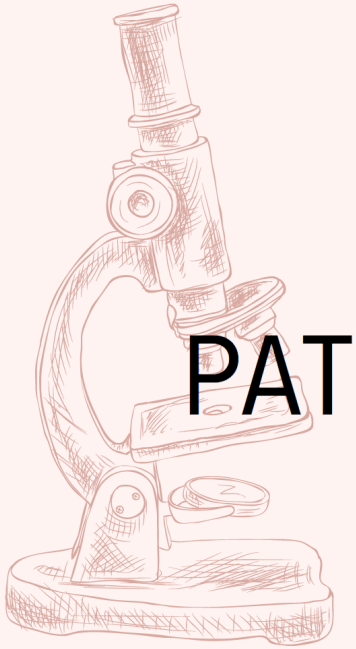

# PATHOLOGY

## Central Nervous System


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# Frontotemporal Lobar Degeneration

- Several or Group of disorders

  → *Different diseases with different (abnormal)* **protein accumulations** → *results in:* ***Neurodegenarative dementia***

- Affect the cerebral cortex*:* **frontal** and/or **temporal** lobes
- **Therefore function is affected**

  Progressive deterioration of language (temporal) and changes in personality (frontal)

  Clinically, these diseases are referred to as frontotemporal dementias.

  **Earliest symptoms are Behavioral and language problems precede memory disturbances, in contrast to AD**

- The onset of symptoms **occurs at younger ages** than for AD.

Extra Video

https://youtu.be/U6B4JNWtNpw

# Frontotemporal Lobar Degeneration

- Two pathologic subgroups (two forms of the disease) with the same clinical manifestations, distinguished based on the composition of the characteristic neuronal **inclusions** that contain **different proteins**:

**1) FTLD tau:** primary tau deposition in the form of neurofibrillary tangles (triangular in shape) in the cytoplasm of neuron which are toxic to the neuron and cause cell death.

→ **Pick disease** (subtype of FTLD-tau): associated with Pick bodies (smooth, eosinophilic, round inclusions) in the cytoplasm.

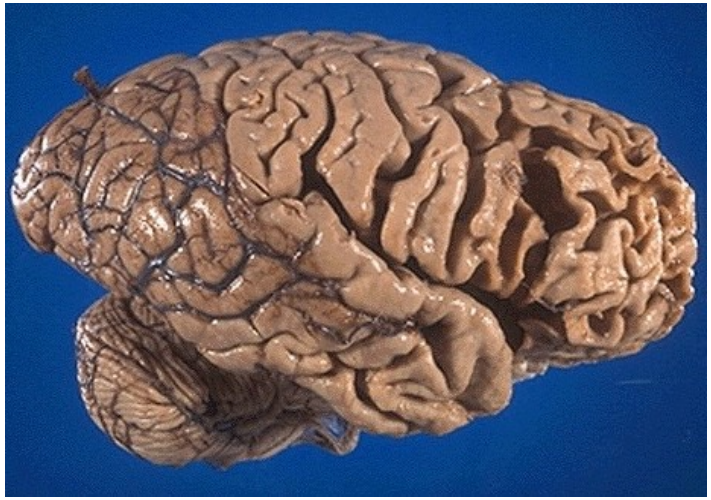
**2) FTLD TDP43** (not discussed)

Genetically different results from abnormal TDP43 protein, but presents with the same symptoms as FTLD-tau.

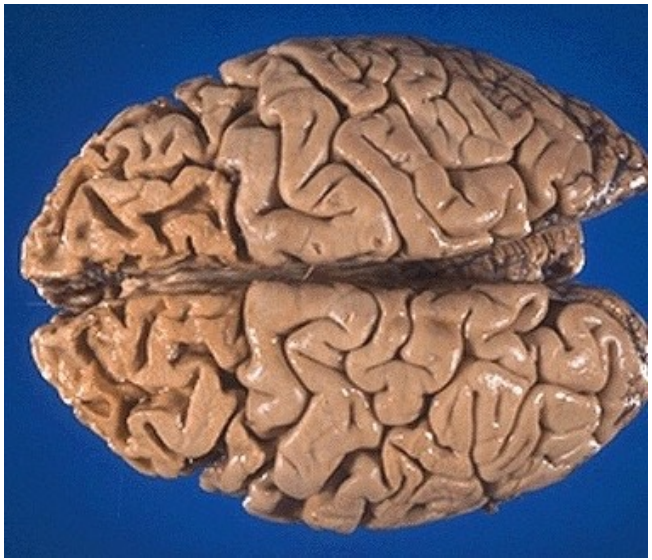
# MORPHOLOGY

- Atrophy of frontal and temporal lobes.
- Neuronal loss and gliosis (Like all neurodegenarative disorder)
- In FTLD-tau, the characteristic neurofibrillary tangles are present, similar to AD (but not associated with Aβ amyloid). In addition to Pick bodies.

