



CNS
Doctor 2021



Pathology

Modified (2)

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Summary for the previous lecture

Neurodegenerative Disease	FTLD (Frontotemporal Lobar Degeneration)	AD (Alzheimer's disease)
Age	Younger ages	Disease of the elderly
Clinical manifestations	Behavioral and language problems are the earliest manifestations & precede memory disturbances	memory disturbances occur first later on with disease progression psychotic & behavioral problems occur
Abnormal protein inclusion	Primary tau or TDP43	A β amyloid and Tau
Location	frontal & temporal lobes	Affects all lobes except occipital (frontal, temporal, and parietal lobes)
Morphology	Atrophy of frontal & temporal lobes	Atrophy of parietal & temporal at first , frontal is later on affected

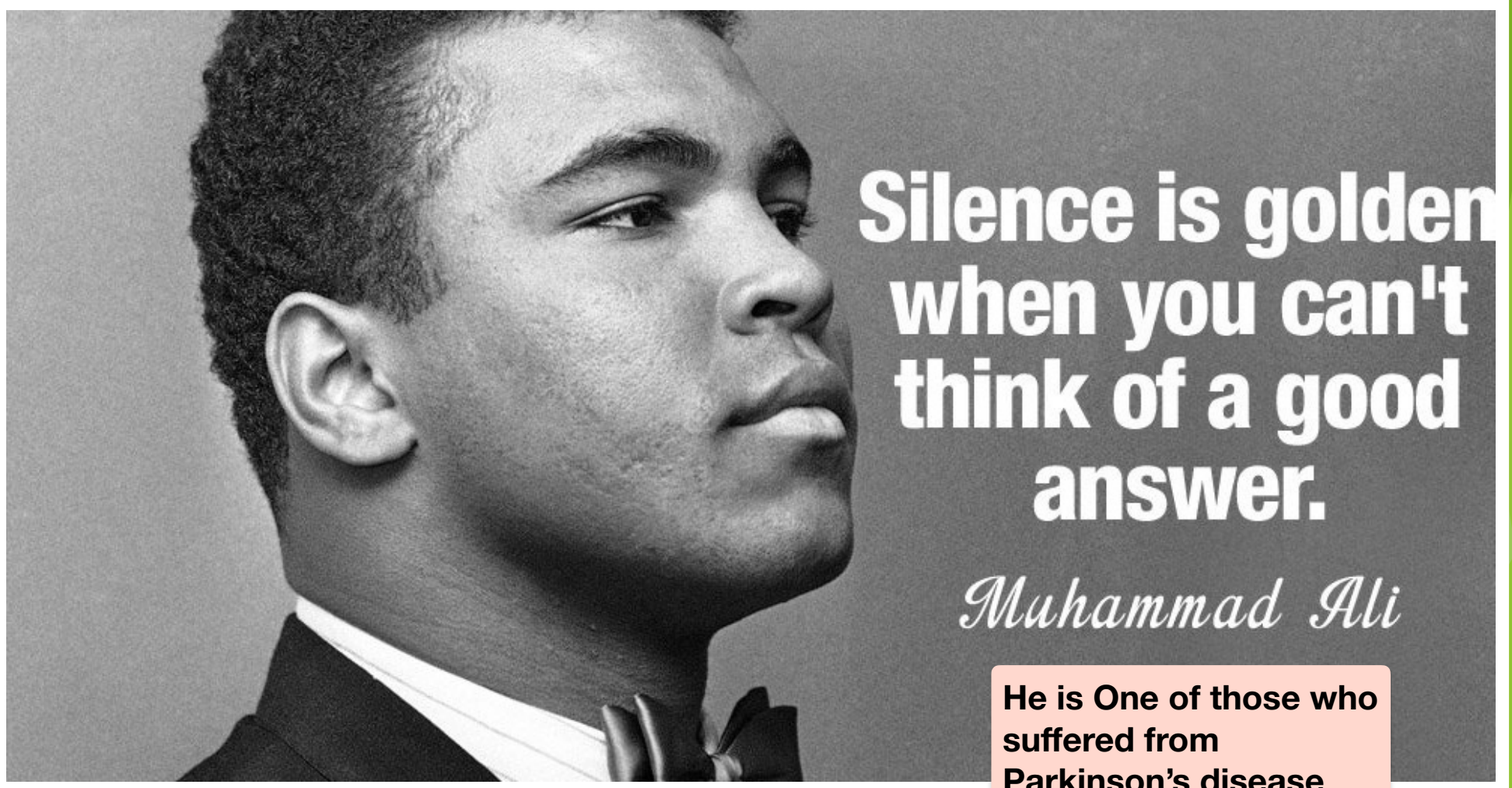
The background features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the left and right sides of the slide, framing the central white area.

