Neurodegenerative disorders-2

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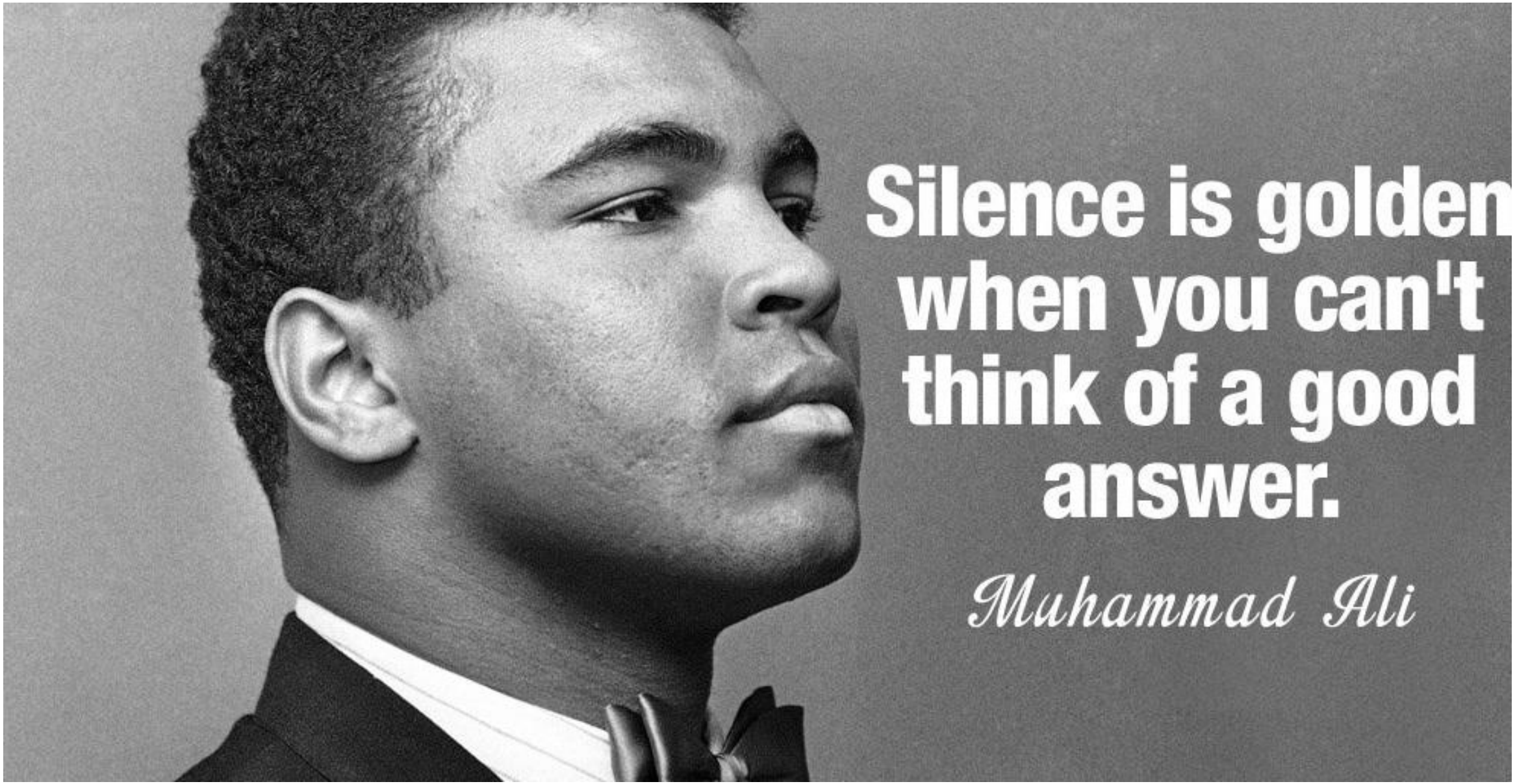
Different diseases

- **Involving the hippocmpus and cortex**>>>> cognitive changes (memory disturbances, behavior and language) >>>> dementia >>>>>ALZHEIMER DISEASE (AD) , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

- **Involving the basal ganglia** >>>>> movement disorders >>>>hypokinesia (PARKINSON DISEASE) or hyperkinesia (HUNTINGTON DISEASE)

- **Involving the cerebellum** >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA, FRIEDRICH ATAXIA, ATAXIA TELANGECTASIA)

- **Involving the motor system** >>> difficulty swallowing and respiration with muscle weakness >> (AMYOTROPHIC LATERAL SCLEROSIS)


Silence is golden
when you can't
think of a good
answer.
Muhammad Ali

Parkinson Disease (PD)

- A hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra.
- Second most common neurodegenerative disorder after Alzheimer's disease
- ***Parkinsonism*** is a clinical syndrome: tremor, rigidity, bradykinesia, and instability.
- Parkinsonism: any damage of dopaminergic neurons, which project from the substantia nigra to the striatum (control of motor activity).