- Very marked **frontal lobe atrophy** and **temporal lobe atrophy**



Frontal lobes are markedly thinned

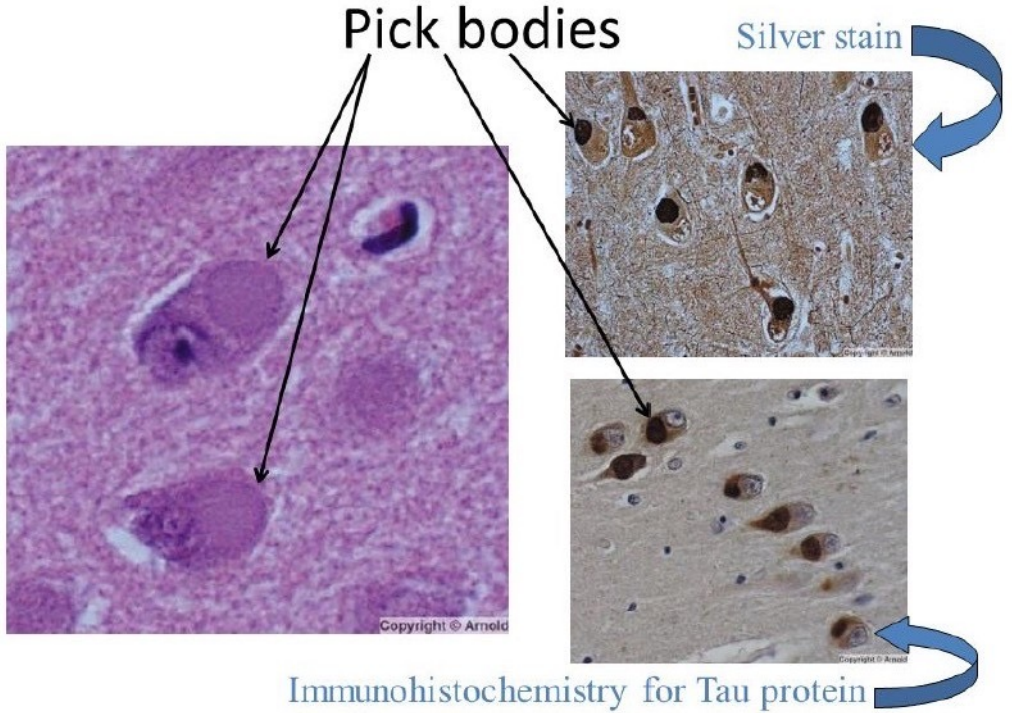


# Microscopically

FTLD that's associated with tau is known as pick disease

Pick bodies are made of tau, Circular deposits present in the cytoplasm.

Highlighted with special stain or by silver stain.