Neurodegenerative disorders-2

Different diseases

Last time we talked about degeneration in the cerebral cortex ,in this lecture we will discuss the diseases that happens due to degeneration of basal ganglia

- ▶ neurodegenerative disease that **Involve the cortex** → cognitive abnormalities of memory, behavior and language → dementia
 - 1) ALZHEIMER DISEASE (AD)
 - 2) FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)
- ▶ Involving the **basal ganglia** → **movement disorders (2 types):**
 - A) **hypokinesia or bradykinesia (PARKINSON DISEASE)**
 - B) **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

**He is One of those who
suffered from
Parkinson's disease**

Parkinson Disease (PD) progressive disease with gradual onset

A hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra in the brain (primary cause)

- Second most common neurodegenerative disorder after Alzheimer's disease.
- **Parkinsonism** is a clinical **syndrome** (groups of symptoms) **characterized by** tremor, rigidity, (muscle spasm), **bradykinesia** (slow movement when walking or getting up or sitting down), and **instability**.
- Tremors in parkinson are coarse resting tremors that disappear with movement unlike Fine tremor in hyperthyroidism-thyrotosis, noticeable when initiating movement.
- Parkinsonism: a disease where there is any damage of dopaminergic neurons, which project from the substantia nigra to the striatum (control of motor activity).
- Parkinsonism is induced by **drugs** such as dopamine antagonists or **toxins** that selectively injure dopaminergic neurons and cause decrease in dopamine.
- Parkinsonism is the general term and Parkinson disease is a form of parkinsonism.

Pathogenesis

As we said before accumulation of proteins inside neurons leads to their death, due to inflammation reactions

- ▶ like any neurodegenerative disorder → 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
- ▶ characteristic feature or protein deposit
 - Lewy body (neuronal inclusions containing mutant α -synuclein, a protein involved in synaptic transmission) A delay in synaptic transmission will occur due to the protein accumulation.
- ▶ Microscopically Lewy bodies are Clue and diagnostic feature of PD, intra-cytoplasmic, eosinophilic pink color in H&E or special immune stain for α -synuclein protein → brown color
- ▶ Most cases sporadic, some are autosomal dominant (mutation of α -synuclein gene)

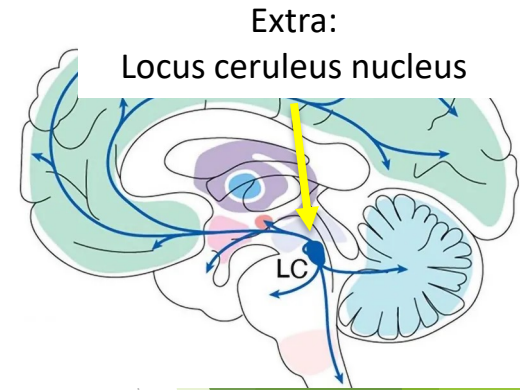
Watch Me



[Osmosis-Parkinson](#)

MORPHOLOGY

- ▶ Pallor of the substantia nigra and locus ceruleus
- ▶ **Loss of the pigmented** neurons in these regions.
- ▶ Gliosis.
- ▶ **Lewy bodies** in neurons (single or multiple, 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 that cannot be detected in H&E sections)
- ▶ With progression changes can appear in: medulla, pons, amygdala, and the cerebral cortex.
PD that involves the cortex \rightarrow Lewy body dementia (LBD)
- ▶ Usually the mental features are preserved in Parkinson patients, disease starts in the basal ganglia but progresses to the outside, when it reaches the cortex \rightarrow parkinson patients will start to complain from dementia.