- Parkinsonism: induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons

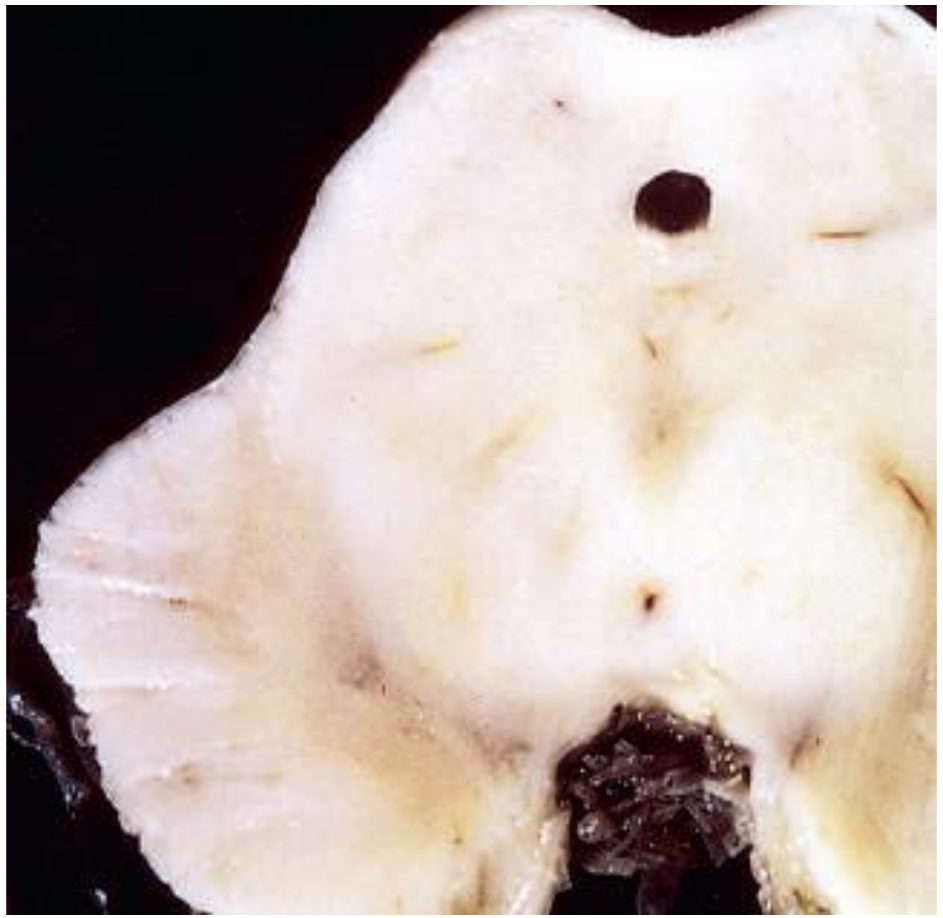
Pathogenesis

- protein accumulation and aggregation , mitochondrial abnormalities and neuronal loss in the substantia nigra and elsewhere in the brain
- Abnormal protein and organelle clearance due to **defects in autophagy and lysosomal degradation**
- Clue and diagnostic feature: Lewy body (neuronal inclusions containing *α-synuclein*, a protein involved in synaptic transmission)
- Most cases sporadic, some are autosomal dominant (mutation of *α-synuclein gene)*