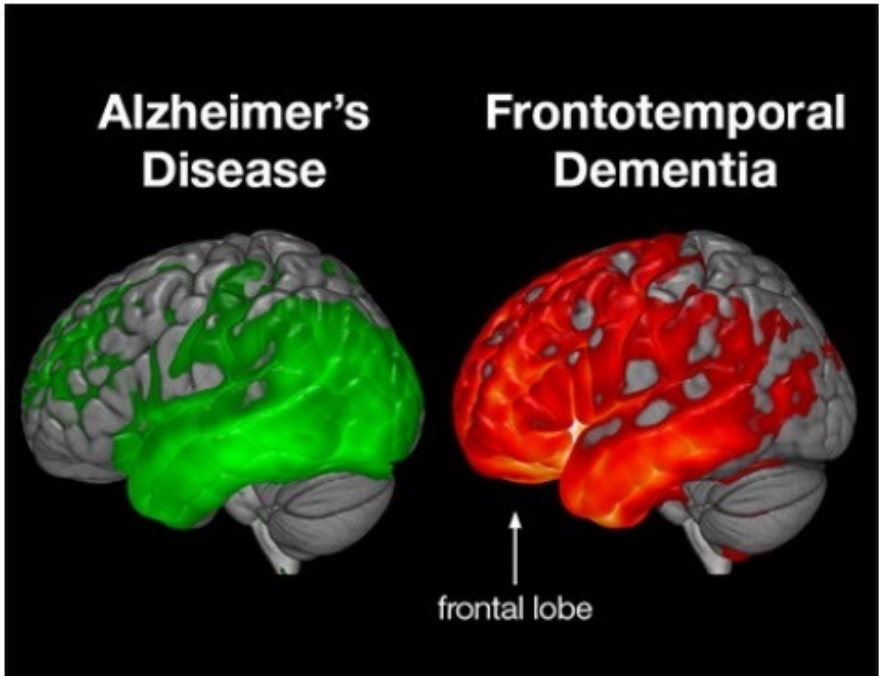


| Neurodegenerative Disease | FTLD (Frontotemporal Lobar Degenration) | AD (Alzheimer's disease) |
|---|---|---|
| **Age** | Younger ages | Disease of the elderly |
| **Clinical manifestations** | **Behavioral and language problems are the earliest** manifestations & precede memory disturbances | **memory disturbances occur first** later on with disease progression psychotic & behavioral problems occur |
| **Abnormal protein inclusion** | Primary tau or TDP43 | Aβ 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 |

- In AD, the temporal & parietal lobes are affected earlier & there is sparing of the frontal lobe, at least at the beginning so behavioural changes are a late manifestation.

- In FTLD, frontal is affected from the beginning so patients present with behavioural problems first.

  Which is morphologically noticeable, the macroscopic appearance the fronto-temporal lobe is atrophied.



# Neurodegenerative disorders-2

# Different diseases

- neurodegenerative disease that **Involve the cortex** → cognitive abnormalities of memory, behavior and language → dementia

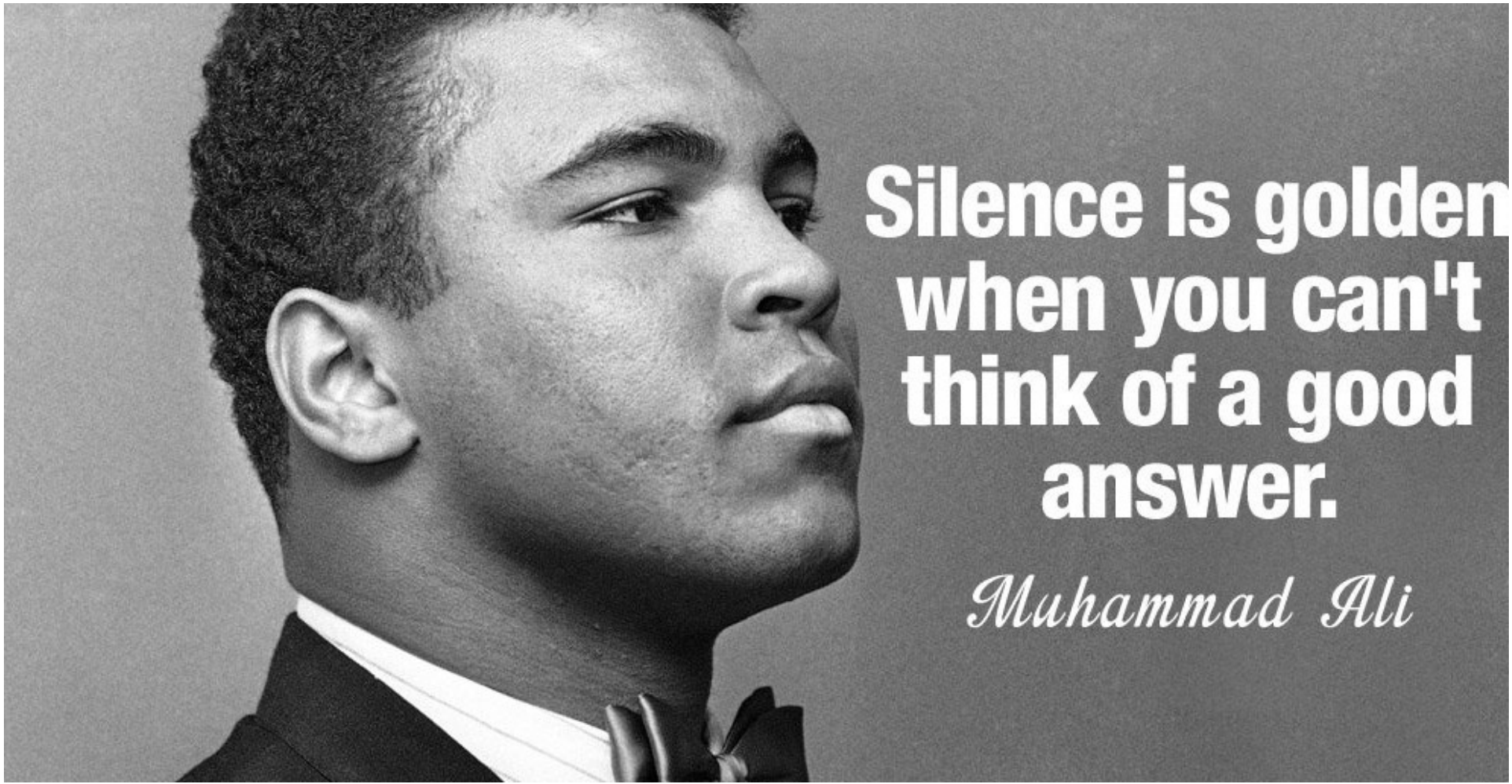
1) ALZHEIMER DISEASE (AD)
2) FRONTOTEMPORAL DEMENTIA (FTD), PICK DISEASE (SUBTYPE OF FTD)

