CNS pathology
Third year medical students 2021

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Lecture 8: neurodegenerative diseases part 2:

Neurodegenerative diseases affecting the basal nuclei

Neurodegenerative diseases affecting the basal nuclei

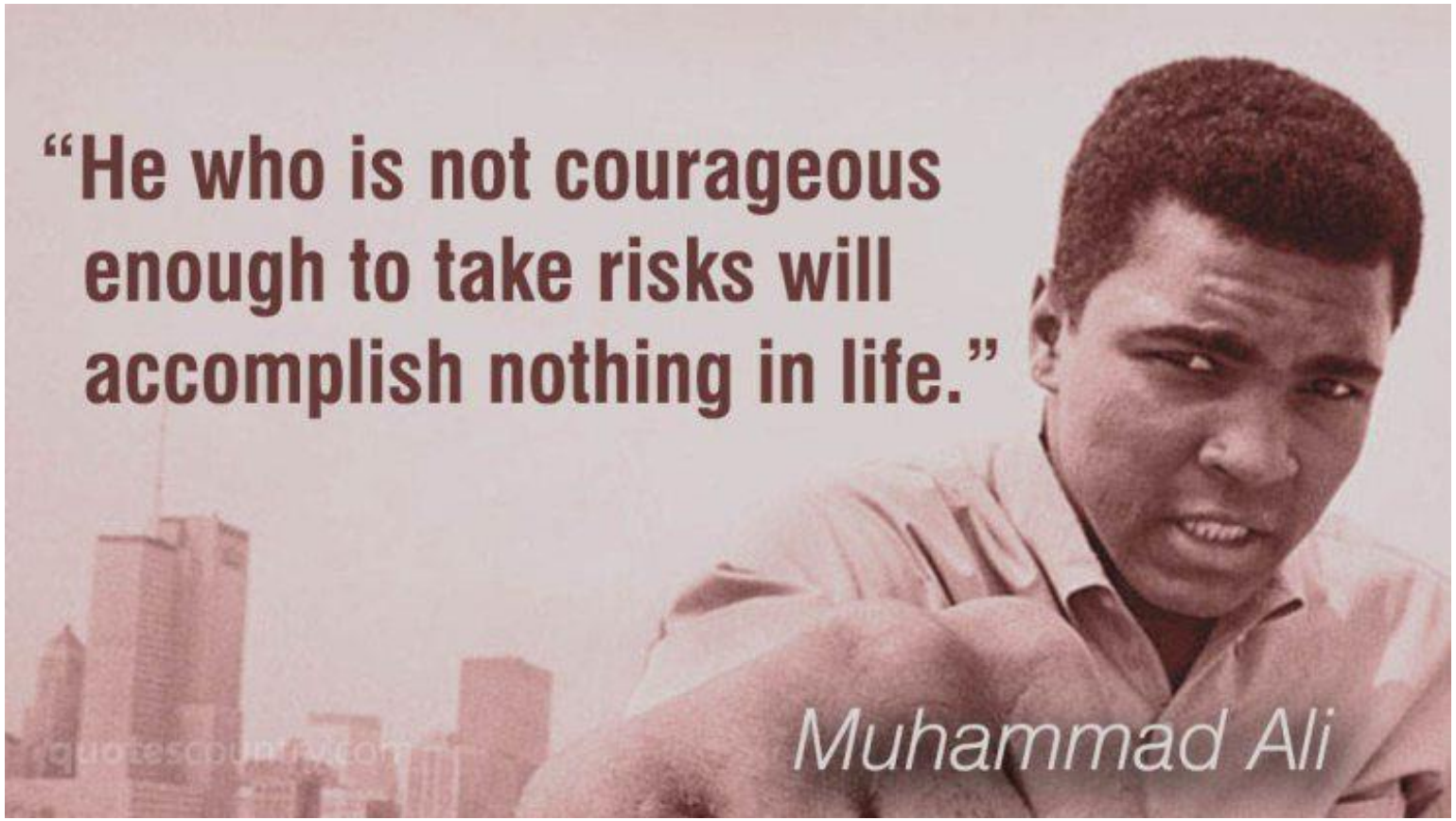
- 1. Parkinson disease
- 2. Huntington chorea

Basal ganglia and movement

- The basal ganglia have several functions, one of which is controlling and regulating movement.
- The basal nuclei interact with each other and with the thalamus and the cortex via 2 pathways: direct and indirect pathways.
- The direct pathway results in increased movement.
- The indirect pathway results in decreased movement.
- The ***balance*** between the two pathways is essential for normal movement.