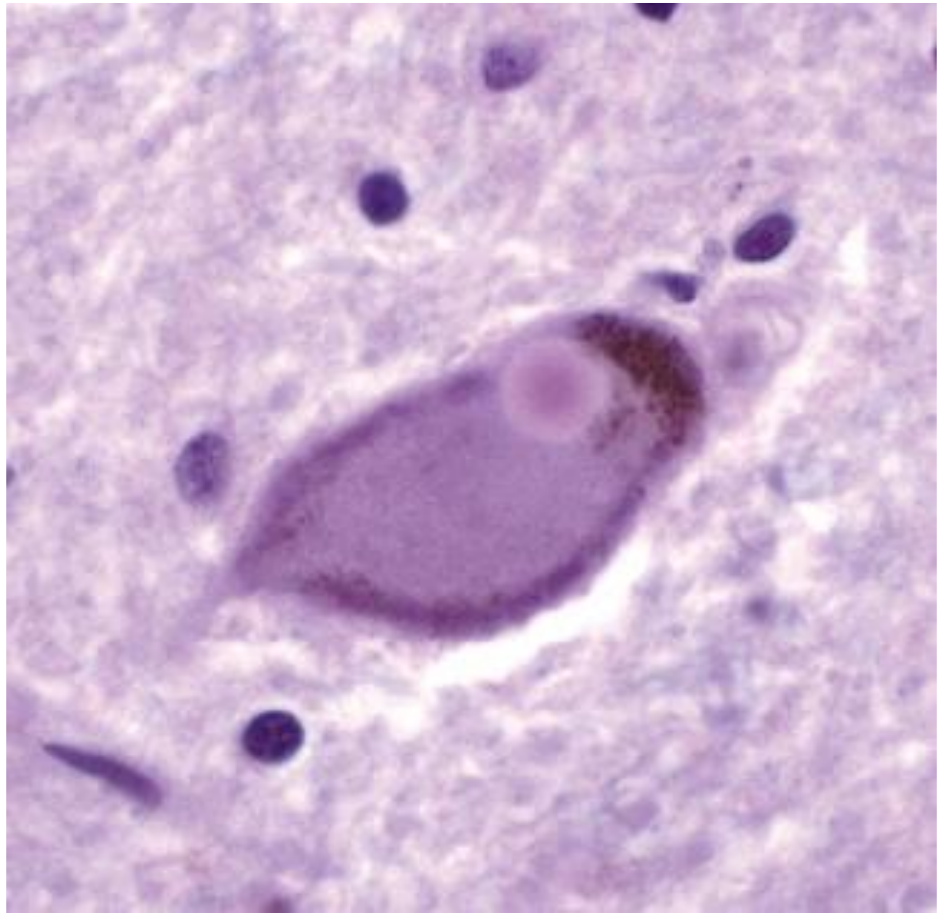
MORPHOLOGY

- Pallor of the substantia nigra and locus ceruleus
- Loss of the pigmented (catecholaminergic) neurons in these regions.
- Gliosis.
- **Lewy bodies** in neurons (cytoplasmic, eosinophilic, round to elongated inclusions)
- **Lewy neurites**: dystrophic neurites that also contain aggregated α-synuclein
- Immunohistochemical staining for α-synuclein (for subtle lewy bodies).
- With progression involvement of: medulla, pons, amygdala, and the cerebral cortex