- **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

# 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-thyrotosicosis, 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

- 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)

- **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

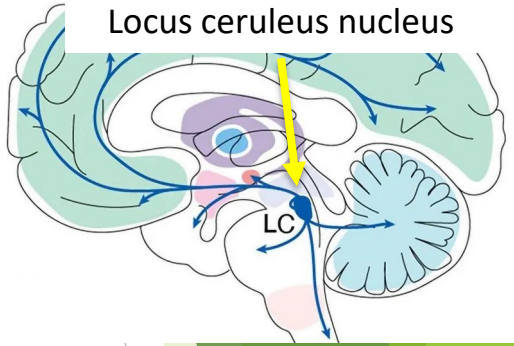
Osmosis-Parkinson

# MORPHOLOGY

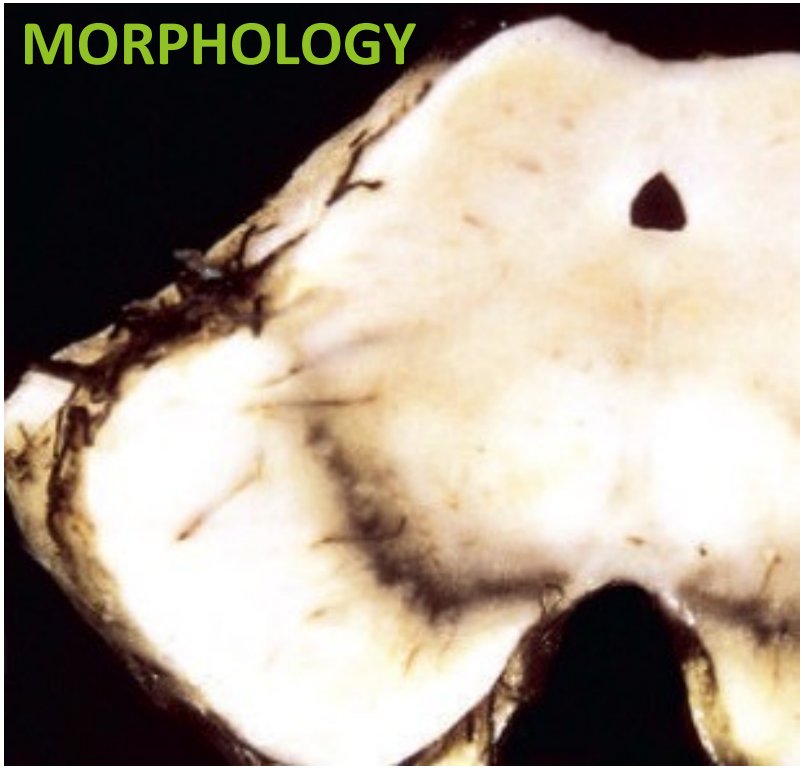
- Pallor of the substantia nigra and locus ceruleus
- **Loss of the pigmented** neurons in these regions.
- Gliosis.
- Lewy bodies in neurons (single or multiple, cytoplasmic, eosinophilic, round to elongated inclusions)
- Lewy neurites: dystrophic neurites that also contain aggregated α-synuclein
- 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 → 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 → parkinson patients will start to complain from dementia.

