Pathology CNS

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Neurodegenerative disorders-2

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ما بدي اعمل فيها بلسم عليكم بسسسس
سهلة وحلوة كتير كتير كتير الصراحة

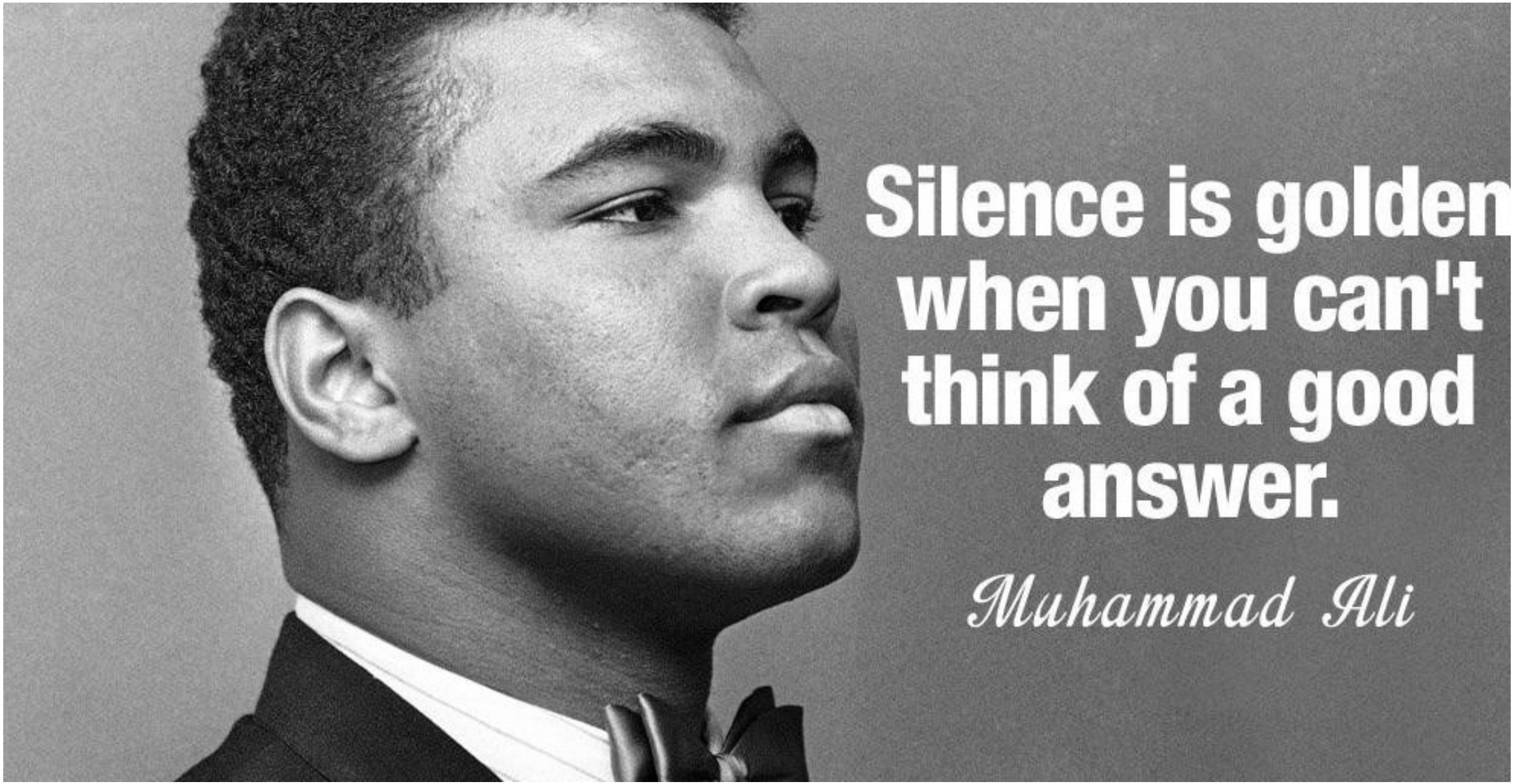
Different diseases

- **Involving the cortex**>>>> cognitive abnormalities of memory, behavior and language >>>> dementia >>>>>ALZHEIMER DISEASE (AD) **-most common neurodegenerative disease-** , FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

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

- **Involving the cerebellum** >>>> ataxia >>> (SPINOCEREBELLAR ATAXIA)

- **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.**

(the dopaminergic neurons give the substantia nigra pigmented color(black/brown) , so loss of the dopaminergic neurons will cause loss of the black color).

