

NEUROSCIENCE PATHOLOGY-II

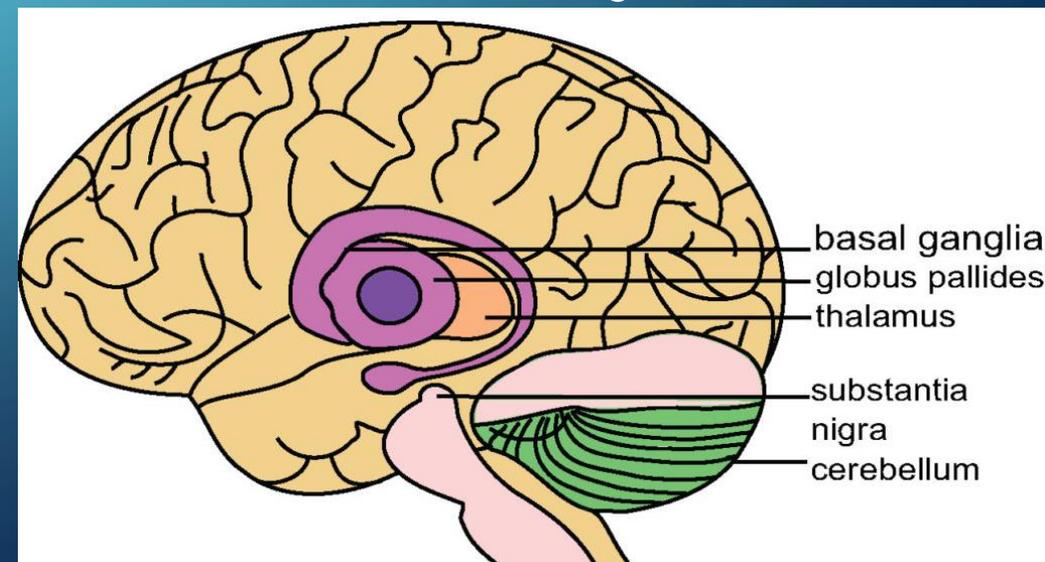
DEGENERATIVE DISEASES OF CNS



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- Movement control is accomplished by complex interactions among various groups of nerve cells in the central nervous system.
- One such important group of neurons is located in the substantia nigra in the ventral midbrain.
- Neurons of the substantia nigra communicate with neurons of the basal ganglia by liberating the neurotransmitter dopamine (DA).
- Such an interaction at the biochemical level is responsible for the fine tuning of an organism's movements.



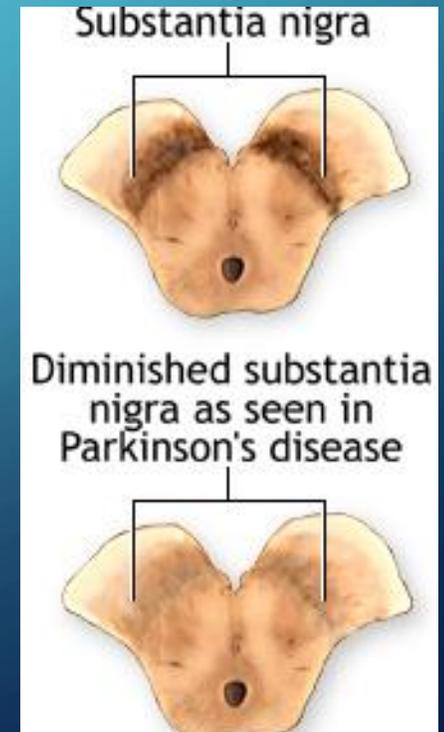
PARKINSON DISEASE (PD)

- Parkinson's disease (PD) is a complex progressive neurodegenerative disease characterized by tremor, rigidity, and bradykinesia, with postural instability appearing in some patients as the disease progresses.
- PD is the second most common neurodegenerative disease after Alzheimer's disease (AD).