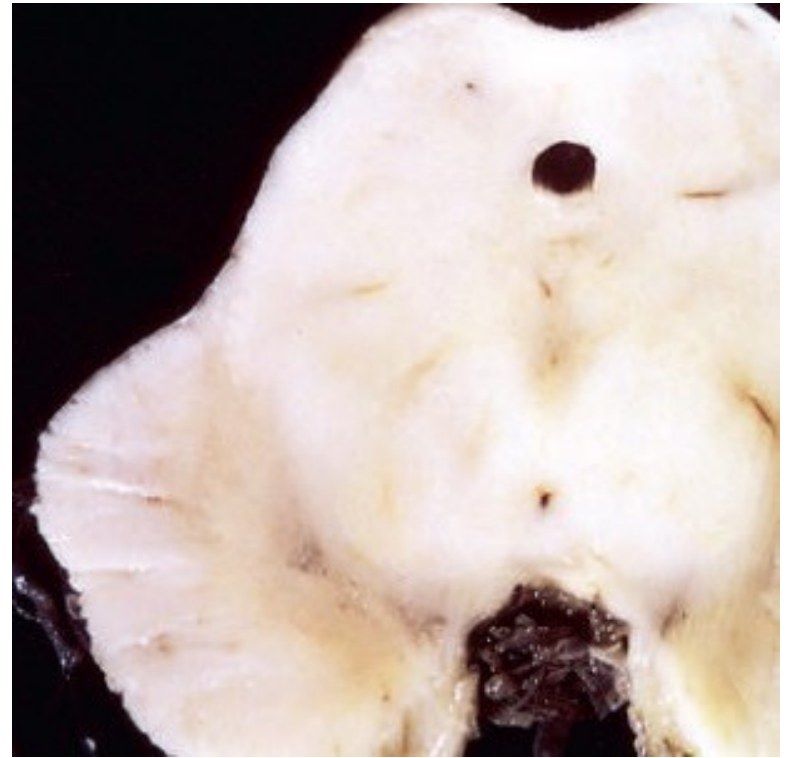
\curvearrowright This should occur within 1 yr of the development of symptoms of Parkinson's disease , if the dementia happened in late stages this may be Alzheimer's

MORPHOLOGY



Normal substantia nigra

Normal pigmented due to the presence of dopaminergic neurons that have cytoplasmic pigment that are seen in H&E sections

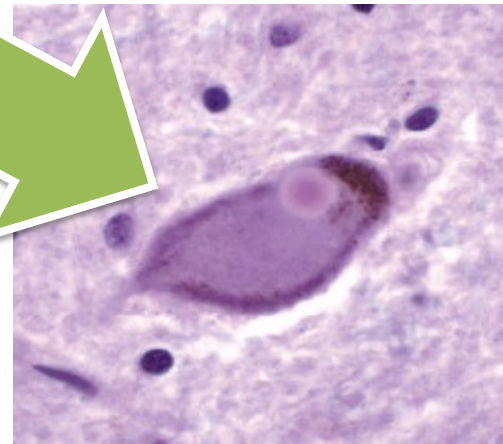
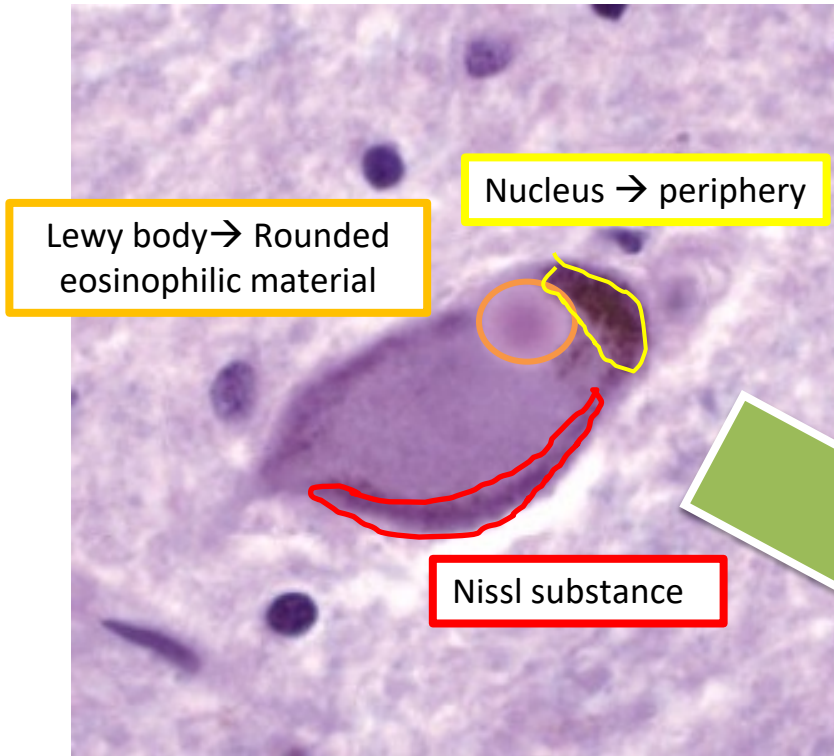