Extra:
Locus ceruleus nucleus

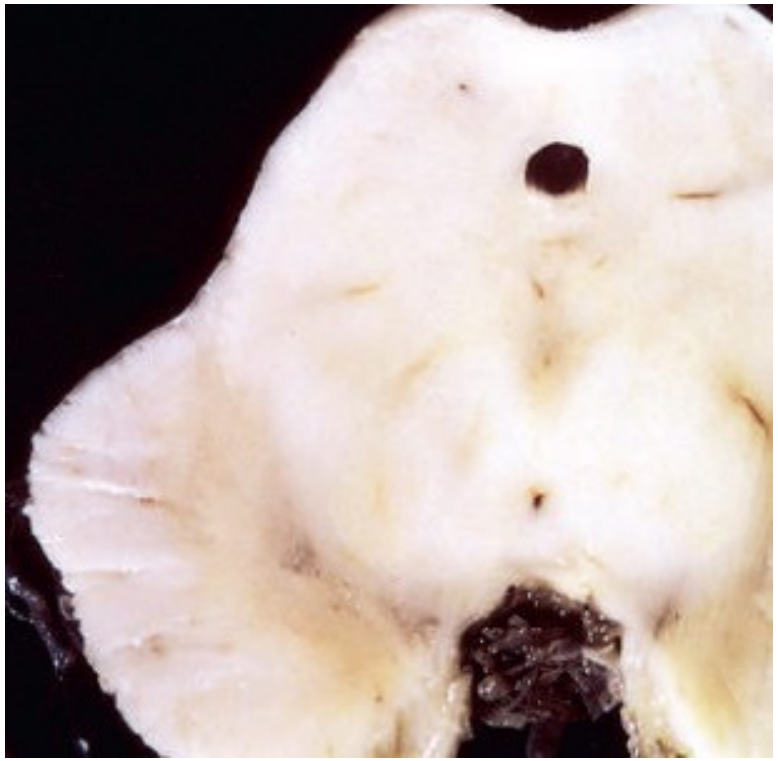


# MORPHOLOGY



## Normal substantia nigra

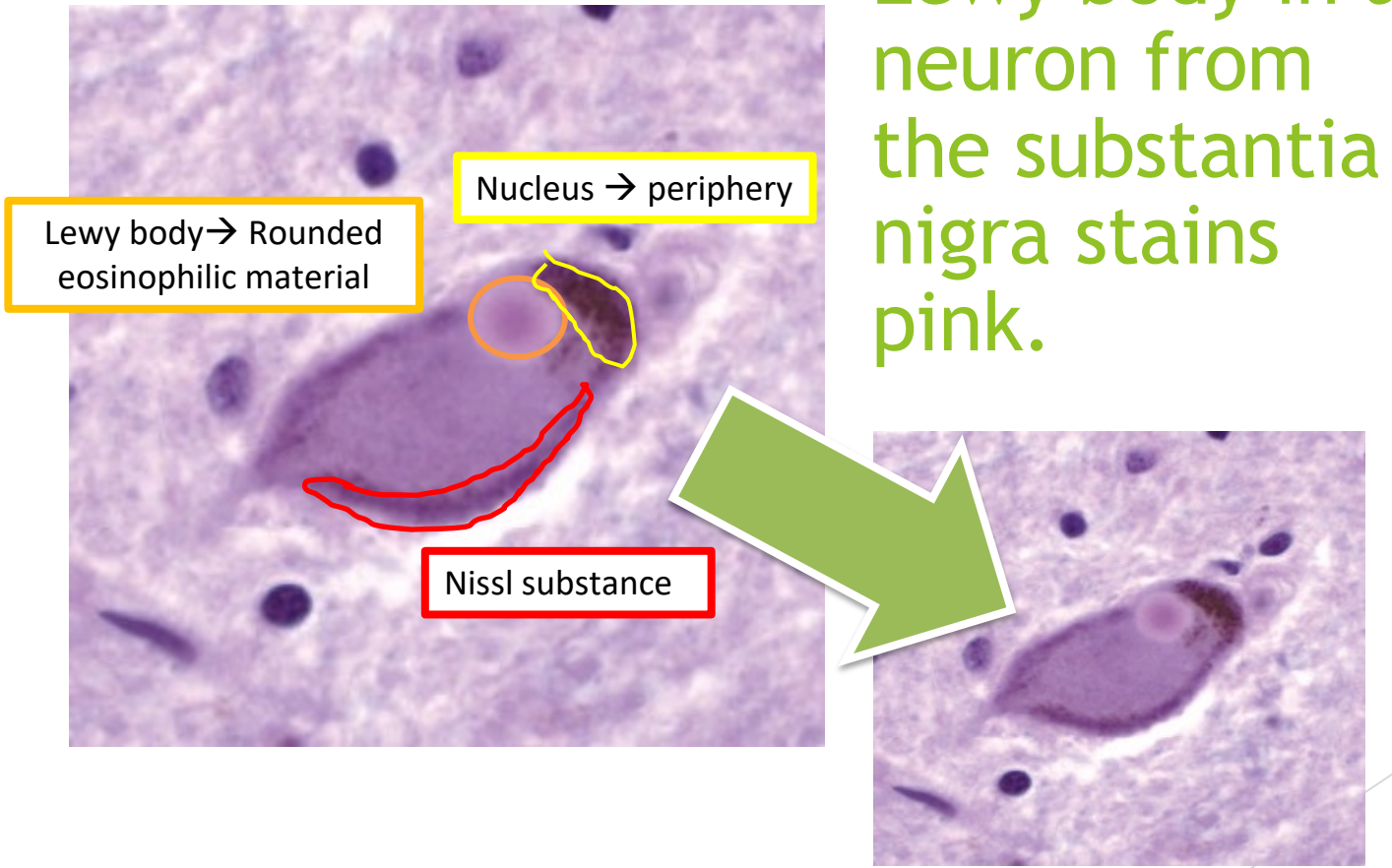
Normall pigmented due to the presence of dopamenergic neurons that have cytoplasmic pigmenet that are seen in H&E sections