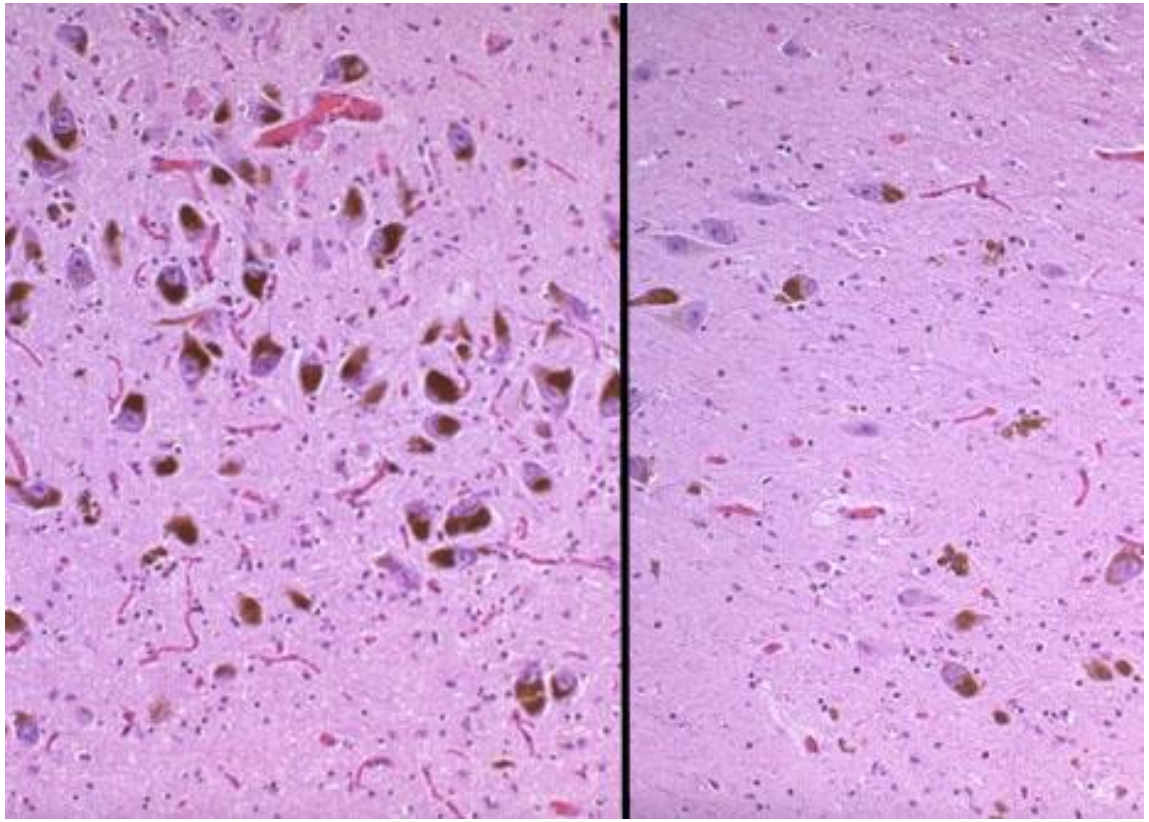
Normal substantia nigra



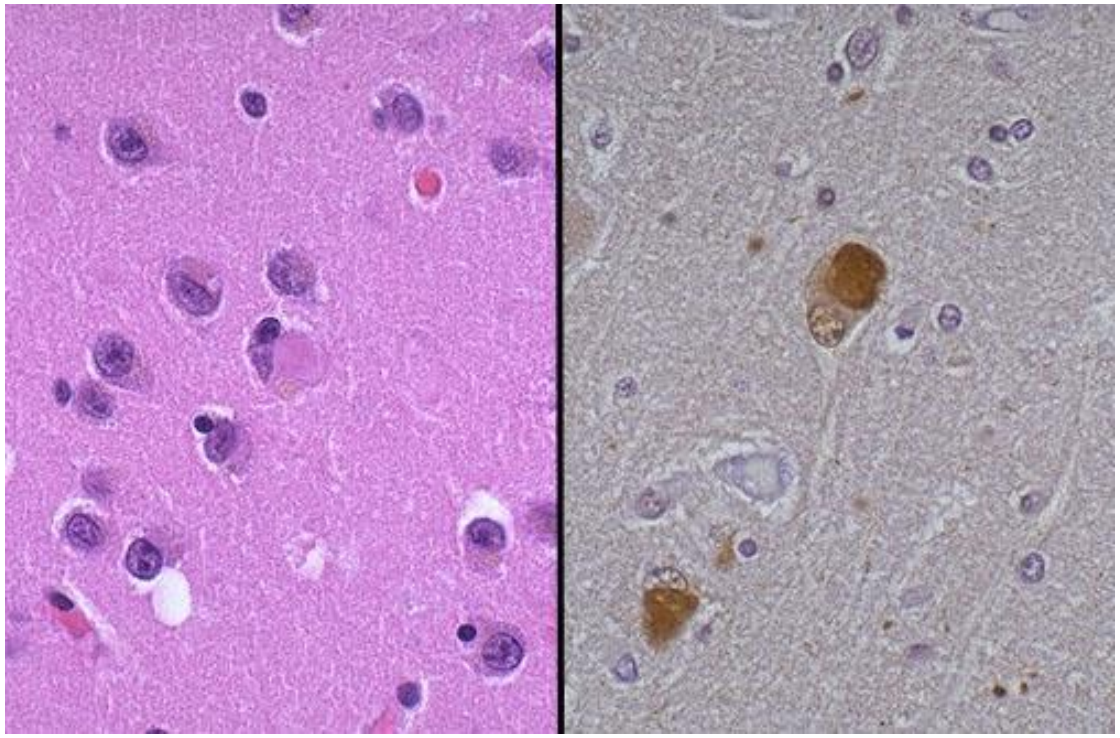
Depigmented substantia nigra in idiopathic Parkinson disease



Lewy body in a neuron from the substantia nigra stains pink.



- Left: normal
- Right: loss of pigmented neurons in SN.



- Immunostaining for ubiquitin to highlight Lewy bodies.