Depigmented substantia nigra in idiopathic Parkinson disease

Pallor of this area

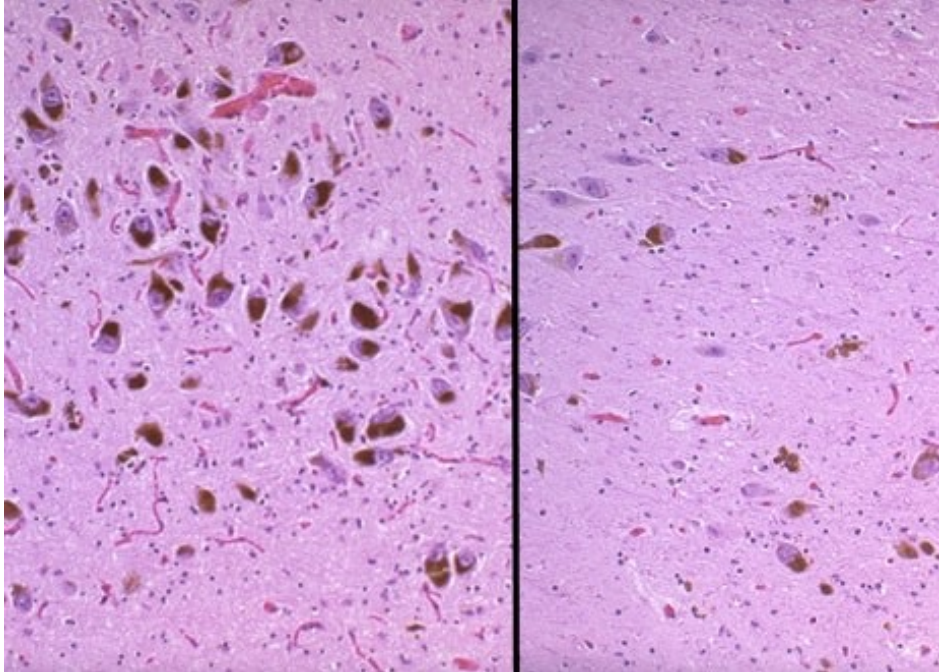
Loss of pigmented neurons

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

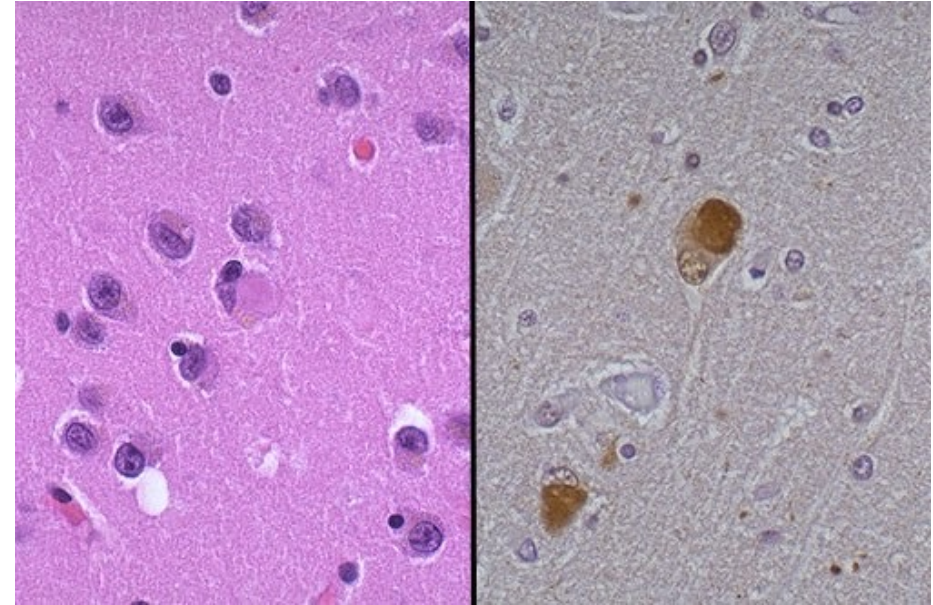


Large cell → neuron

H&E sections from substantia nigra



- ▶ Left: normal dopaminergic neurons
- ▶ Right: loss of pigmented neurons in SN.
Drop in number (Characteristic of parkinson)



- ▶ Immunostaining with antibodies
Anti- α -synuclein
OR ubiquitin ABs to highlight
Lewy bodies.