Accumulation of proteins in the CNS (like all other neurodegenerative diseases, with differences in the type of protein and the site of accumulation), this accumulation leads to death of neurons because they become toxic.

- Second most common neurodegenerative disorder after Alzheimer's disease
- ***Parkinsonism*** is a clinical syndrome characterized by: tremor, muscle rigidity, bradykinesia, and gate instability.

- Parkinsonism: any damage of dopaminergic neurons, which project from the substantia nigra to the striatum (control of motor activity).

-Before we diagnose Parkinson disease, we should exclude all other causes of parkinsonism.

- Parkinsonism: induced by drugs such as dopamine antagonists(cause the same effect as loss of dopaminergic neurons) or toxins that selectively injure dopaminergic neurons

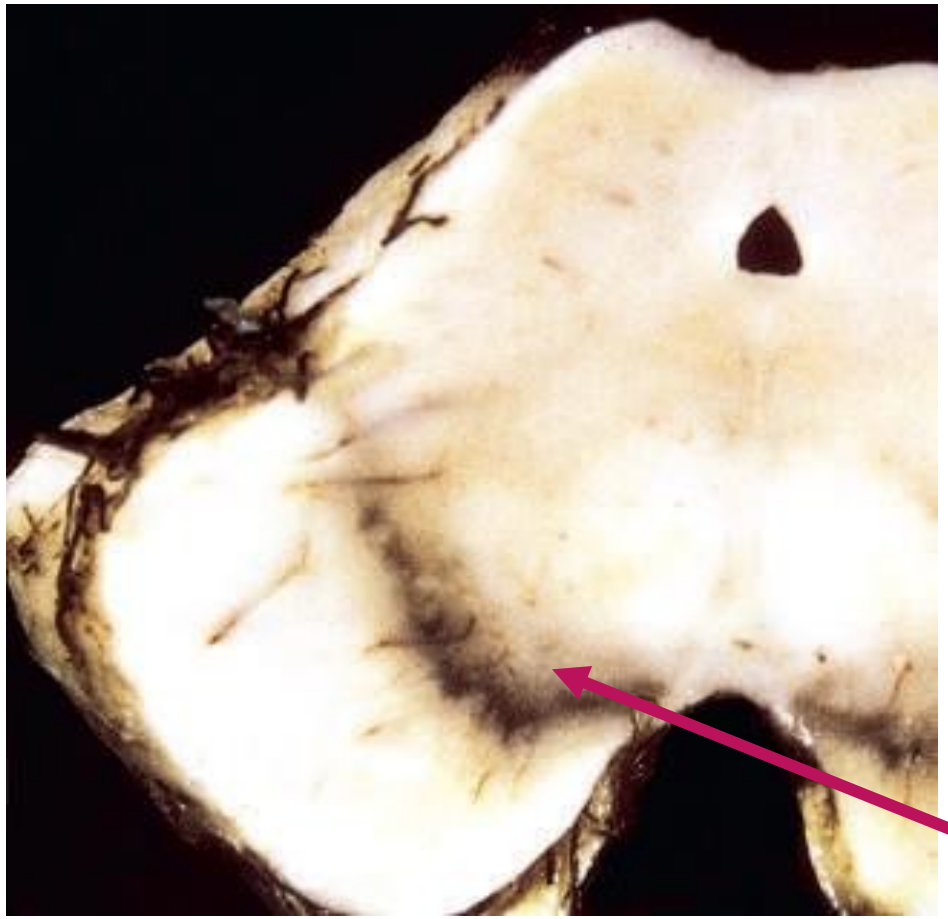
Pathogenesis

- Protein accumulation (*α-synuclein) in the cytoplasm of the neuron* 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**

