# NEUROSCIENCE PATHOLOGY-II

# DEGENERATIVE DISEASES OF CNS

DR.EMAN KREISHAN, M.D.

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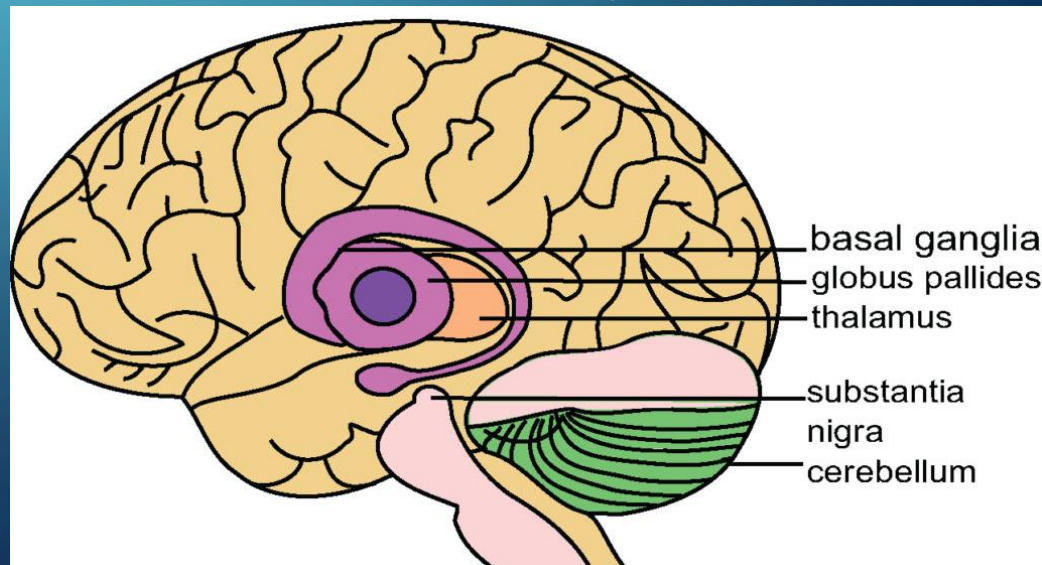
- Movement control is accomplished by complex interactions among various groups of nerve cells in the central nervous system.
- One such important group of neurons is located in the substantia nigra in the ventral midbrain.
- Neurons of the substantia nigra communicate with neurons of the basal ganglia 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).

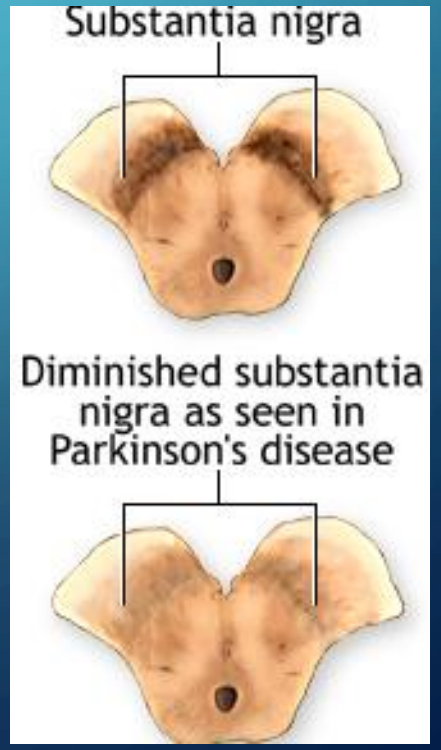
# PATHOGENESIS

- PD is pathologically characterized by degeneration and loss of nigrostriatal dopaminergic innervation.