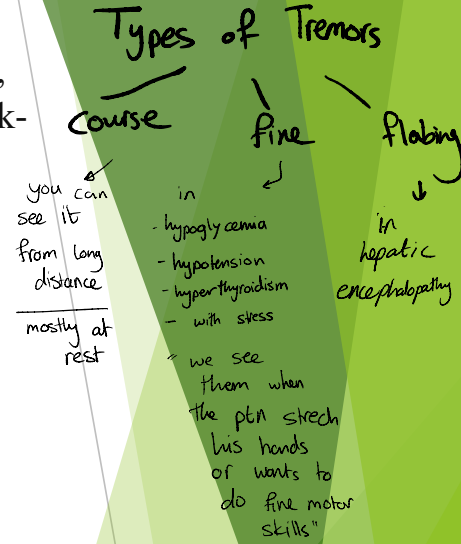
Clinical Features

- ▶ Progresses over 10 to 15 years (worsening & progression over time)
- ▶ Eventually producing severe motor slowing or near immobility.
(Risk of falling down is high)
- ▶ Death due to aspiration pneumonia (muscle spasms) or trauma from falls caused by postural instability (Unstable gait → fracture)
- ▶ Initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment less effective with disease progression
- ▶ Over time, L-DOPA becomes less effective
L-DOPA does not slow disease progression or reverse morphologic findings
- ▶ Another Tx: deep brain stimulation

After this procedure, the doctor may reduce the dose of dopamine used by the patient

SYMPTOMS

- ▶ **Tremor. (coarse & resting)** 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 another type of tremor)
- ▶ **Slowed movement (bradykinesia)** : steps may become shorter, difficult to get out of a chair. Patients drag their feet as they try to walk caused by rigidity
Characteristic movement (Shuffling , festinating gait)
Involuntary hands movement are absent, normally present when walking, Slow movements
- ▶ **Rigid muscles (rigidity)**: The stiff muscles can be painful and limit the range of motion.
- ▶ **Impaired posture and balance. Caused by muscle rigidity** stooped posture (leaning forward) an attempt from the patient to stabilize themselves, and balance problems
- ▶ **Loss of automatic movements.:** decreased ability to perform unconscious, involuntary 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 & difficult to write because of muscle rigidity
- ▶ **Diminished facial expressions** (Masked facies) – characteristic
- ▶ **Slow voluntary movement** to get up from chair or comb hair



SYMPTOMS

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



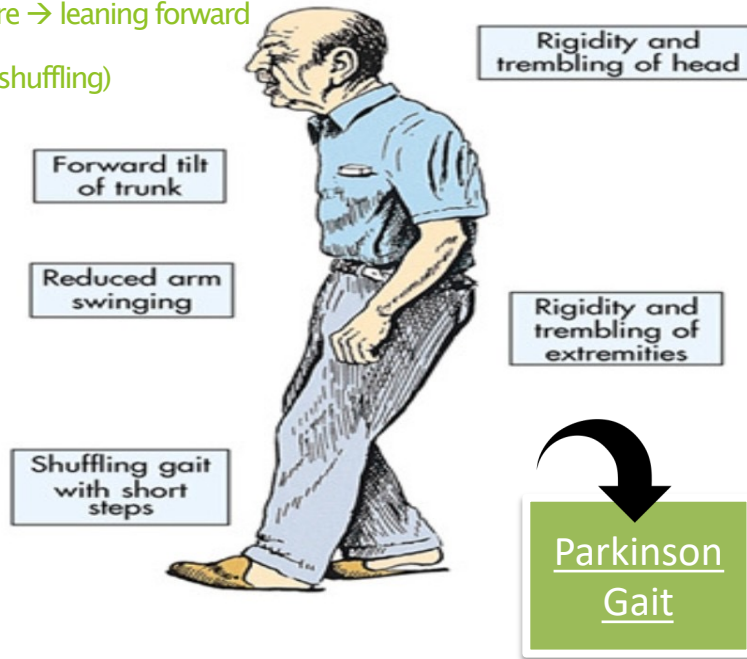
Parkinson Symptoms

Stooped posture

Patient tries to stabilize their posture



Stoop posture → leaning forward
Short steps (shuffling)



Pill rolling tremor



Huntington Disease

- ▶ movement disorder that results from neurodegenerative disease affecting the basal ganglia

Autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen) that lie on the sides of the ventricles.