PATHOGENESIS

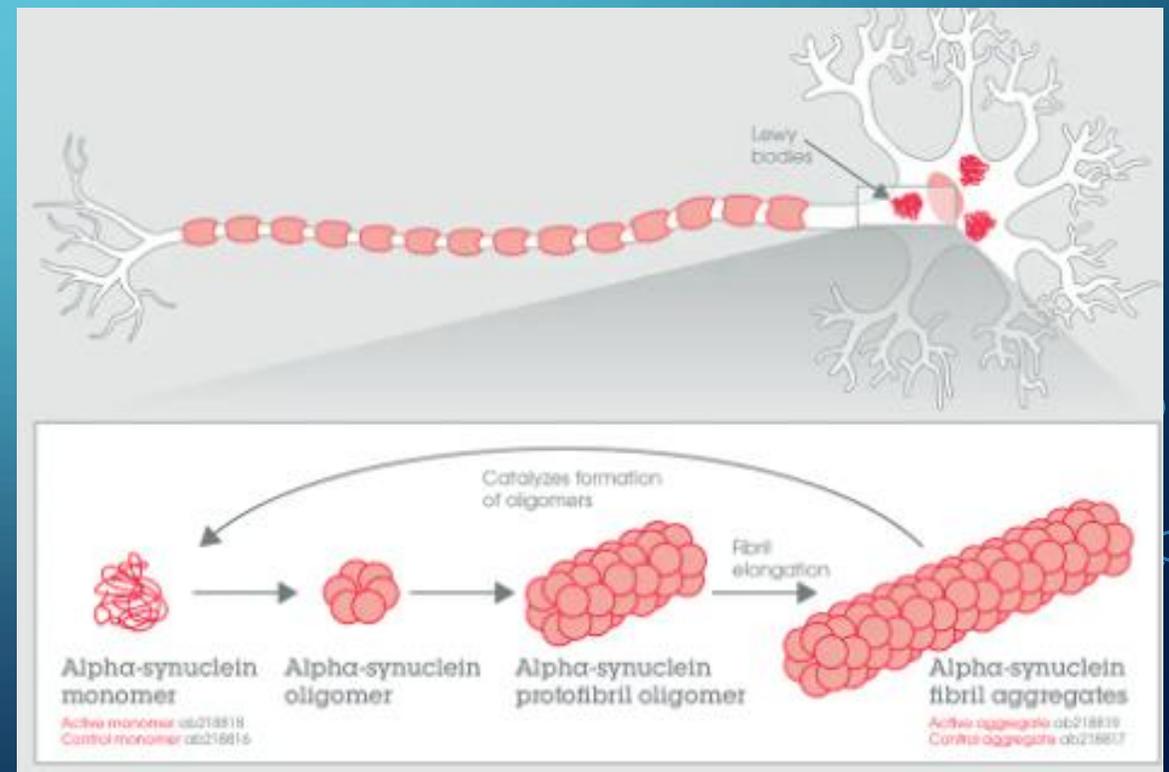
- PD is pathologically characterized by degeneration and loss of nigrostriatal dopaminergic innervation.
- PD has characteristic neuronal inclusions containing α -synuclein. (Lewy bodies).

Whats α -synuclein???



PATHOGENESIS

- Alpha-synuclein is a protein which is abundant in dopamine producing nerve cells, normally cleared by autophagy.
- In Parkinson's alpha-synuclein mis-folds and aggregates into clumps called Lewy Bodies, due to failed clearance caused by defects in autophagy & lysosomal degradation.



PATHOGENESIS CONT

- as a result, the amount of DA available for neurotransmission in the corpus striatum is reduced leading to:
 - gradual slowness of spontaneous movement.
 - loss of postural reflexes.
 - poor balance and motor coordination.

} typical clinical symptoms
Of PD

CLINICAL PRESENTATION

- Typical symptoms :tremor, rigidity, & bradykinesia.
- 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.

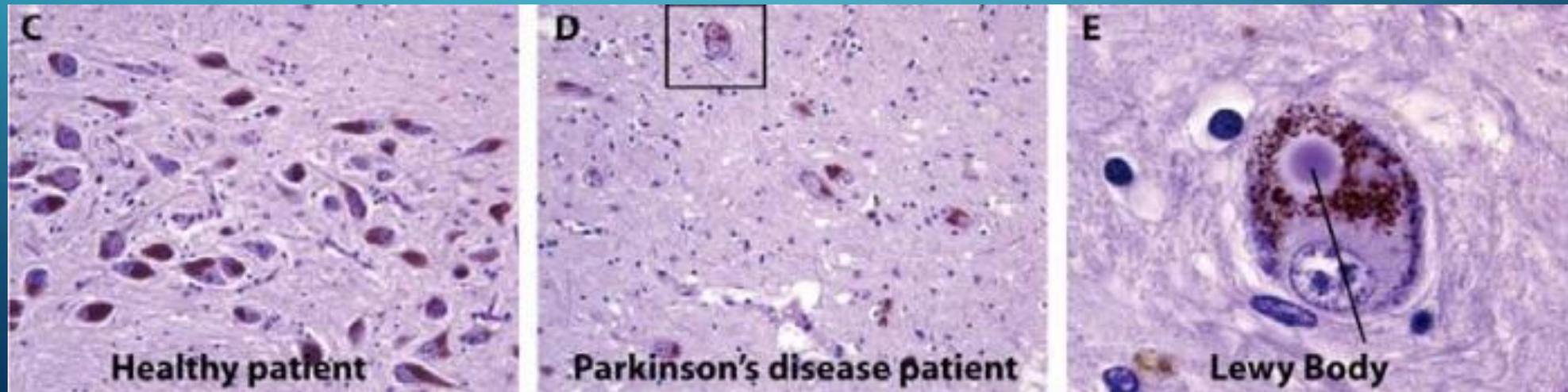
GROSS FEATURES

- Pathological examination of a healthy patient (A) reveals typical pigmented DA neurons in the SN .
- loss of SN neurons leads to pigment disappearance in the PD brain (B, arrows).