- Disorders that involve the basal ganglia produce dysfunction by causing an imbalance between the direct and indirect pathways.
- An increase in the relative activity in the **direct** pathways results in **hyperkinetic** movements (Huntington). This could be a result of decreased activity of the indirect or increased activation of the direct pathway
- Increased relative activity in the **indirect** pathway is associated with **hypokinetic** movement (Parkinson)

Parkinson disease



Parkinson disease

- Parkinson disease is one of the causes of Parkinsonism.
- Parkinsonism is characterised by: Tremors, rigidity, bradykinesia (Slow movement) and instability.
- Parkinsonism is caused by damaged dopaminergic neurones that project from substantia nigra
- Parkinsonism can be due to
- 1) dopamine antagonists ,
- 2) toxins
- 3) Or: can be caused by Parkinson disease (neuro-degenerative disorder)

Epidemiology

Parkinson’s disease is the second most common neurodegenerative disorder after Alzheimer’s disease

Incidence increases with ages

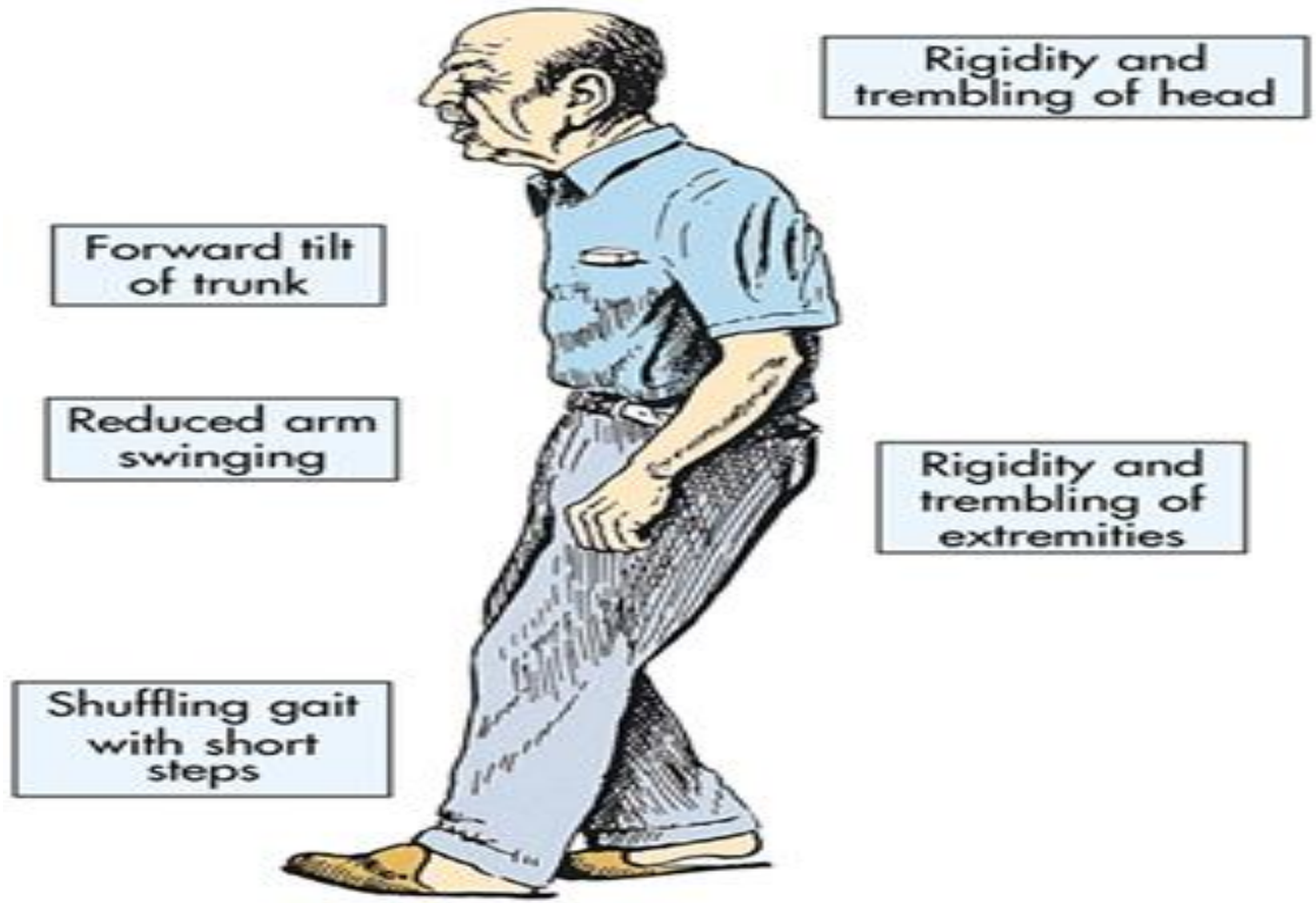
Can be familial or sporadic.