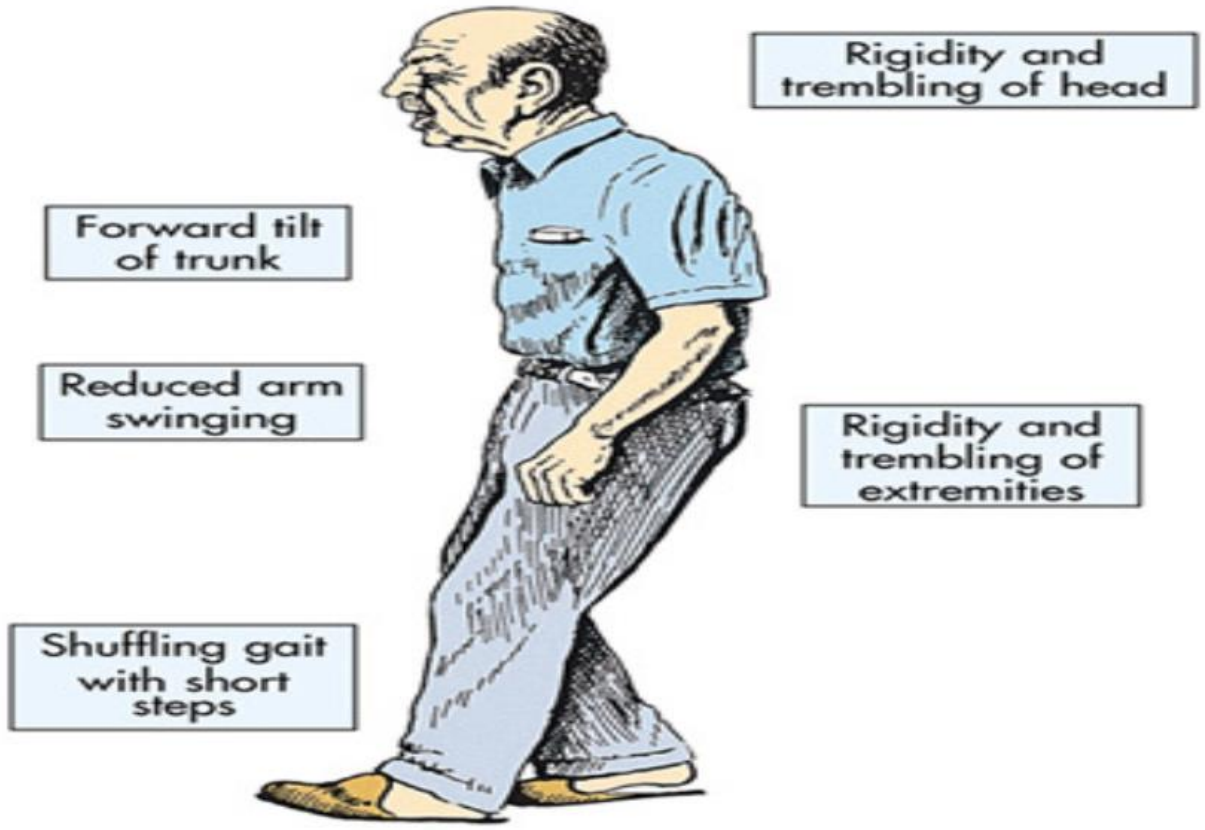
Clinical Features

- Progresses over 10 to 15 years
- Eventually: severe motor slowing or near immobility.
- Lewy body dementia when dementia develops within 1 year of PD
- Death due to aspiration pneumonia or trauma from falls caused by postural instability.
- Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings
- Over time, becomes less effective
- Another Tx: deep brain stimulation

SYMPTOMS

- **Tremor.** involuntary shaking, usually at rest and disappears with movement, begins in a limb, often in the hands or fingers. Patients might rub their thumb and forefinger back-and-forth (pill-rolling tremor.)
- **Slowed movement (bradykinesia) :** steps may become shorter, difficult to get out of a chair. Patients drag their feet as they try to walk.(Shuffling , festinating gate)
- **Rigid muscles (rigidity):** The stiff muscles can be painful and limit the range of motion.
- **Impaired posture and balance.** stooped posture (leaning forward), and balance problems

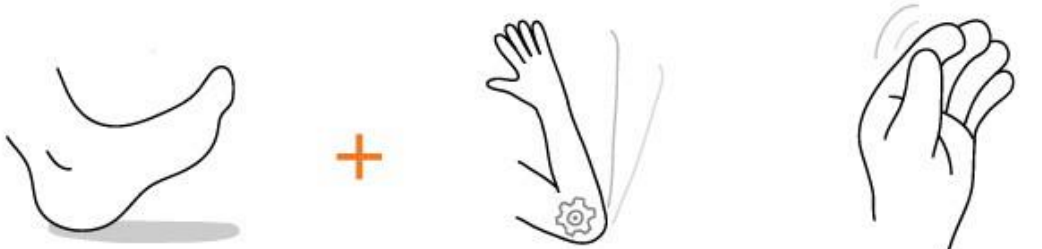
- **Loss of automatic movements.:** decreased ability to perform unconscious movements, including blinking, smiling or swinging arms during walking
- **Speech changes.** Patients might speak softly, quickly, slur or hesitate before talking.
- **Writing changes.** It may become hard to write
- Diminished facial expressions (Masked facies)
- Slow voluntary movement


Rigidity and trembling of head
Forward tilt of trunk
Reduced arm swinging
Rigidity and trembling of extremities
Shuffling gait with short steps

Stooped posture

Pill rolling tremor

Parkinson's Disease

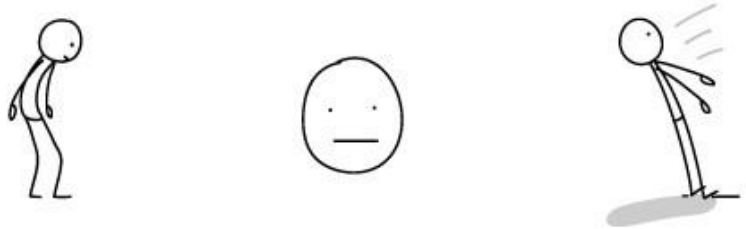


Bradykinesia
(as seen in toe tapping)

Cogwheel Rigidity

Resting Tremor
(pill rolling tremor)

Other motor features:



Shuffling Gait

Mask-like Expression

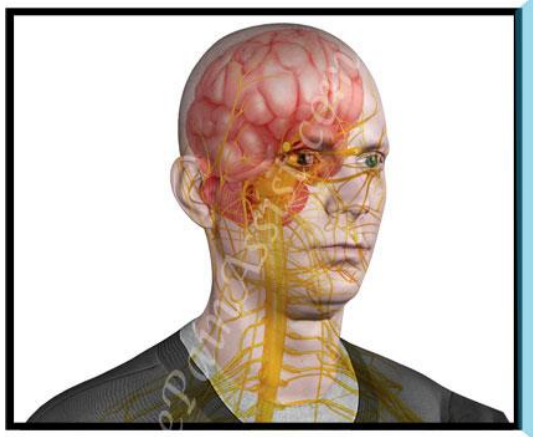
Postural Instability

Huntington Disease

- Autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen)