MICROSCOPIC FEATURES

- C: SN area reveals a dense network of melanin-pigmented SN neurons in the healthy brain.
- D: most of SN neurons are lost in PD .
- E: Some of the remaining neurons in PD contain insoluble cytoplasmic protein aggregates (Lewy Bodies).



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).
- Usually progressive, resulting in death after an average 15 years.

HD – PATHOGENESIS

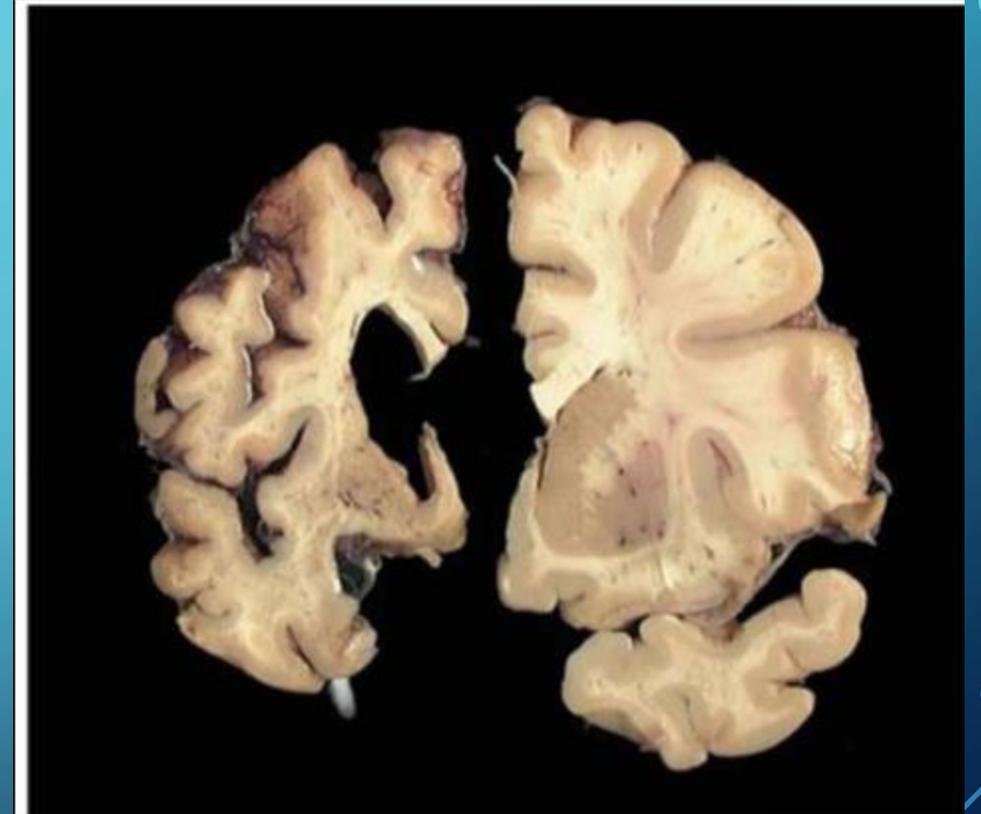
- Autosomal dominant trinucleotide CAG repeat in the huntingtin gene (*HTT*) on chromosome 4 leading to a mutant protein product mHTT.
- Normal alleles contain 6 to 35 copies of the repeat; in HD the number of repeats is increased.
- Mutant protein aggregates are potentially injurious.

CLINICAL FEATURES

- Disease progression can be divided into phases :
- Presymptomatic phase: Neuropsychiatric: irritability, disinhibition
- Diagnostic phase:
 - ✓ Hyperkinetic phenotype: prominent chorea (uncontrollable jerking movements) and dystonia (involuntary muscle contractions, often painful)
 - ✓ Hypokinetic phenotypes: bradykinesia (slowness of movement), gait disturbance, imbalance
 - ✓ Cognitive dysfunction: poor executive function and speech impairment
 - ✓ Neuropsychiatric: depression and suicidal ideation

GROSS FEATURES

- ✓ coronal slices through human brain showing a normal brain on the right and an advanced HD brain on the left. Note the profound shrinkage of cortex and caudate



AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- Amyotrophic lateral sclerosis (ALS) is a chronic, progressive neurologic disease characterized by degeneration of upper (cerebral cortex) and lower motor neurons (spinal cord and brain stem).
- Motor neuron loss results in progressive and irreversible loss of motor function, muscle weakness and wasting and ultimately death, usually due to respiratory failure

ALS – PATHOGENESIS

- Mutations in the superoxide dismutase gene, SOD1, on chr. 21, leading to aggregation of misfolded SOD1 protein which trigger 'unfolded protein response' in cells and apoptosis.
- Death of upper motor neurons, causes degeneration of the descending corticospinal tracts.
- Death of anterior horn cells (lower motor neurons) with loss of innervation causes atrophy of skeletal muscles.