## Depigmented substantia nigra in idiopathic Parkinson disease

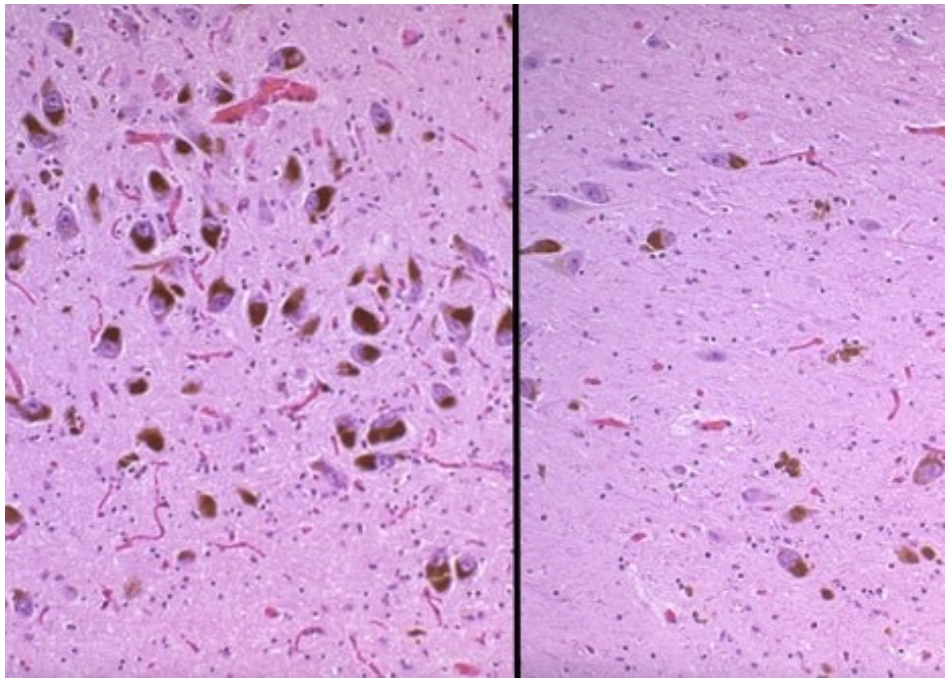
Loss of pigmented neurons

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



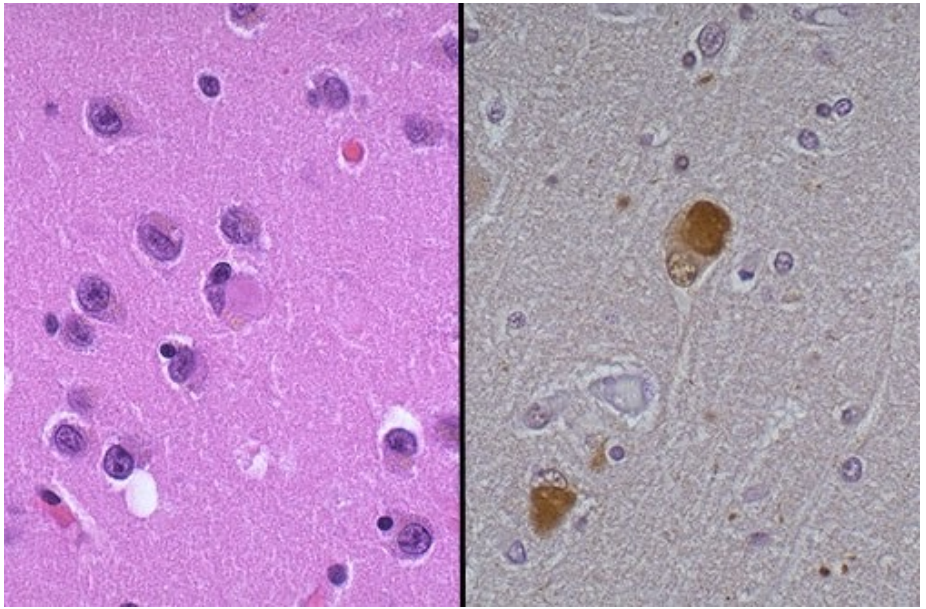

Large cell → neuron

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

# SYMPTOMS

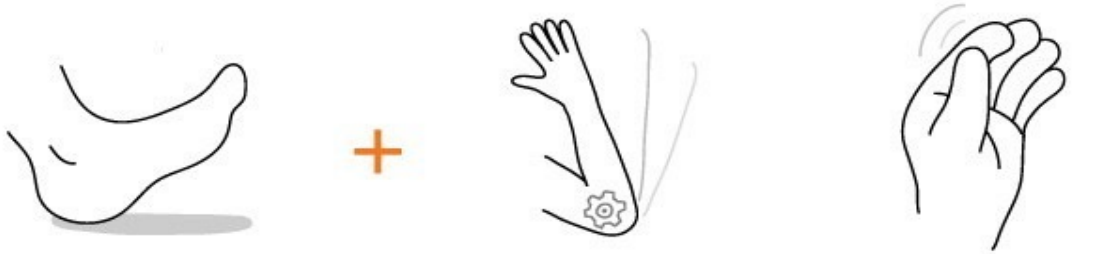
TRIAD

- 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 gate)
  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

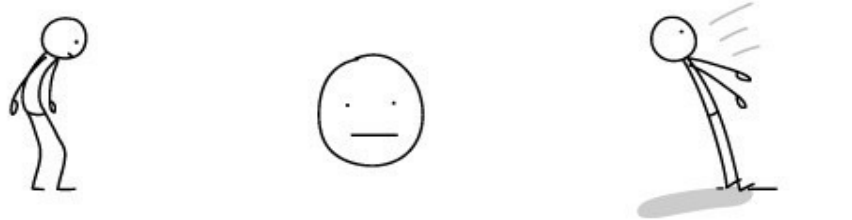


Bradykinesia
*(as seen in toe tapping)*

Cogwheel Rigidity

Resting Tremor