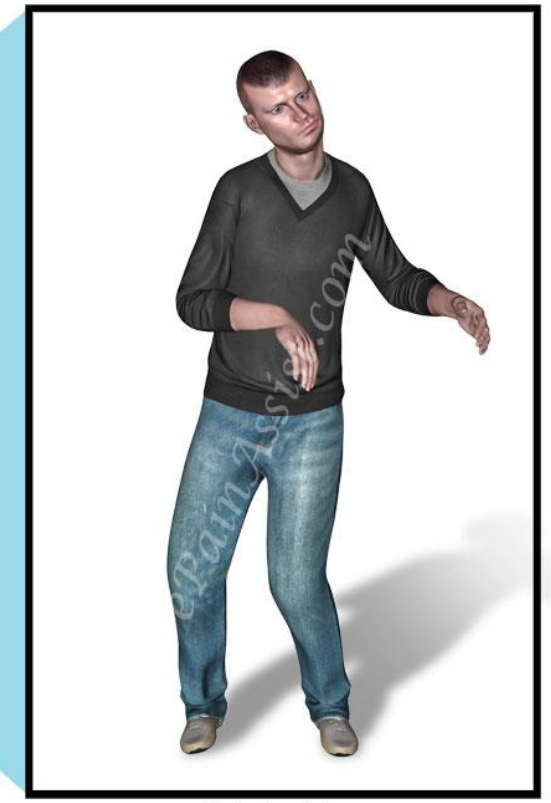
- Involuntary jerky movements of all parts of the body; writhing movements of the extremities .
- Progressive , death after an average 15 years
- Early cognitive symptoms (forgetfulness and thought and affective disorders, severe dementia).
- Increase risk of suicide.

Chorea



This is a genetic disorder which affects the functioning of the brain

Chorea is a medical condition and a type of movement disorder



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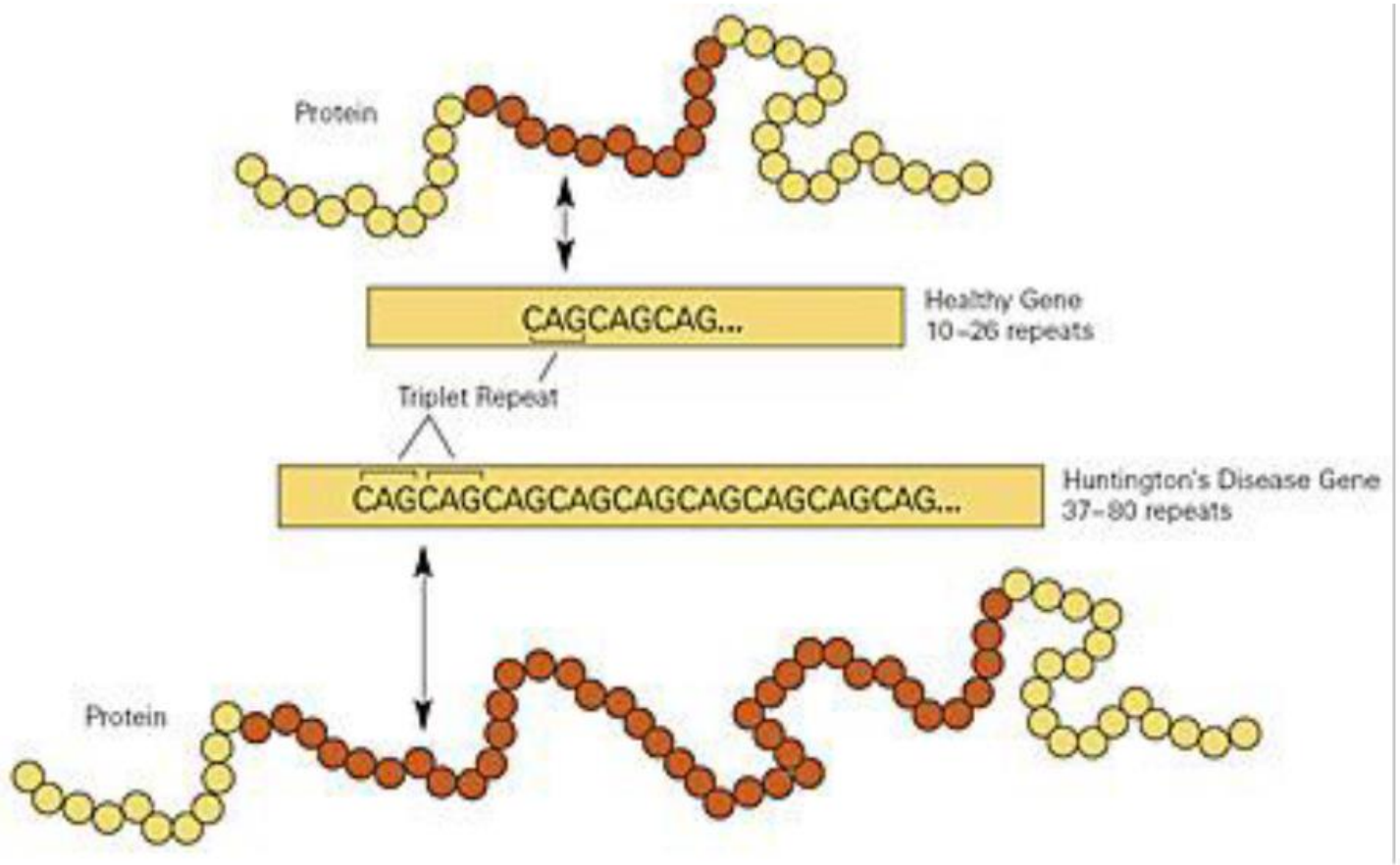
Pathogenesis