- PD has characteristic neuronal

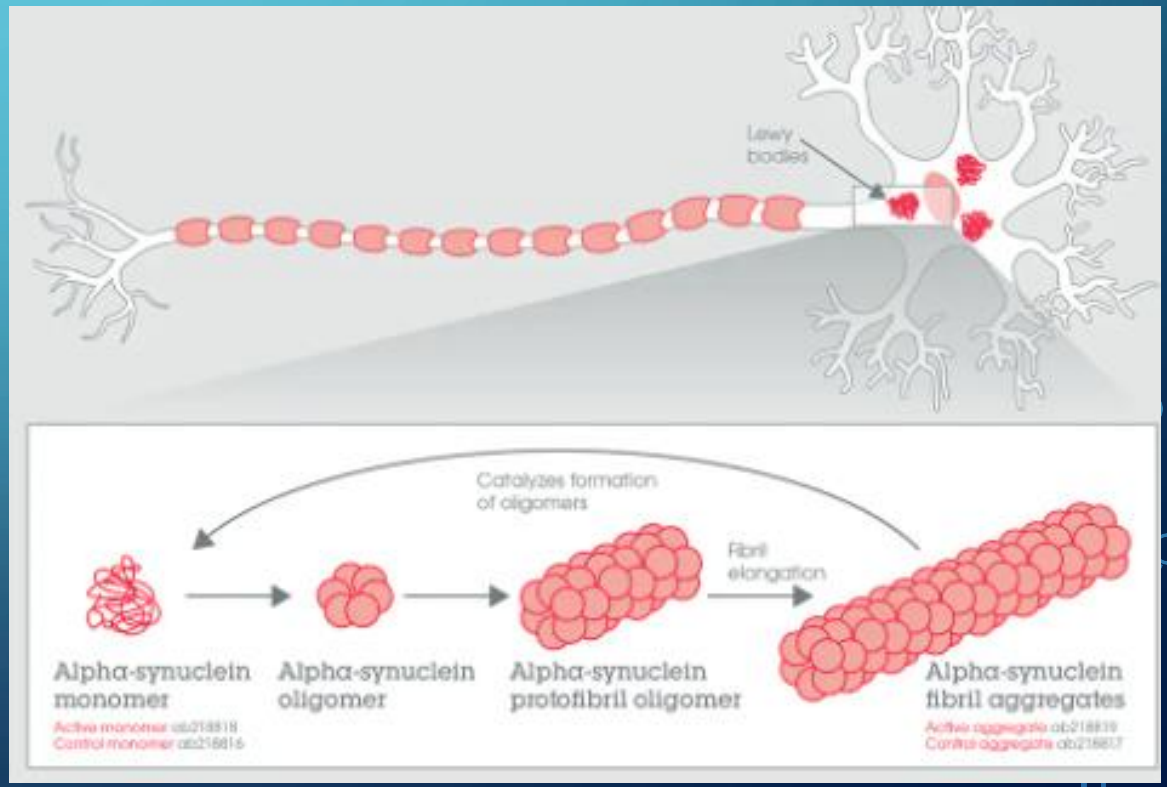
inclusions containing α-synuclein. (Lewy bodies).

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.