→ Morphologically: Atrophy of these structures & enlargement of ventricles

- ▶ Not sporadic but inherited same as AD pattern

- ▶ **characterized by chorea** : Involuntary jerky movements of all parts of the body from head to toe; writhing movements of the extremities .

- ▶ Progressive starts in 40s-50s , death after an average 15 years

- ▶ **Early** cognitive symptoms (forgetfulness and thought and affective disorders, severe dementia). Memory abnormalities, mental retardation

→ Unlike parkinson where cognitive symptoms appear very late in the disease

- ▶ Increase risk of suicide.

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

Dancing movements

Starting from the head, limbs, trunk and toes



CoverP

Morphology: macroscopic

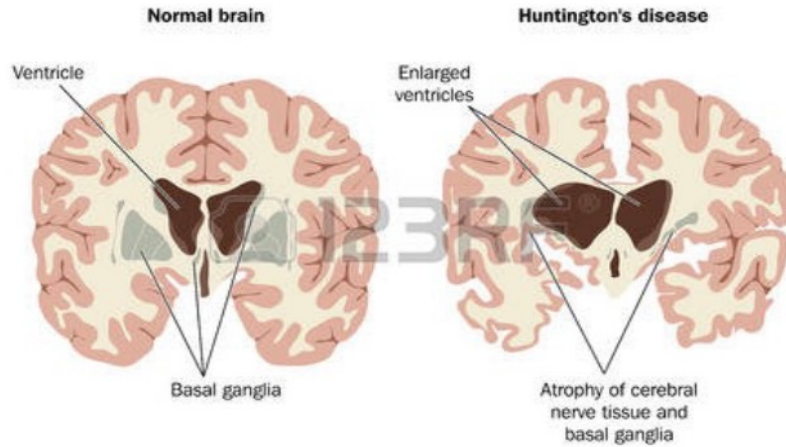
- ▶ Brain is small
- ▶ Striking atrophy of the caudate nucleus and the putamen
- ▶ Secondary atrophy of globus pallidus
- ▶ Atrophy frequently also is seen in the frontal lobe.
- ▶ Dilated lateral and third ventricles

And that's why they show cognitive impairment

Compensatory dilatation

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.



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



Pathogenesis

▶ characteristic: Expansion of a small DNA focus

CAG trinucleotide repeat expansions in huntingtin protein gene located on 4p16.3 (Polyglutamine)

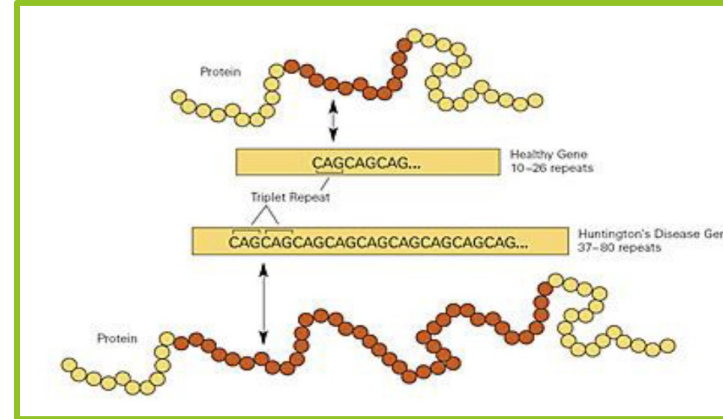
- ▶ Normal alleles contain 11 to 34 copies of the repeat. (35+ copies → Huntington)
- ▶ Disease-causing alleles, number of repeats is increased (may be hundreds)
- ▶ Larger numbers of repeats results in earlier-onset disease.

Accumulation of Huntington protein

- ▶ mechanism of the disease: transcription of Mutant Huntingtin protein is subject to proteolysis >>> fragments (by products) deposition

can form large intranuclear aggregates >>> toxic → neuronal loss & atrophy of the affected sites

- ▶ Age of onset: 40-50 years; related to the length of CAG repeats (more repeats; earlier age of onset), presentation of the disease at any age depends on the number of repeats



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.

Thank you :)

Here's a tip when doing clinical-scenario questions (scan read thru the paragraph) since not all info are equally important & to detect **key-info** quickly

- ▶ 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

Ans: A

Chorea, multiple family members (inherited) → Huntington

- ▶ 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

Ans: C

Tremor is gone with movement, No loss of mental ability

Sullen → mask face

If cognitive abnormalities are present → Lewy body dementia