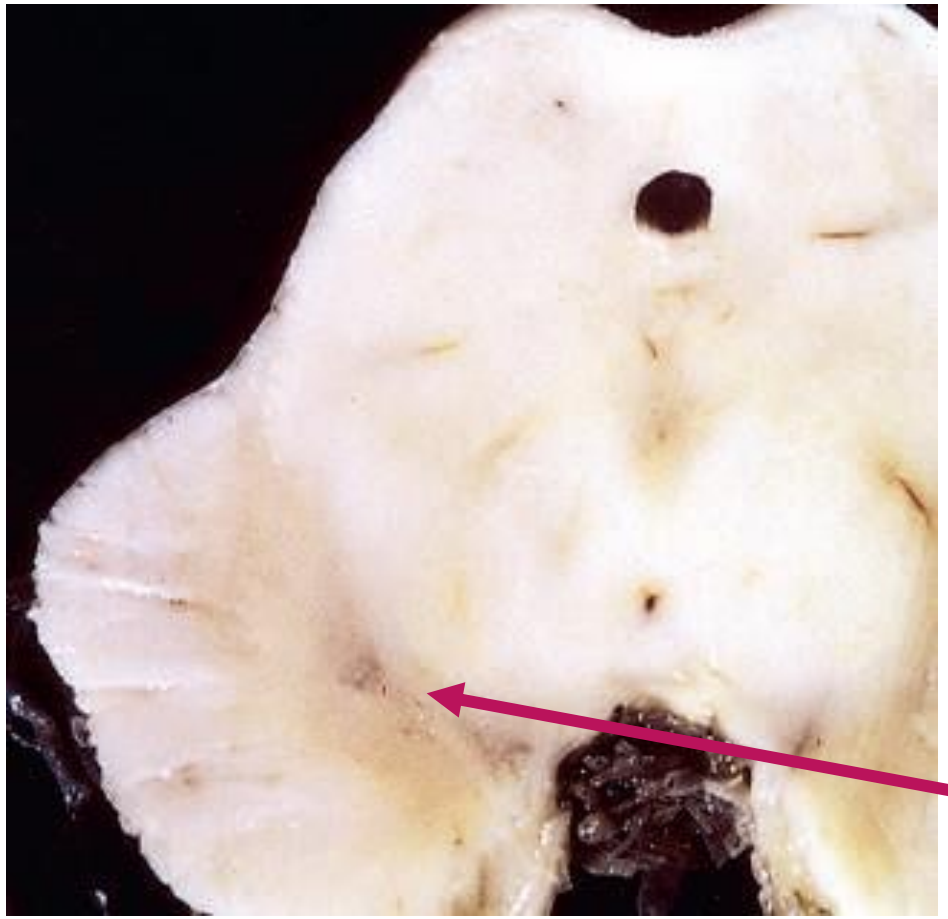
- Clue and diagnostic feature: Lewy body (neuronal inclusions containing *α-synuclein*, a protein involved in synaptic transmission)

- Most cases sporadic, some are autosomal dominant (mutation of *α-synuclein gene)*