*(pill rolling tremor)*

*Other motor features:*



Shuffling Gait

Mask-like Expression

Postural Instability

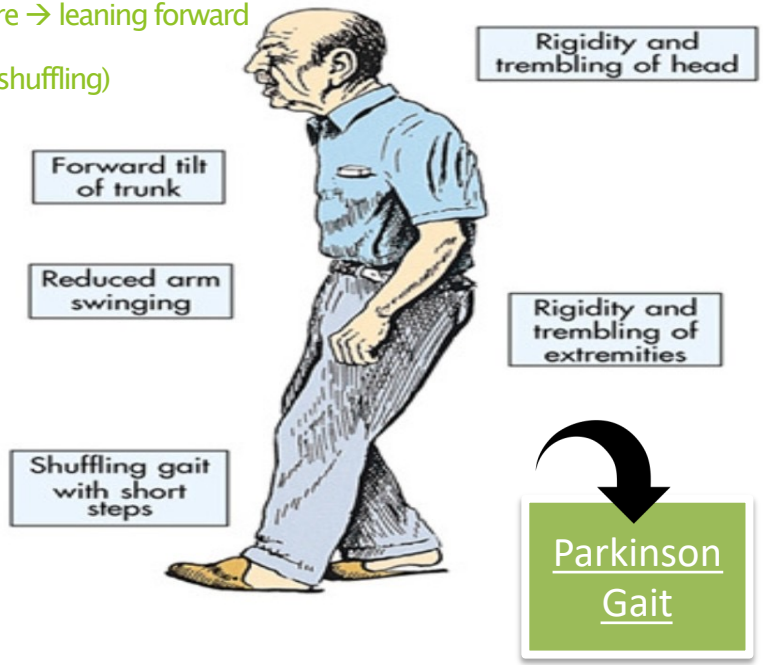
Parkinson Symptoms

# Stooped posture

Patient tries to stabilize their posture

Stoop posture → leaning forward

Short steps (shuffling)




Parkinson Gait

## Pill rolling tremer

# Huntington Disease

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

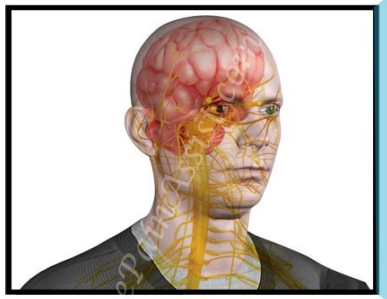
  Autosomal dominant movement disorder associated with degeneration of the striatum (caudate and putamen) that lie on the sides of the ventricles.