- CAG trinucleotide repeat expansions in huntingtin protein gene located on 4p16.3 (Polyglutamine)
- Normal alleles contain 11 to 34 copies of the repeat.
- Disease-causing alleles: number of repeats is increased (may be hundreds)
- Larger numbers of repeats results in earlier-onset disease.
- Mutant protein is subject to proteolysis >>> fragments can form large intranuclear aggregates >>> toxic

Pathogenesis:

- Age of onset:40-50 years; related to the length of CAG repeats (more repeats; earlier age of onset)
- Anticipation: Further expansions of the CAG (glutamine-encoding) repeats during spermatogenesis>>> (paternal transmission) >>> earlier onset in the next generation.

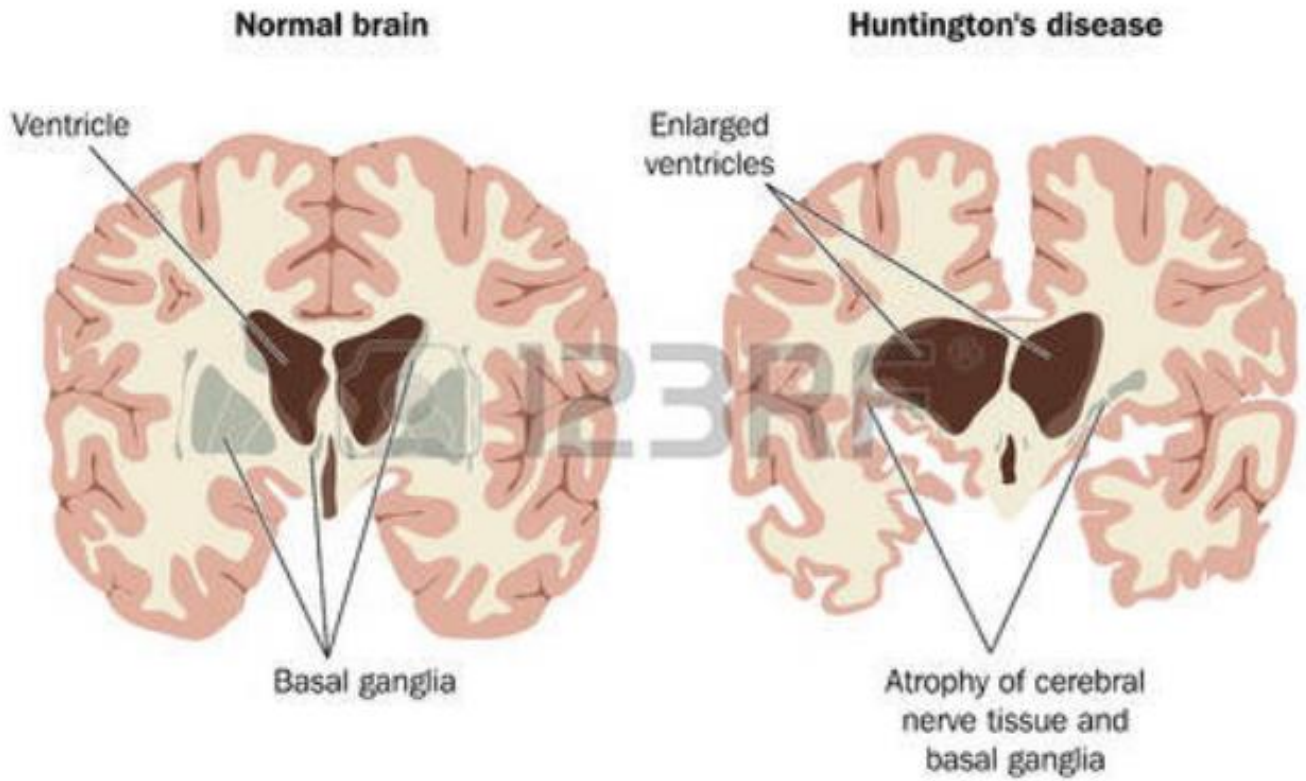

Protein
CAGCAGCAG...
Healthy Gene
10–26 repeats
Triplet Repeat
CAGCAGCAGCAGCAGCAGCAGCAGCAG...
Huntington's Disease Gene
37–80 repeats
Protein