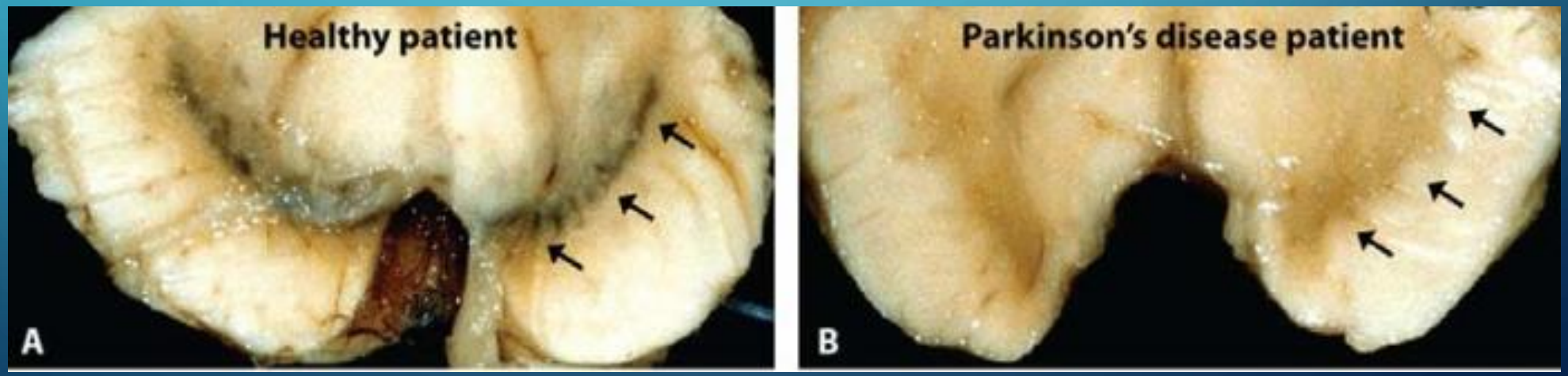
} typical clinical symptoms Of PD

# 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.

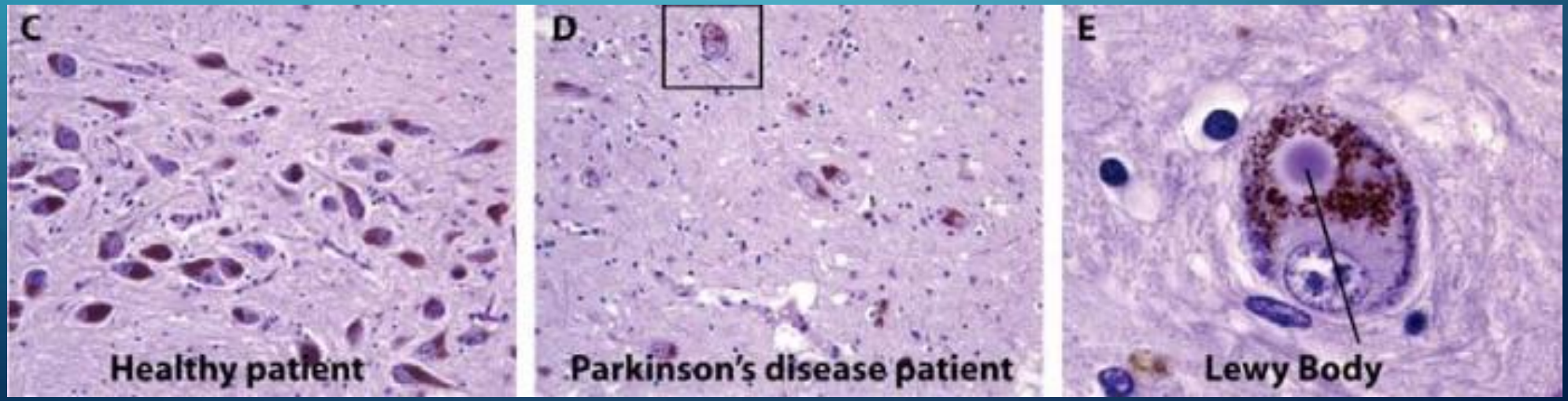
# GROSS FEATURES

- 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)

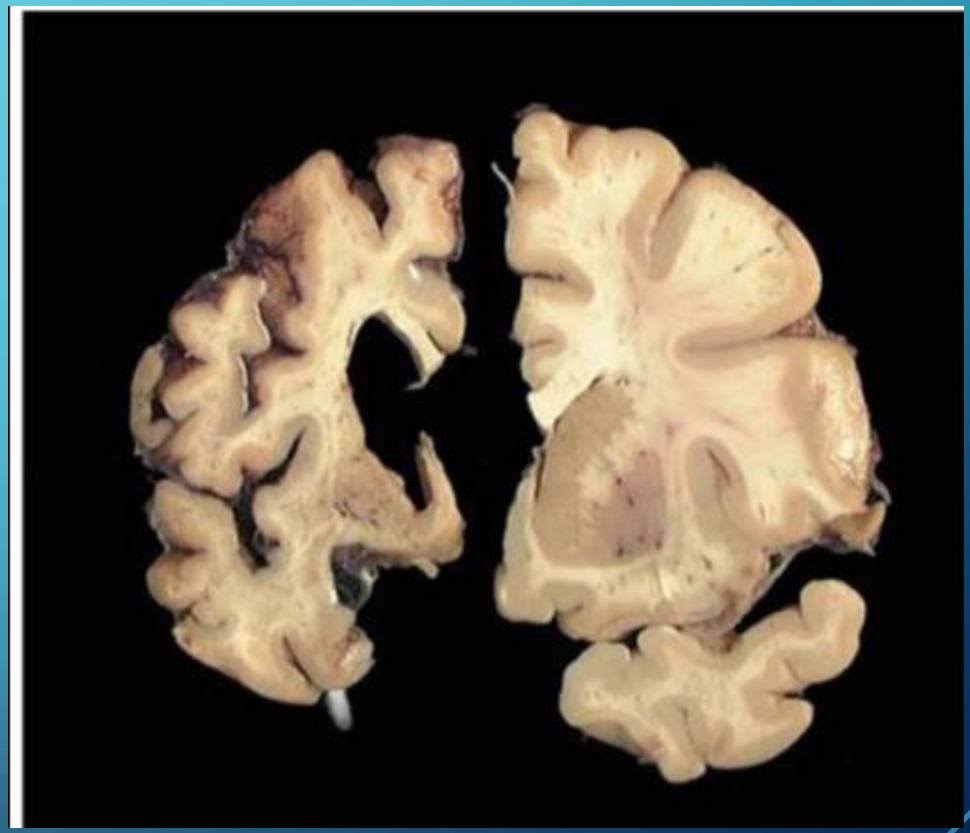
✓ Hypokinetic phenotypes: bradykinesia (slowness of movement), gait disturbance, imbalance

