

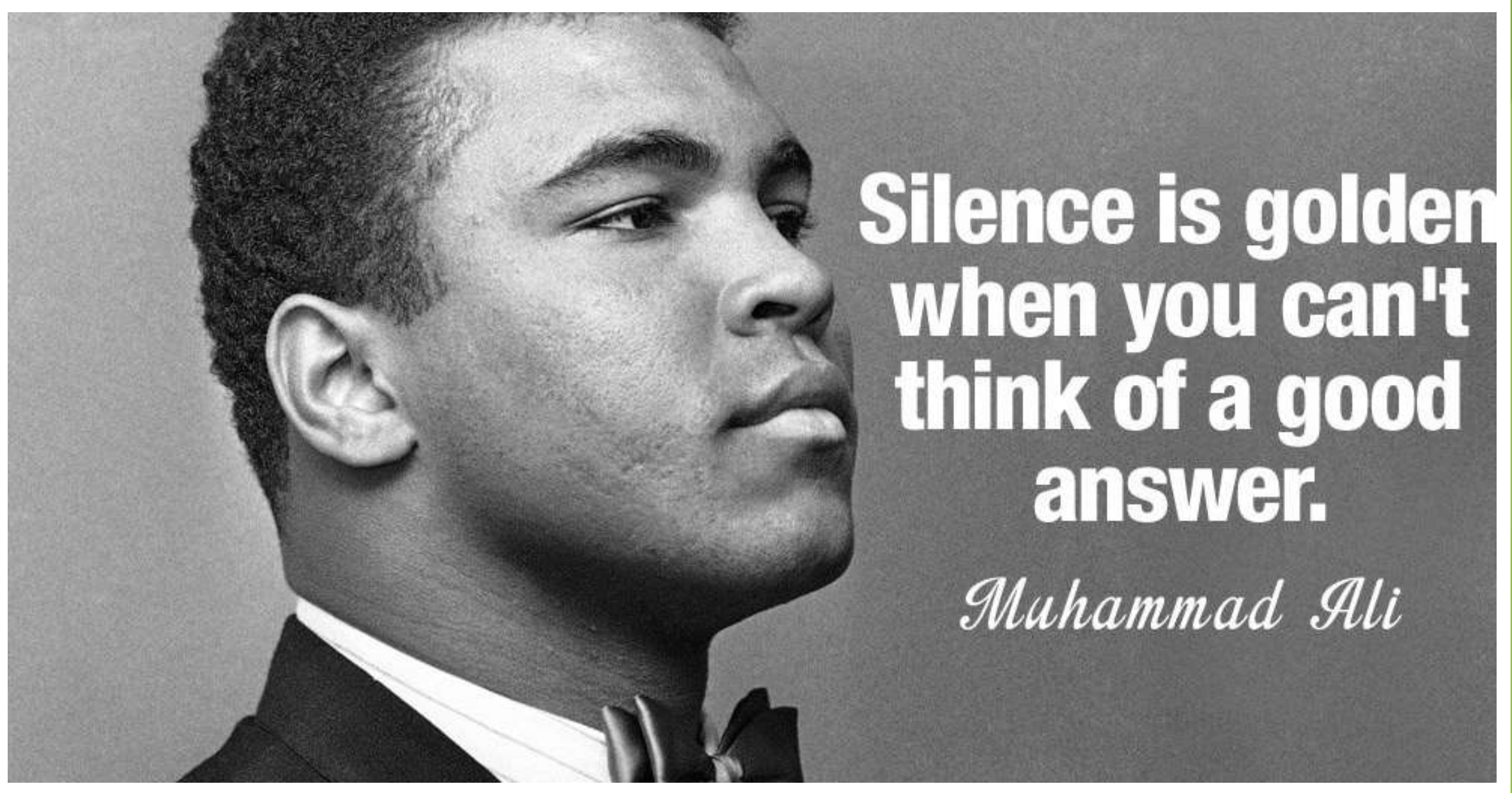
Neurodegenerative disorders-2

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Different diseases

- ▶ **Involving the hippocampus and cortex**>>>> cognitive changes (memory, behavior and language disturbances) >>>> 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.**
- ▶ **Dopaminergic neurons project from substantia nigra to the striatum, involved in motor control.**
- ▶ **Parkinsonism is a clinical syndrome: tremor, rigidity, bradykinesia, and instability due to damage of dopaminergic neurons.**
- **Can be 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.**