Normal substantia nigra

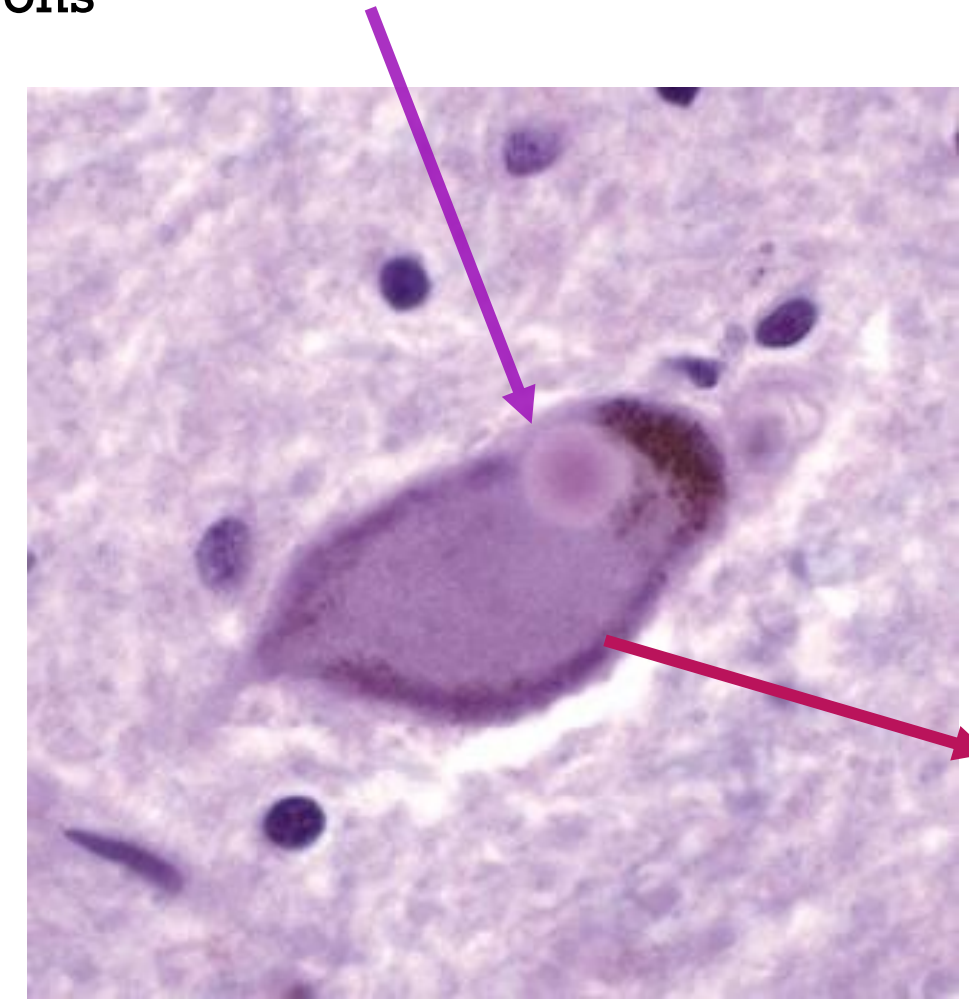
Normal pigmented area



Depigmented substantia nigra in idiopathic Parkinson disease

Loss of pigmented dopaminergic neurons

Lewy body: pink, homogenous, rounded to oval inclusions in the cytoplasm of the neurons



body in a neuron from the substantia nigra stains pink.

Nissl substance

Diagnosis of Parkinson disease isn't based on histopathology or biopsy, it's a clinical diagnosis after exclusion of secondary causes of parkinsonism.

MORPHOLOGY

- Pallor of the substantia nigra and locus ceruleus
- Loss of the pigmented neurons in these regions.

} macroscopic

- Gliosis and proliferation of the microglial cells in the involved area .(reaction of the innate immune system)
- Lewy bodies in neurons (single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions)
- Lewy neurites: dystrophic neurites that also contain aggregated α-synuclein
- Immunohistochemical (antibody against antigen that gives lewy bodies a brown color under the microscope) staining for α-synuclein (for subtle lewy bodies).
- With progression changes can appear in: medulla, pons, amygdala, and the cerebral Cortex (+Lewy body dementia LBD).

Lewy body dementia: when the disease reaches the cortex, it will cause loss of cognitive features, behavioral changes and memory disturbances ,but Parkinson without involvement of the cerebral cortex doesn't cause cognitive features.