✓ Cognitive dysfunction: poor executive function and speech impairment

✓ Neuropsychiatric: depression and suicidal ideation

# GROSS FEATURES

coronal slices though 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; short lived and severe condition
- ❑ 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

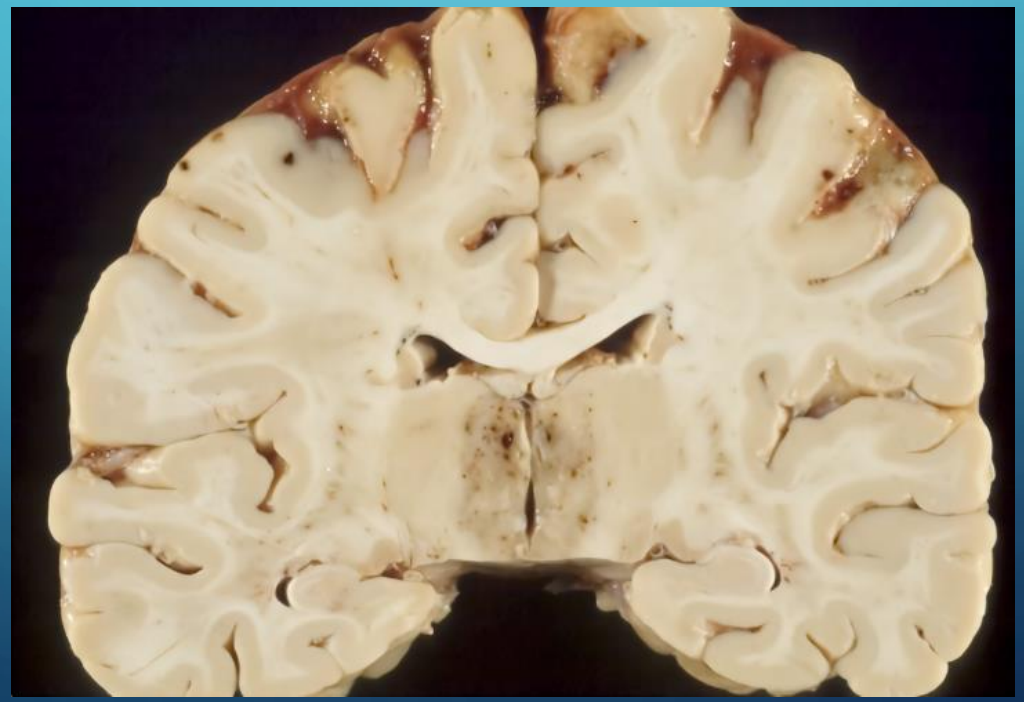
✓Ataxia.

- Korsakoff syndrome:

✓ profound anterograde amnesia and temporally graded retrograde amnesia with confabulation

# 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