- ▶ **Clue and diagnostic feature: Lewy body (neuronal inclusions containing α -synuclein, a protein involved in synaptic transmission)**
- ▶ **Defects in autophagy and lysosomal degradation >> Abnormal protein and organelle clearance.**
- ▶ **Most cases sporadic, some are autosomal dominant (mutation of α -synuclein gene)**

MORPHOLOGY

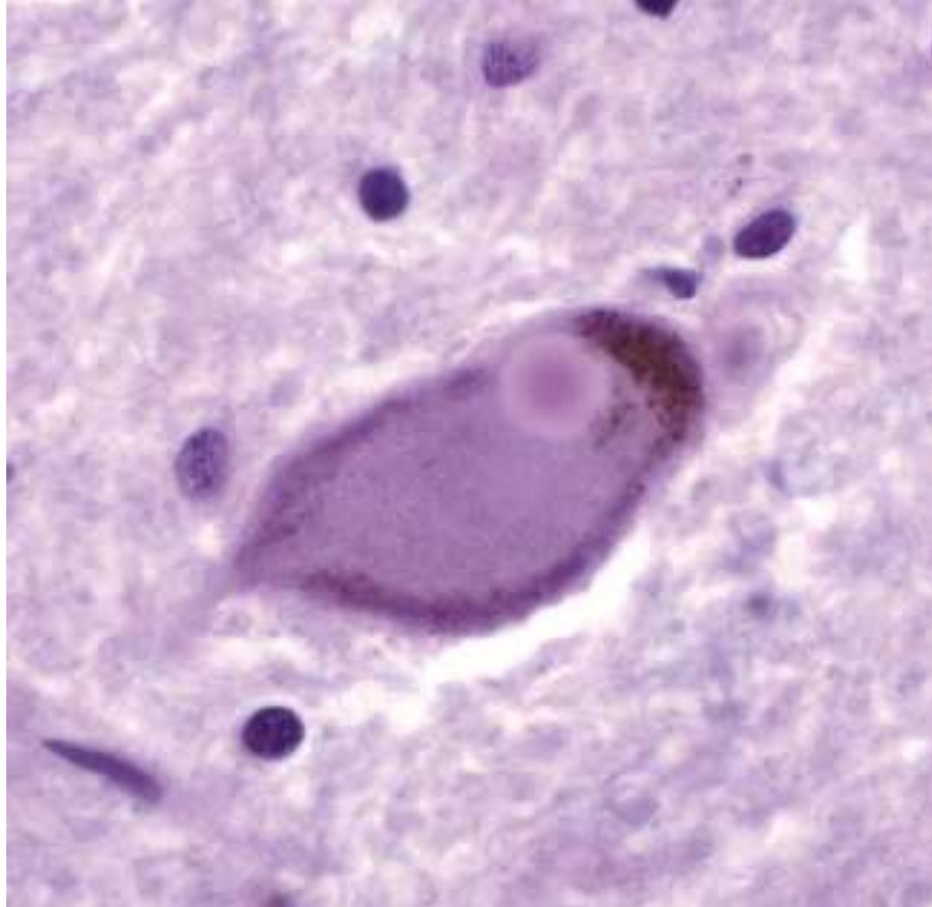
- ▶ **Pallor of the substantia nigra and locus ceruleus**
- ▶ **Loss of the pigmented (catecholaminergic) neurons in these regions with gliosis.**
- ▶ **Lewy bodies in neurons (cytoplasmic, eosinophilic, round to elongated inclusions)**
- ▶ **Lewy neurites: dystrophic neurites that also contain aggregated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