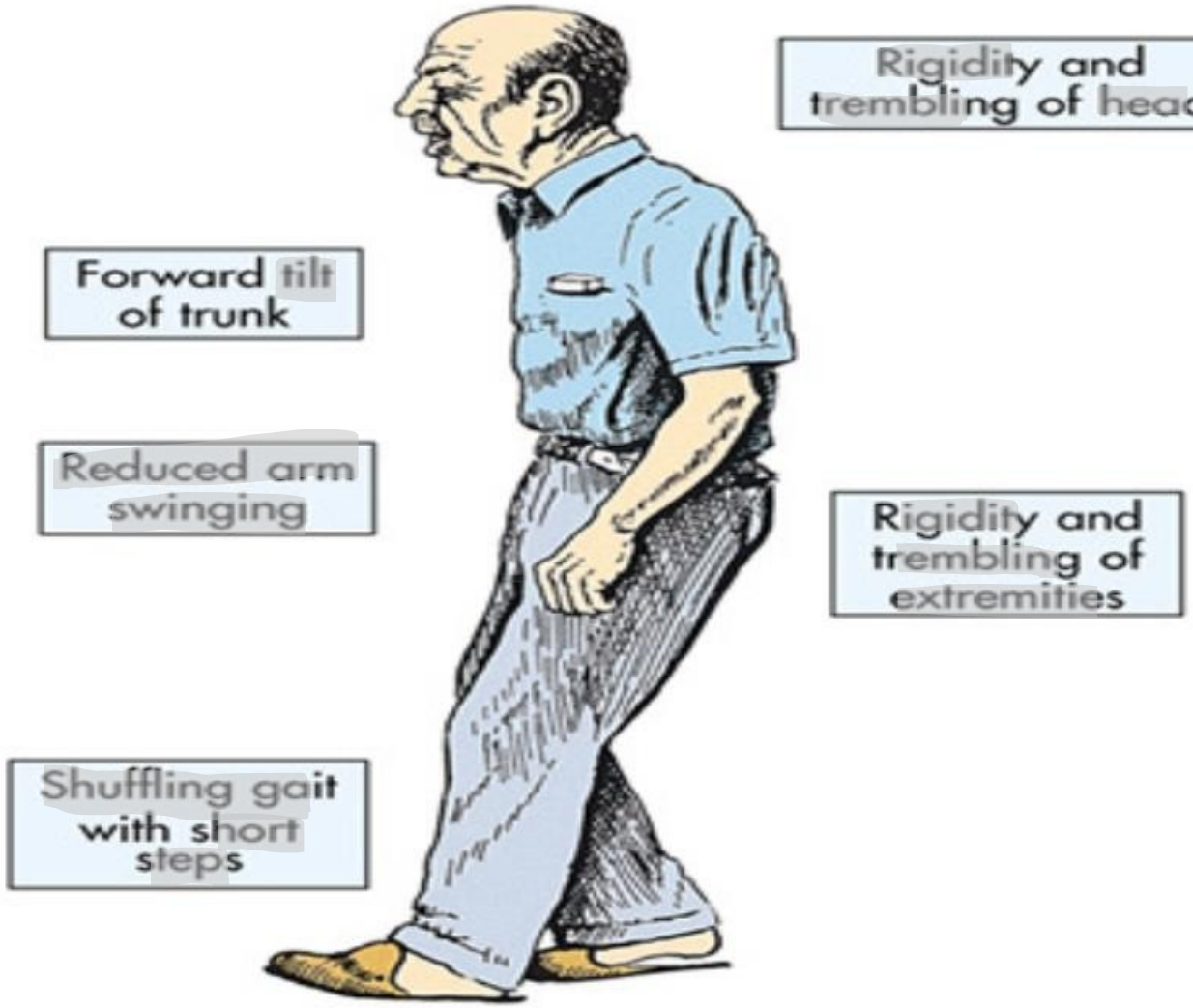
Clinical Features

- Progresses over 10 to 15 years (gradual).
- Eventually producing severe motor slowing or near immobility.
- Death due to aspiration pneumonia or trauma from falls caused by postural (gate) instability.
- Initially respond to L-dihydroxyphenylalanine (L-DOPA)(dopaminergic agonists), but this treatment does not slow disease progression or reverse morphologic findings, it just treats the symptoms, but not the progression of the disease (will not stop loss of neurons or protein aggregation).
- Over time, L-DOPA becomes less effective, so we need a larger dose to have the same effect.
- Another Tx: deep brain stimulation

SYMPTOMS

- **Tremor (course 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.** 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 (mask facies) 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 (rigidity and slowing of movement)

- Diminished facial expressions (Masked facies)
- Stooped posture (leaning forward)
- Slow voluntary movement (bradykinesia)
- Rigidity
- Pill rolling tremor
- Festinating gait= progressively shortened accelerated steps.


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 termer

Patients might rub their thumb and forefinger back-and-forth

Parkinson's Disease

Other motor features:

They exaggerate and become more severe, but cognition and memory will not be affected unless we have deposition of Lewy body in the cortex (Lewy body dementia.

يلا ما تلتهي...قدامي للمرض الي بعده اشوف

Huntington Disease **Hyper mortality**

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

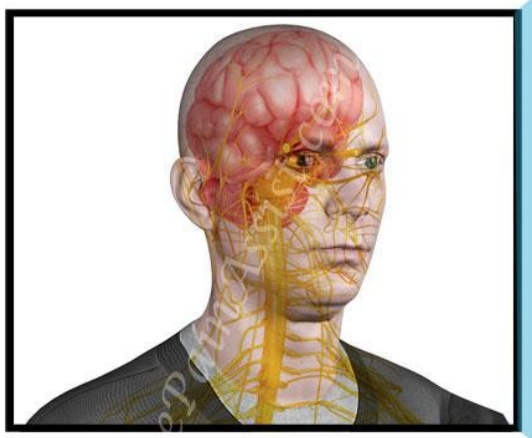
Loss of neurons due to accumulation of proteins in the Basil ganglia

