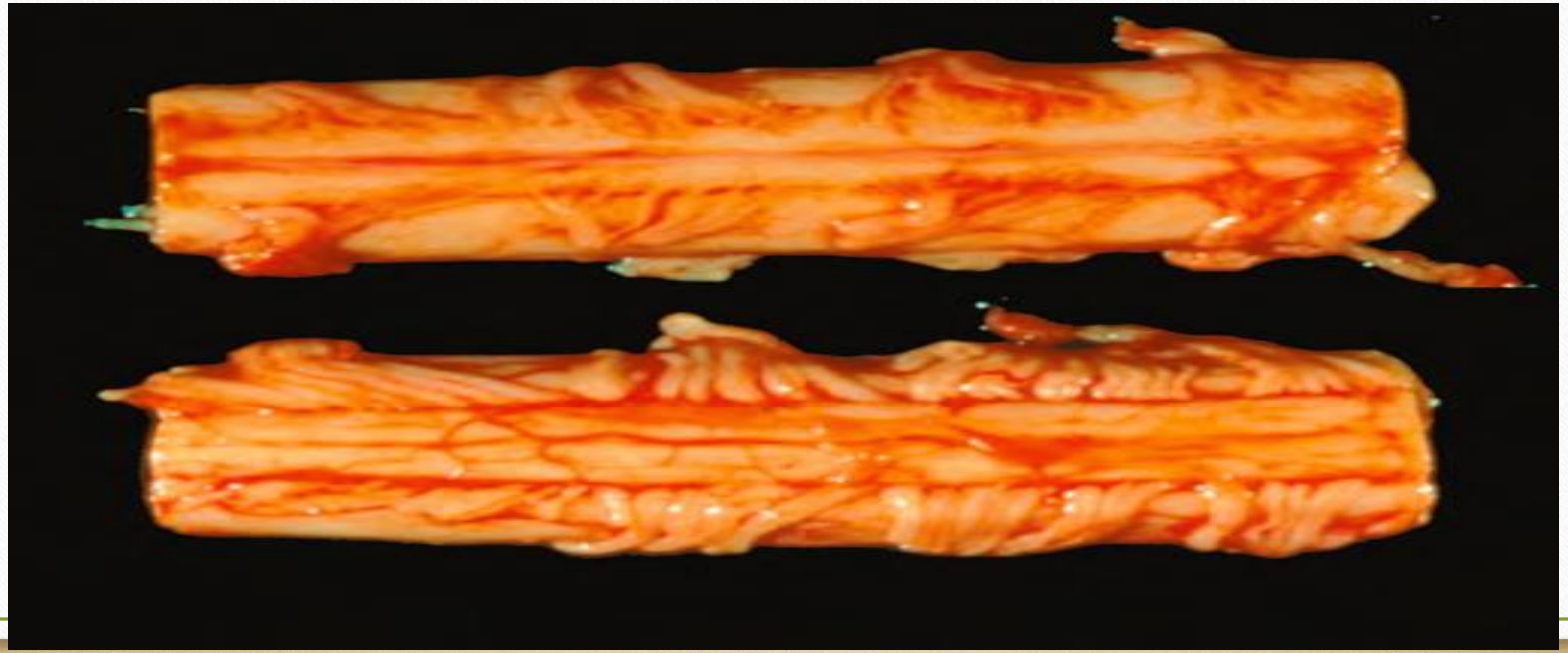
- Mutations in the superoxide dismutase gene, *SOD1*, on chr. 21 were the first identified genetic cause of ALS.
- Abnormal misfolded forms of the SOD1 protein are generated→ trigger 'unfolded protein response' in cells → apoptosis.

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)

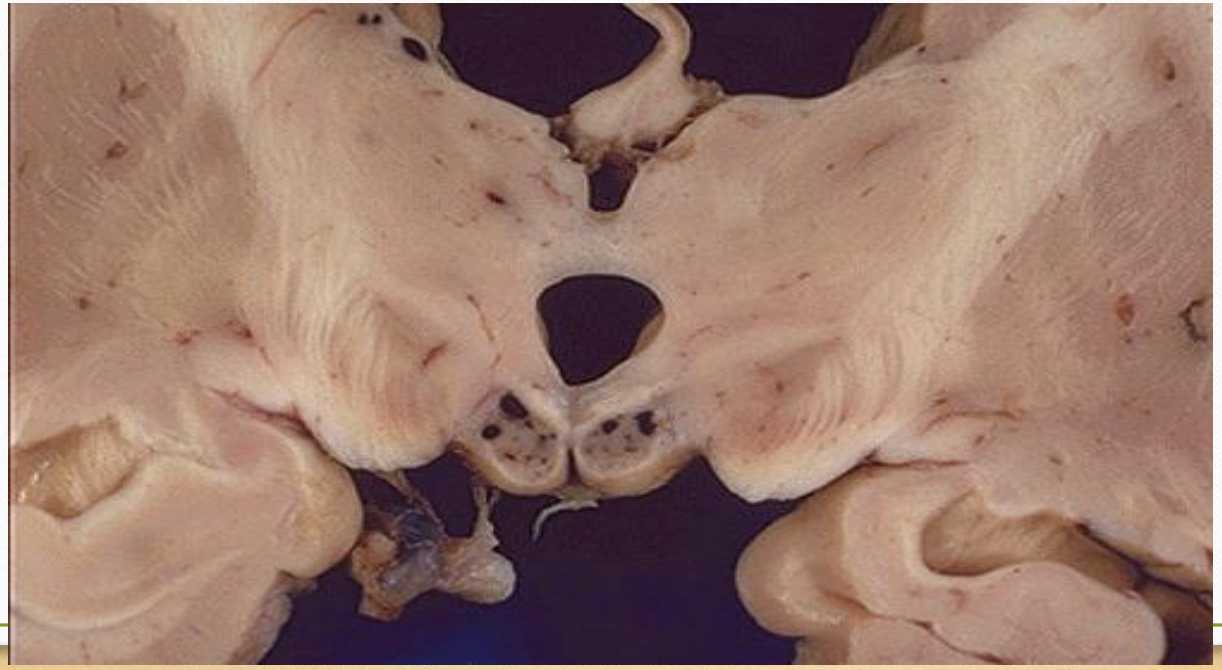
Wernicke encephalopathy

- 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.
- 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.