signs and 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.** 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

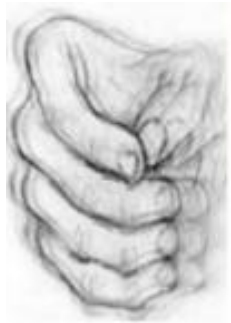
Parkinson disease
signs and symptoms

- Diminished facial expressions (Masked facies)
- Stooped posture
- Slow voluntary movement
- 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 tremor



Tremor

- Parkinsomiam tremor is described as resting tremor as it is typically present at rest and disappears with voluntary movement
- Manifests as pill – rolling tremor of hand
- Resting tremors may also be seen in the forearm , jaw, or tongue
- Lower limb tremors as apparent when the patients lies supine
- Postural tremor is seen in head and trunk when patients tries to maintain upright position against gravity
- COMPLETELY DIMINISH DURING SLEEPS

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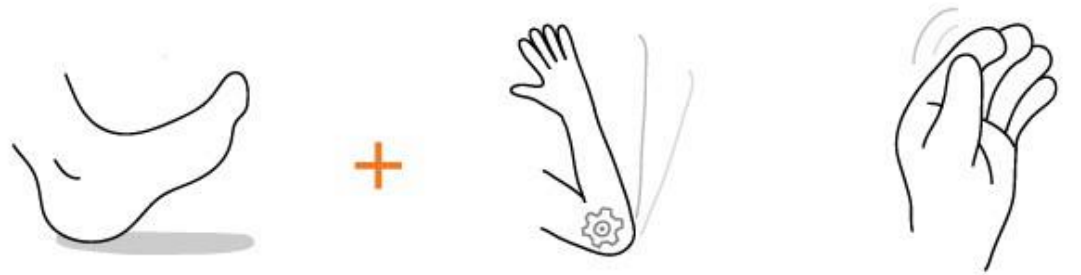
Parkinson's Disease

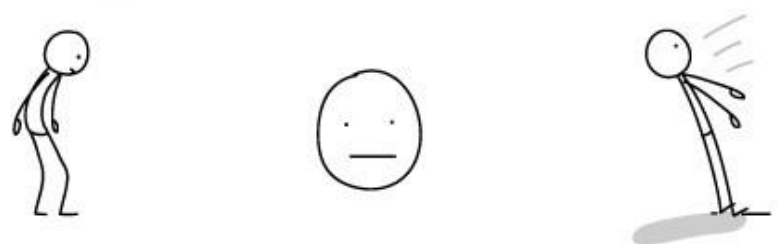


Bradykinesia
(as seen in toe tapping)

Cogwheel Rigidity

Resting Tremor
(pill rolling tremor)

Other motor features:



Shuffling Gait

Mask-like Expression

Postural Instability

Clinical features

- Movement disorder.
- Progresses over 10-15 years.. Severe motor slowing
- Death: infections and trauma due to falls (instability)
- Dementia can develop
- If dementia within first year of diagnosis: lewy body dementia.

pathogenesis

- Majority: sporadic
- Autosomal dominant and recessive forms exist

Due to mutations of genes coding for alpha synuclein protein.

- The abnormal accumulation of **alpha synuclein** is thought to be the main cause of symptoms

-patients have neural inclusions containing alpha synuclein; a protein involved in synaptic transmission.