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

Dancing movements all over the body

Chorea is a medical condition and a type of movement disorder

Chorea



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

ePainAssist.com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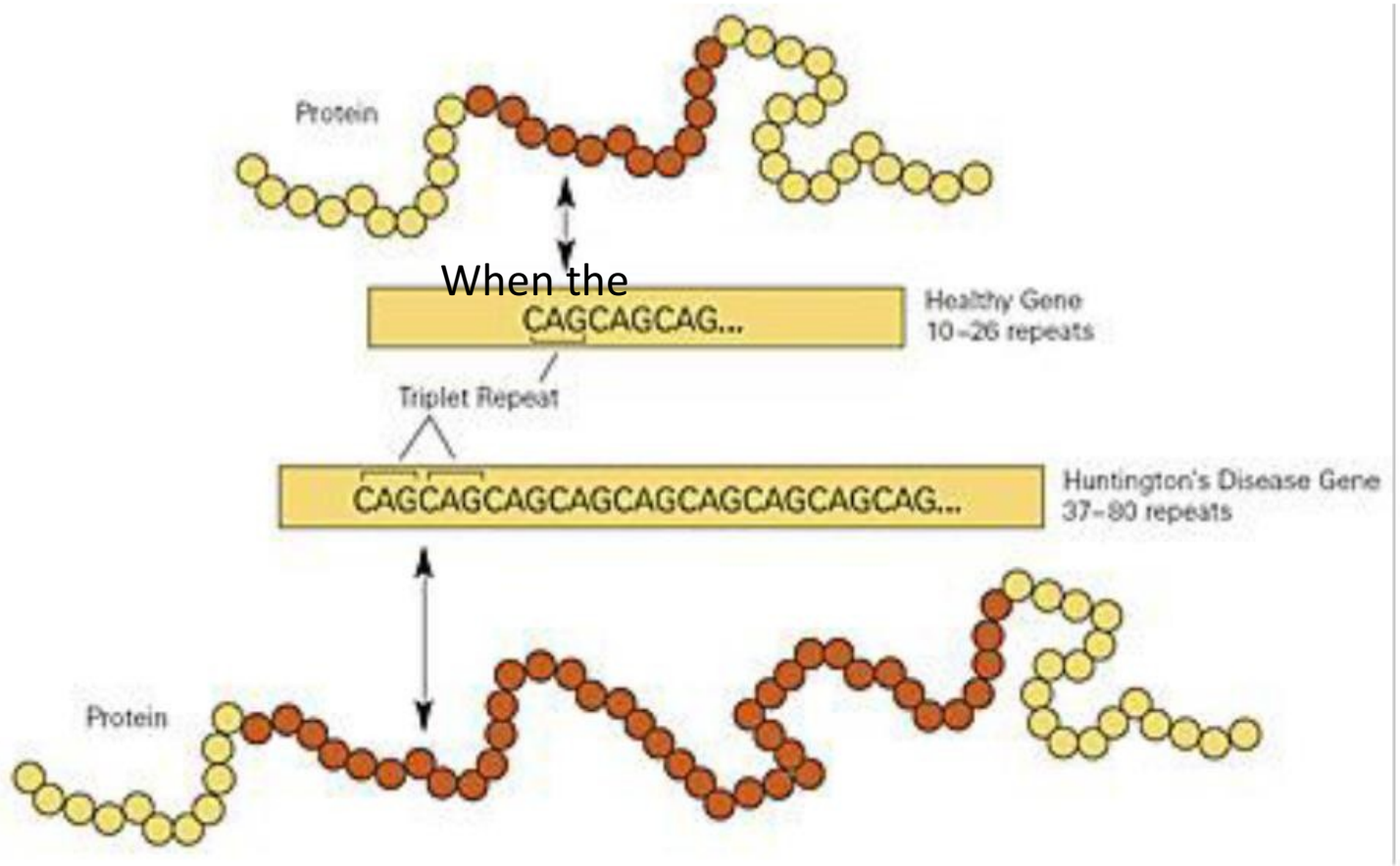
Pathogenesis