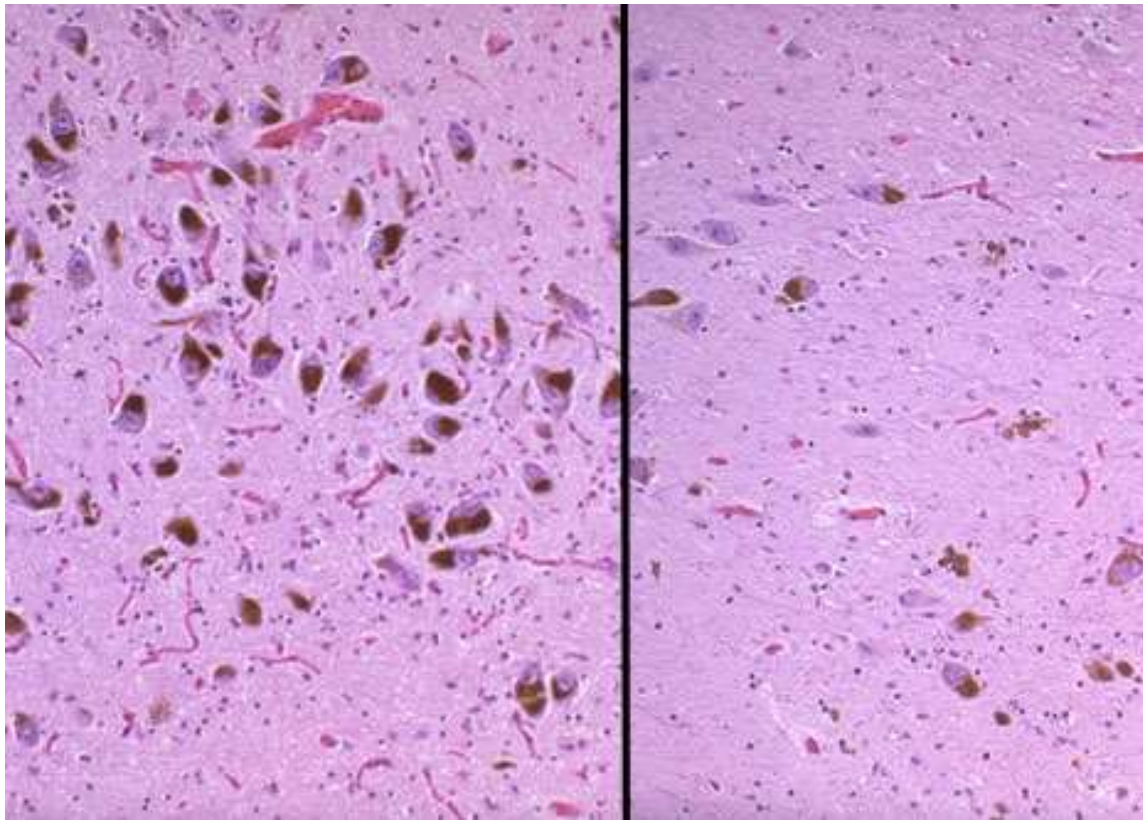
Normal
substantia
nigra



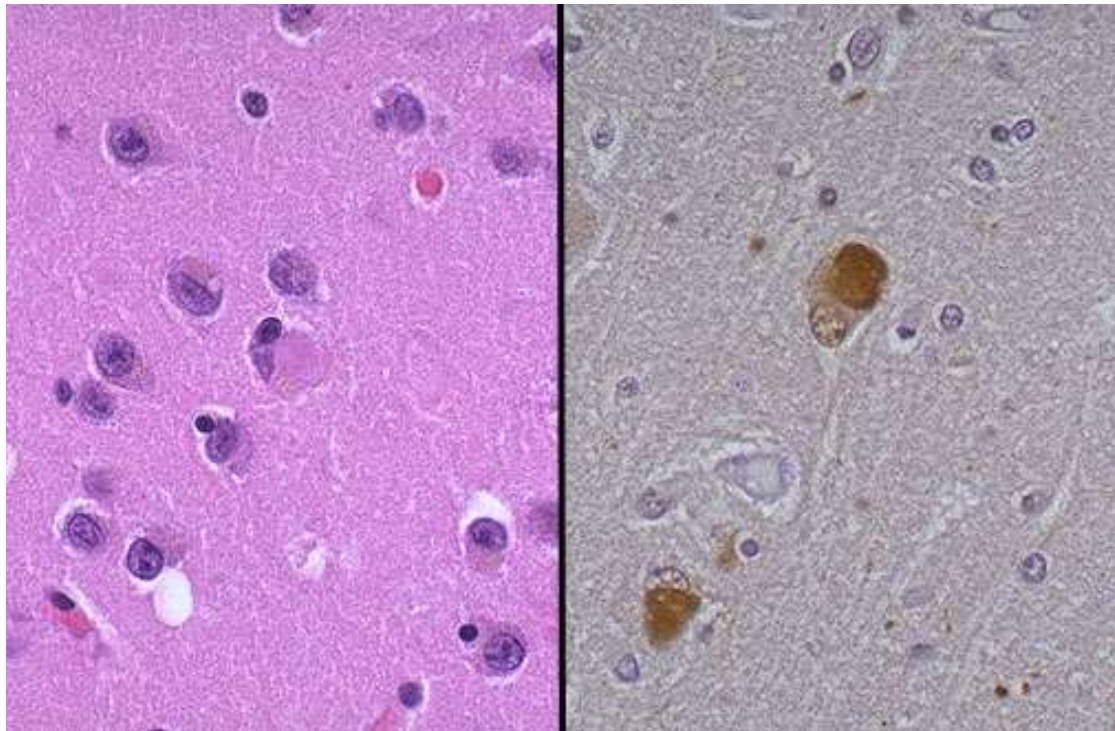
Depigmented
substantia nigra
in idiopathic
Parkinson
disease



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



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



- ▶ Immunostaining to highlight Lewy bodies.
- ▶ Contain alpha synuclein and ubiquitin.

Clinical Features

- ▶ **Characteristic symptoms: tremor, bradykinesia and rigidity.**
- ▶ **Tremor described as pill-rolling, occur at rest.**
- ▶ **Progresses over 10 to 15 years**
- ▶ **Eventually: severe motor slowing or near immobility.**
- ▶ **Death due to aspiration pneumonia or trauma from falls caused by postural instability.**
- ▶ **When dementia develops within 1 year of onset of motor symptoms: Lewy body dementia (LBD).**