→ 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

# Chorea



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

Chorea is a medical condition and a type of movement disorder

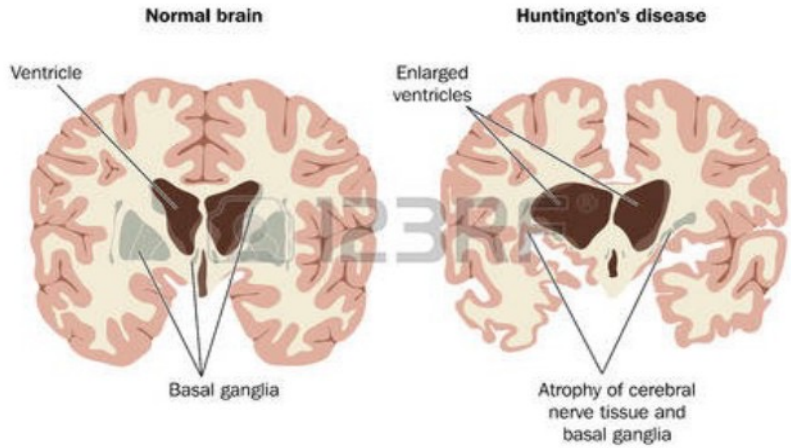

Dancing movements

Starting from the head, limbs, trunk and toes

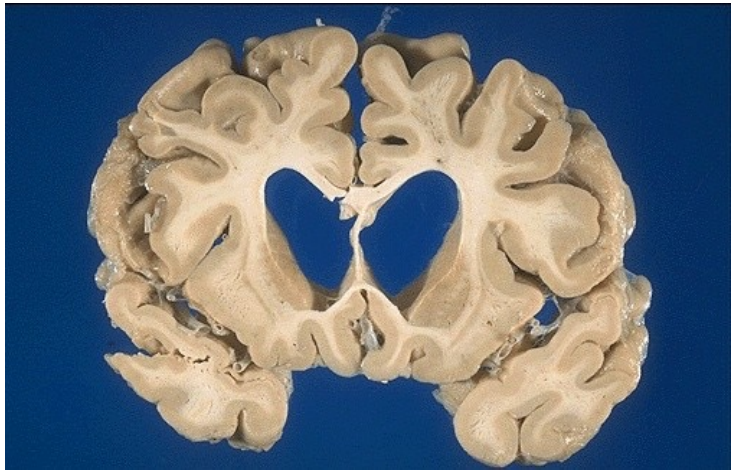
# Morphology:

- Brain is small
- 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)

Damaged proteins are directed for ubiquitination, Inclusions can be highlighted by ubiquitin stain.




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

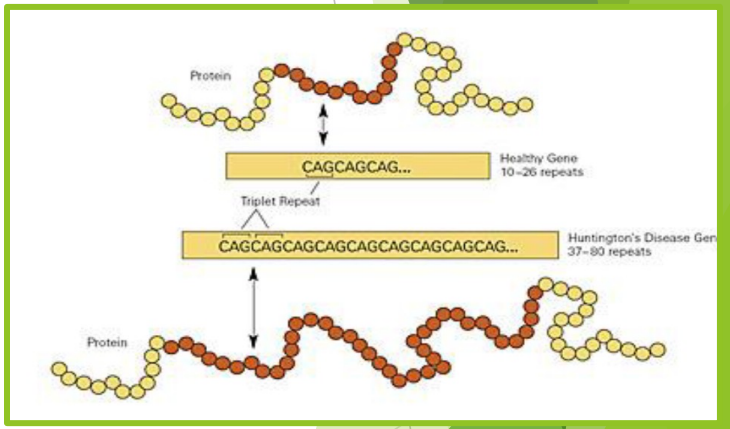


# Pathogenesis

- **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 → hungtiton)
- Disease-causing alleles, number of repeats is increased (may be hundreds)
- **Larger** numbers of repeats results in **earlier-onset** disease.




- mechanism of the disease: transcription of Mutant Huntington

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

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