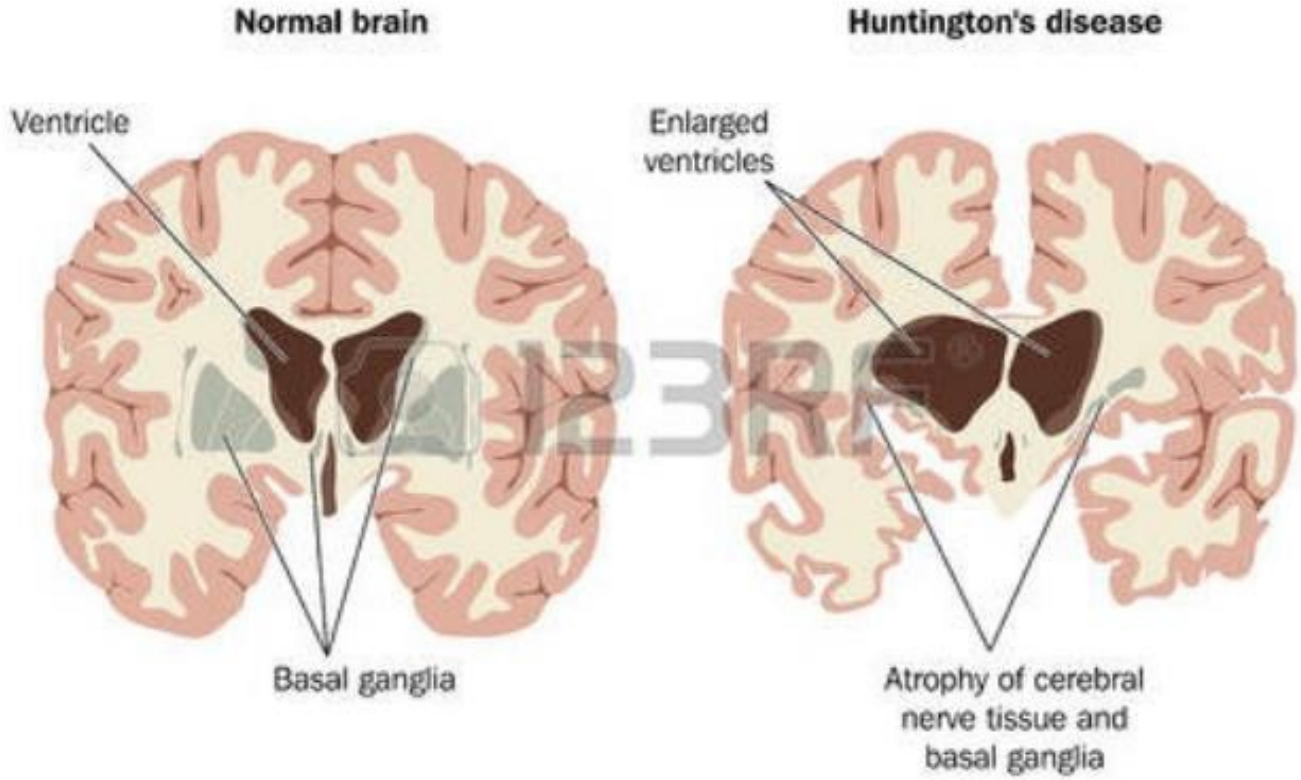
- CAG trinucleotide repeat expansions in huntingtin protein gene located on chromosome 4p16.3 (Polyglutamine)
- Normal alleles contain 11 to 34 copies of the repeat. **(when the number of copies becomes more than 35 -> disease condition)**
- Disease-causing alleles, number of repeats is increased (may be hundreds)
- Larger numbers of repeats results in earlier-onset disease.
- Mutant protein is subject to proteolysis >>> fragments can form large intranuclear aggregates >>> toxic (**proteins deposits in the nucleus-which is toxic to the neurons)**
- Age of onset:40-50 years; related to the length of CAG repeats (more repeats; earlier age of onset)



Longer CAG repeats > the disease earlier onset

Morphology:

- Brain is small (**atrophy in the cortex (gyri atrophied and sulci enlarged**)
- Striking atrophy of the caudate nucleus and the putamen
- Atrophy of globus pallidus
- Dilated lateral and third ventricles
- 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)


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

- 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

- 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 (mask face), 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

C