CLINICAL FEATURES

- Progressively worsening muscle weakness, leading to loss of mobility and respiratory failure
- Upper motor neuron specific signs and symptoms
 - Brisk tendon reflexes
 - Spasticity
- Lower motor neuron specific signs and symptoms
 - Skeletal muscle weakness and wasting
 - Fasciculations

ACQUIRED METABOLIC DISEASES

- Metabolic disarray may disrupt the brain function but without detectable morphological changes.
- Examples:
 - ✓ hypoglycemia may lead to necrosis.
 - ✓ hyperglycemia can lead to confusion, stupor and eventually coma.
 - ✓ Certain vitamin deficiency: B12, thiamine.

WERNICKE ENCEPHALOPATHY

- Acute and chronic neuropsychiatric condition secondary to thiamine (vitamin B1) deficiency
 - Wernicke encephalopathy (WE): neuropsychiatric syndrome resulting from thiamine (vitamin B1) deficiency.
 - Korsakoff syndrome (KS): Disturbances of short term memory.
- Common in chronic alcoholism, secondary to thiamine deficiency

CLINICAL FEATURES

- Wernicke encephalopathy: Triad

- ✓ Mental status abnormality

- ✓ Ocular abnormalities

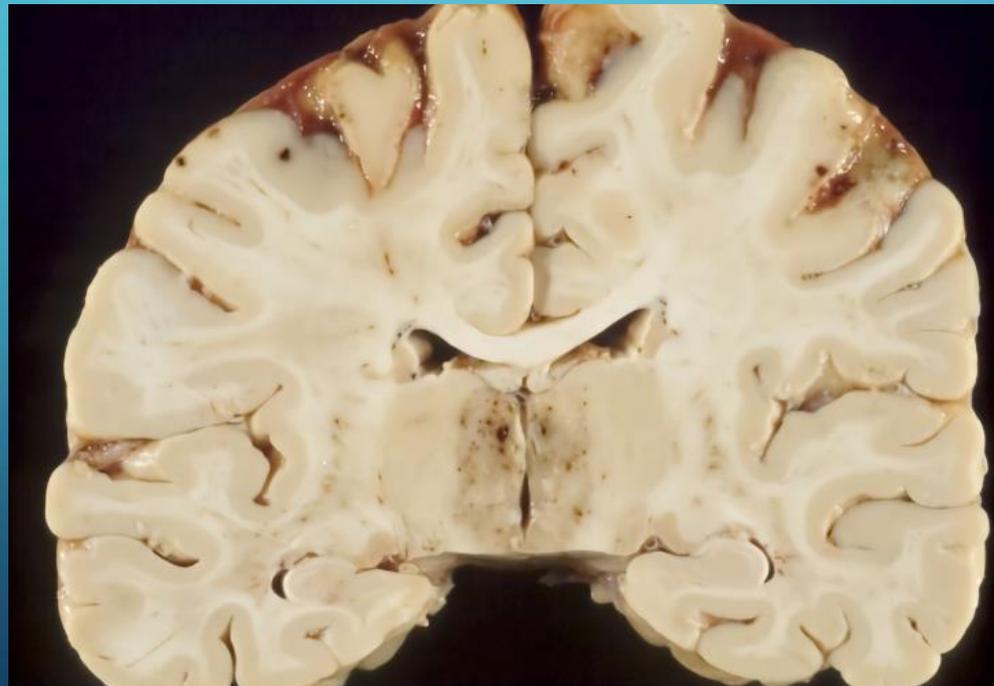
- ✓ Ataxia.

- Korsakoff syndrome:

- ✓ profound anterograde amnesia and temporally graded retrograde amnesia .

GROSS FEATURES

- Petechial hemorrhages involving mammillary bodies and bilateral subcortical regions of periventricular (third and fourth) areas.



SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

- Acquired myelopathy caused by vitamin B12 (cobalamin) deficiency, caused by a defect in myelin formation.
- Affect Posterior and lateral columns of spinal cord.
- Etiology
 - Cobalamin deficiency: vegetarian diet
 - Impaired absorption of cobalamin intrinsic factor (IF) complex: pernicious anemia / atrophic gastritis.
- **Clinical features**
 - Progressive sensory abnormalities, ascending paresthesia's, weakness, ataxia, loss of sphincter control and gait impairment