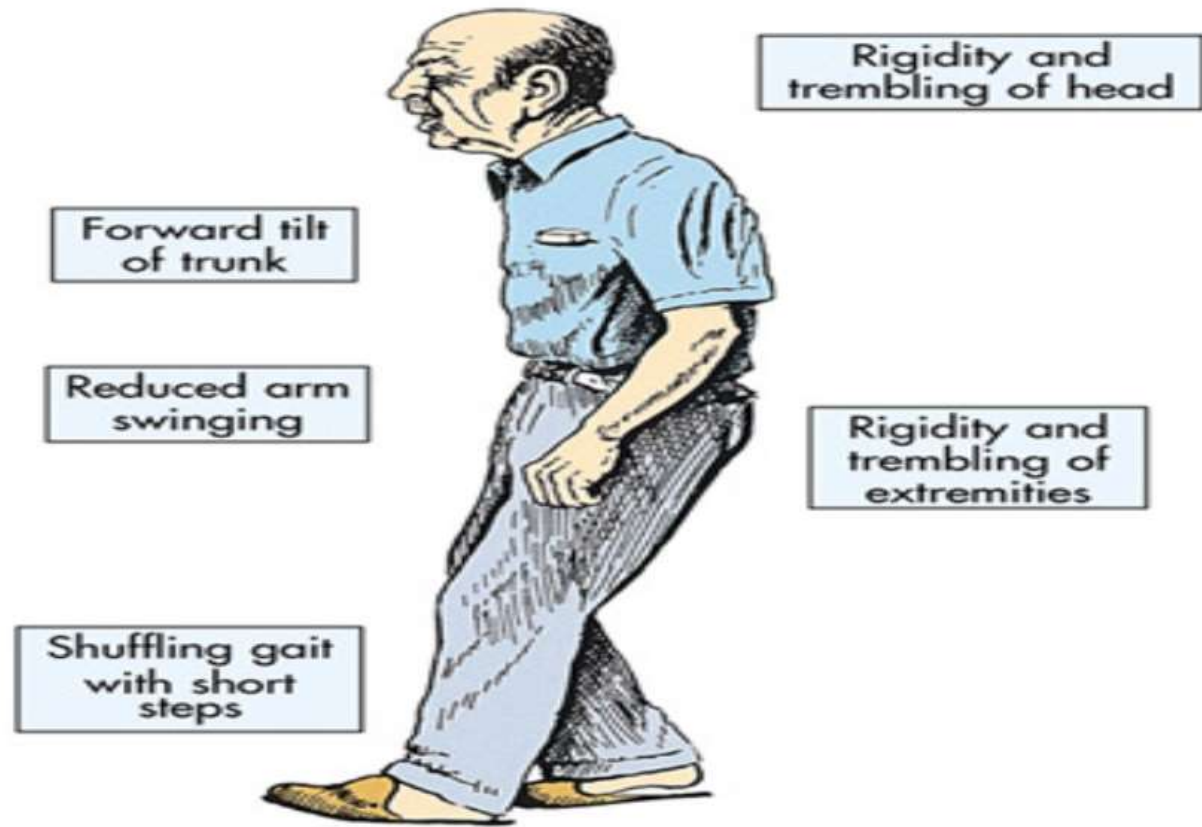
Management:

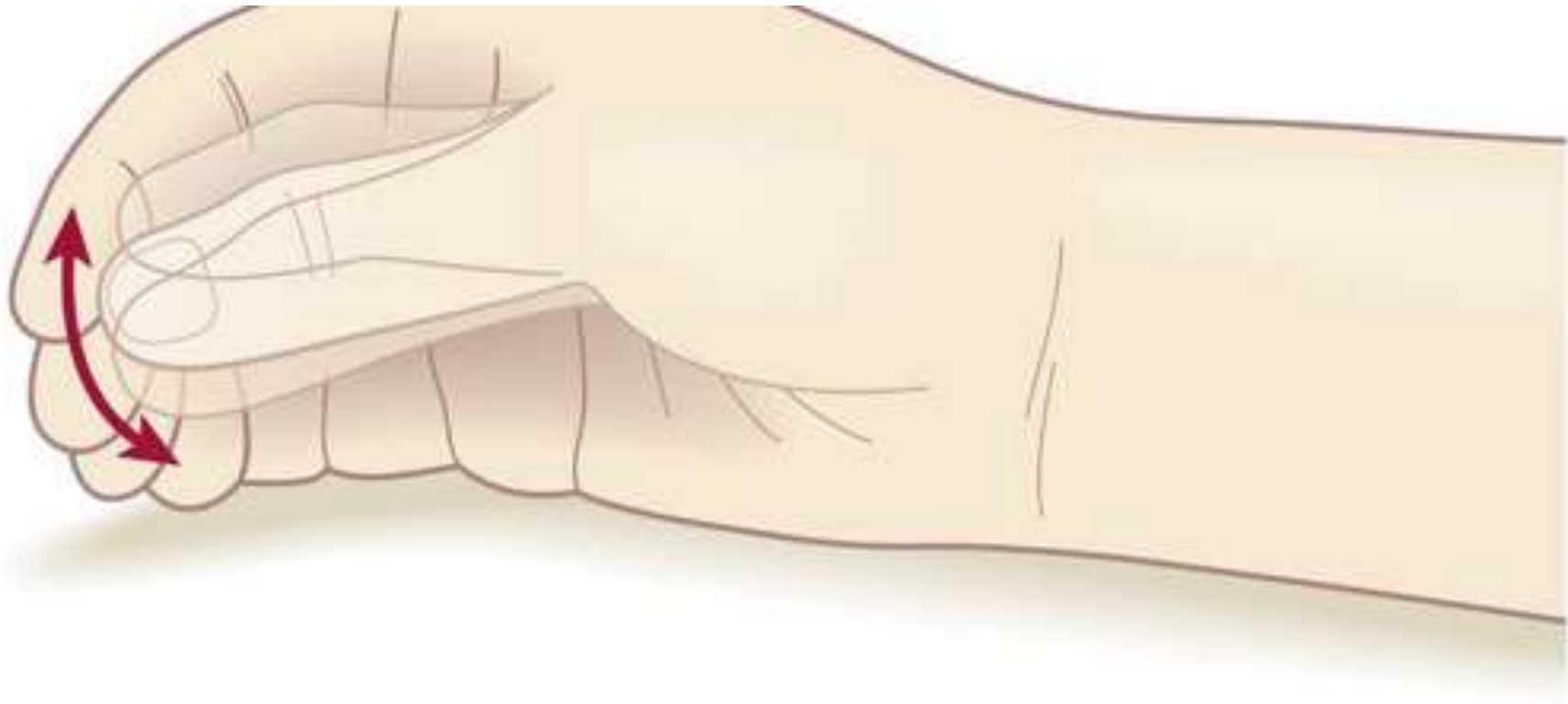
- ▶ **Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression or reverse morphologic findings.**
- ▶ **Over time, becomes less effective**
- ▶ **Another Tx: deep brain stimulation**