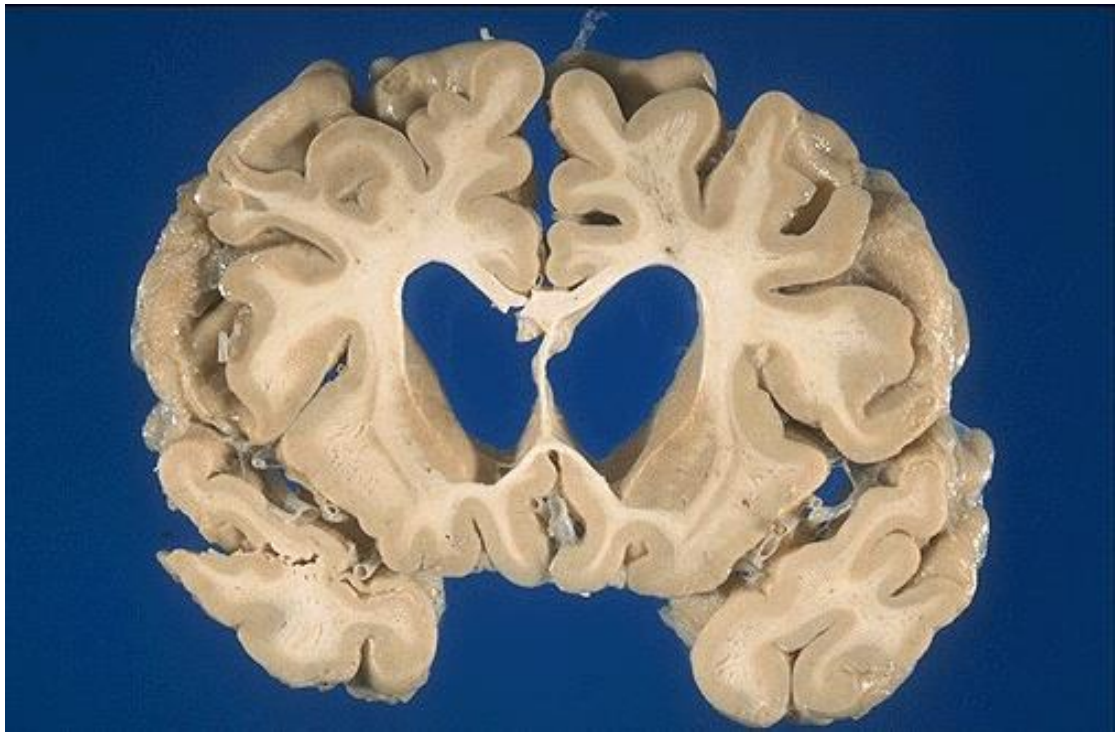
Morphology: macroscopic

- Brain is small
- Striking atrophy of the caudate nucleus and the putamen
- Secondary atrophy of globus pallidus
- Atrophy frequently also is seen in the frontal lobe.
- Dilated lateral and third ventricles

Morphology: microscopic

- Severe loss of neurons from affected regions of the striatum + gliosis
- Spiny neurons that release γ-aminobutyric acid (GABA), enkephalin, dynorphin, and substance P are especially sensitive, disappearing early.
- Intranuclear inclusions (aggregates of ubiquitinated huntingtin protein)
- Strong correlation between degeneration in the striatum and severity of motor symptoms; and between cortical neuronal loss and dementia.


Normal brain
Huntington's disease
Ventricle
Enlarged ventricles
Basal ganglia
Atrophy of cerebral nerve tissue and basal ganglia



- Enlargement of the ventricles seen here is due to **atrophy** of the head of the caudate.

- Several members of a large family are affected by the onset of decreasing mental function and motor coordination when they reach middle age. Their extremity movements are marked by choreoathetosis. Genetic testing reveals increased trinucleotide CAG repeats. Which of the following intracranial structures is most likely to appear grossly abnormal with radiologic imaging of these affected persons?
- A Caudate nucleus
- B Midbrain
- C Temporal lobe
- D Locus ceruleus
- E Spinal cord

- A 66-year-old man is finding that he has more difficulty getting up and moving about for the past year. He is annoyed by a tremor in his hands, but the tremor goes away when he performs routine tasks using his hands. His friends remark that he seems more sullen and doesn't smile at them, but only stares with a fixed expression on his face. He has not suffered any loss of mental ability. Which of the following conditions is he most likely to have?
- A Amyotrophic lateral sclerosis (ALS)
- B Huntington disease
- C Parkinson disease
- D Niemann-Pick disease
- E Tuberous sclerosis