SYMPTOMS

- ▶ **Tremor: involuntary shaking, at rest, 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 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**





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, thought and affective disorders, severe dementia).**

Chorea



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

Chorea is a medical condition and a type of movement disorder



ePainAssist.com

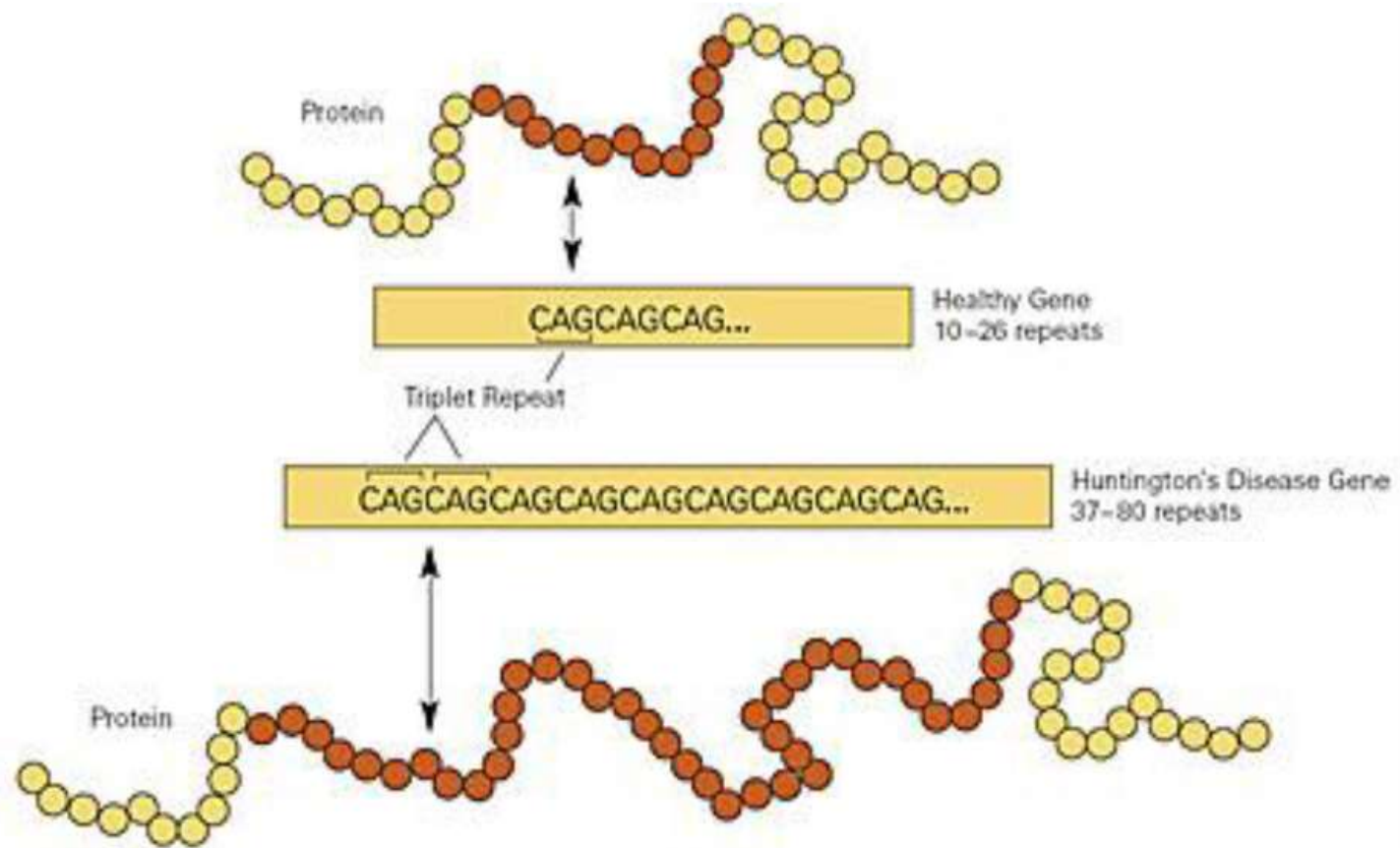


Pathogenesis

- ▶ **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.**



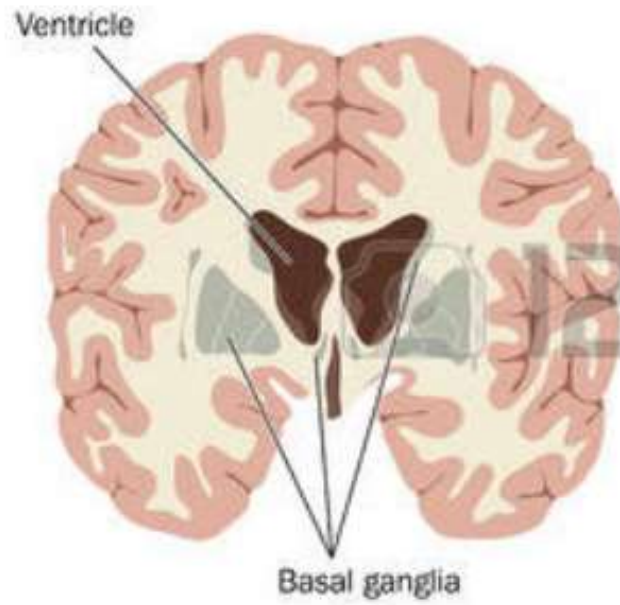
Morphology: macroscopic

- ▶ **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**

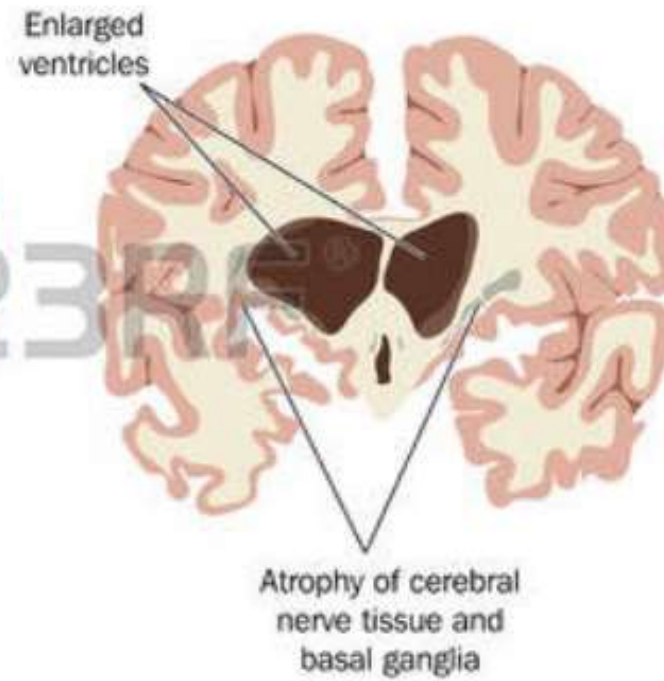
Morphology: microscopic

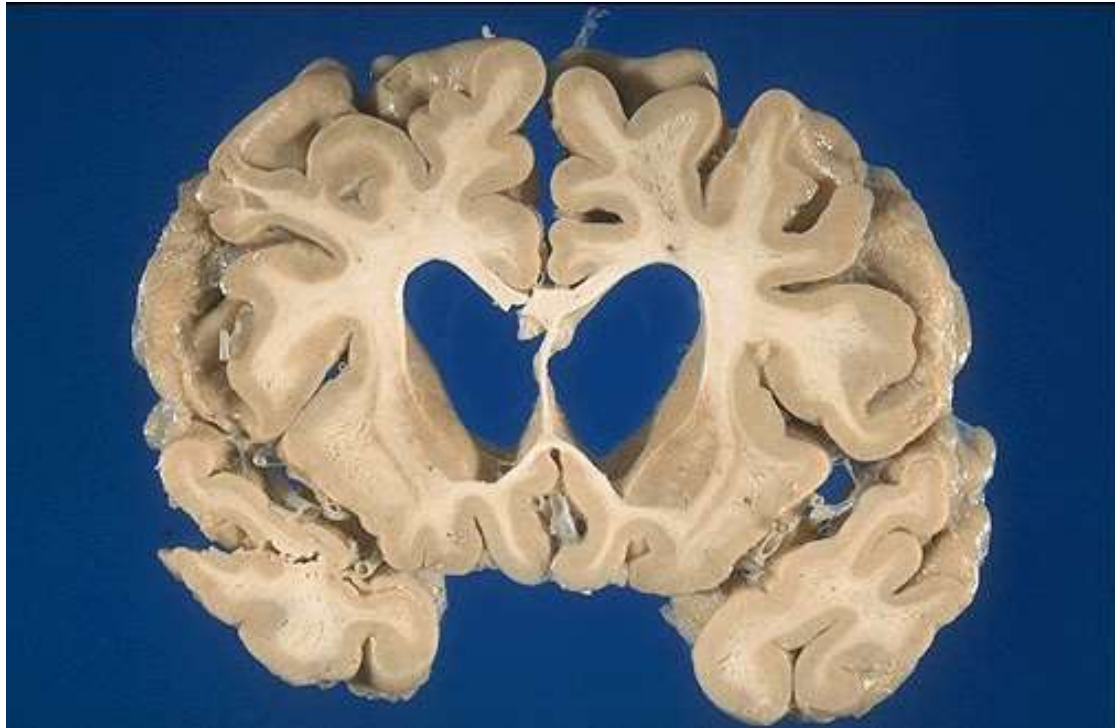
- ▶ Severe loss of neurons from affected regions of the striatum + gliosis
- ▶ Spiny neurons that release γ -aminobutyric acid (GABA), enkephalin, dynorphin, and substance P are especially sensitive, disappearing early.
- ▶ Intranuclear inclusions (aggregates of ubiquitinated huntingtin protein)
- ▶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

Normal brain





Huntington's disease





- ▶ 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