- These inclusions= **Lewy bodies**

NOTE

Parkinson disease is not restricted to the basal ganglia; there is evidence from pathologic investigations that the degeneration of the substantia nigra represents a mid-stage in a progressive disease that **begins lower in the brainstem and can eventually progress to involve the cerebral cortex, leading to cognitive impairment.**

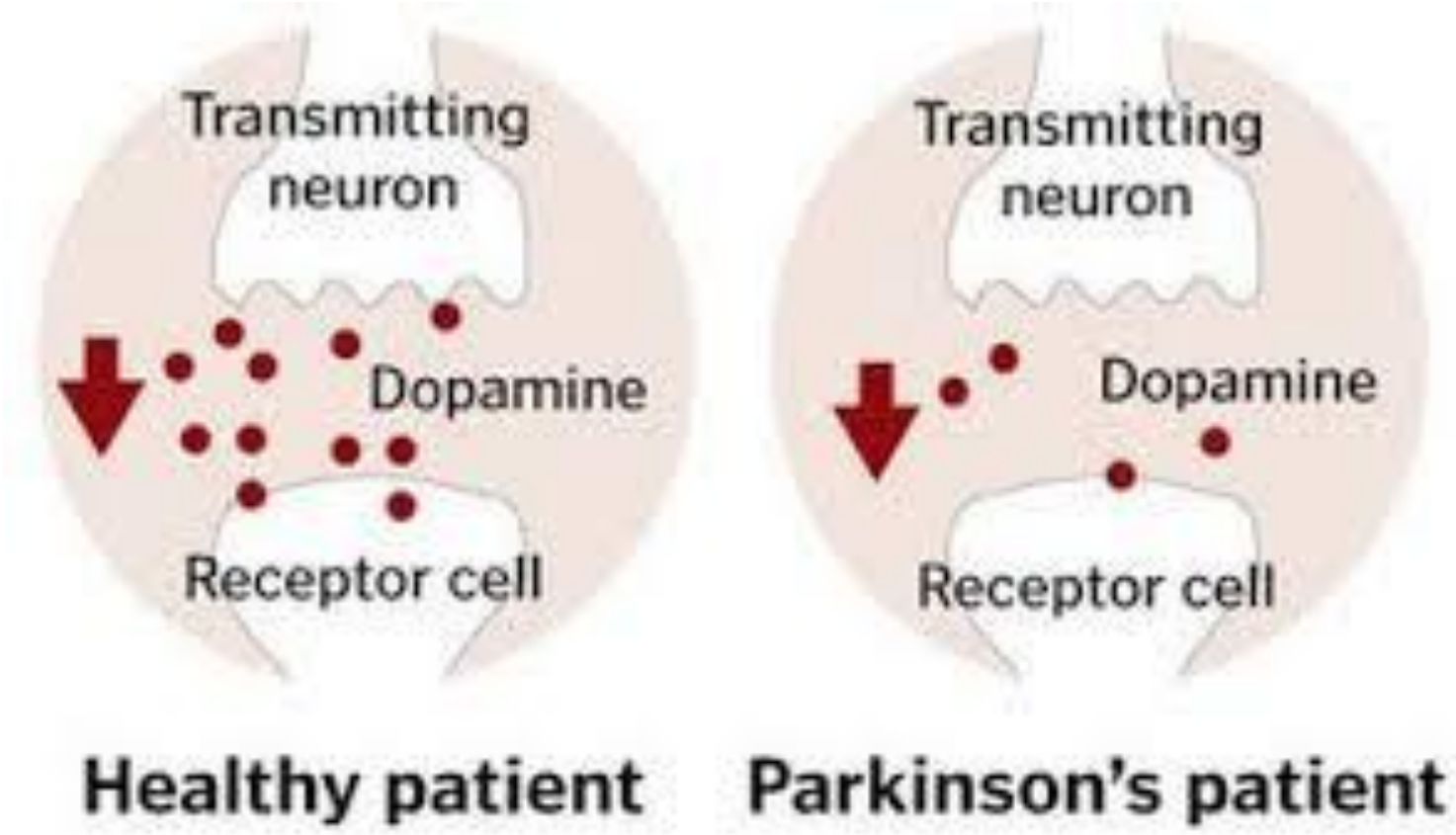
Alpha synculin aggregates can be released from one neuron and taken up by another, suggesting a capacity for a prion-like pattern of spread within the brain.

Consistent with this idea, α-synuclein containing aggregates (in the form of Lewy bodies)first appear in the medulla and then in contiguous areas of the brain, ascending through the brainstem and extending into limbic structures and finally the neocortex.

- About 10% to 15% of individuals with PD develop dementia, particularly with advancing age. Characteristic features of this disorder include a fluctuating course, hallucinations.

- most prominent histologic correlate is the presence of **widespread Lewy bodies** in neurons in the cortex and brainstem. So, more Lewy bodies means more advanced symptoms.

there is loss of dopaminergic neurones in Parkinson disease



L DOPA

-replacement therapy with L-DOPA (the immediate precursor of dopamine) can help in controlling the symptoms

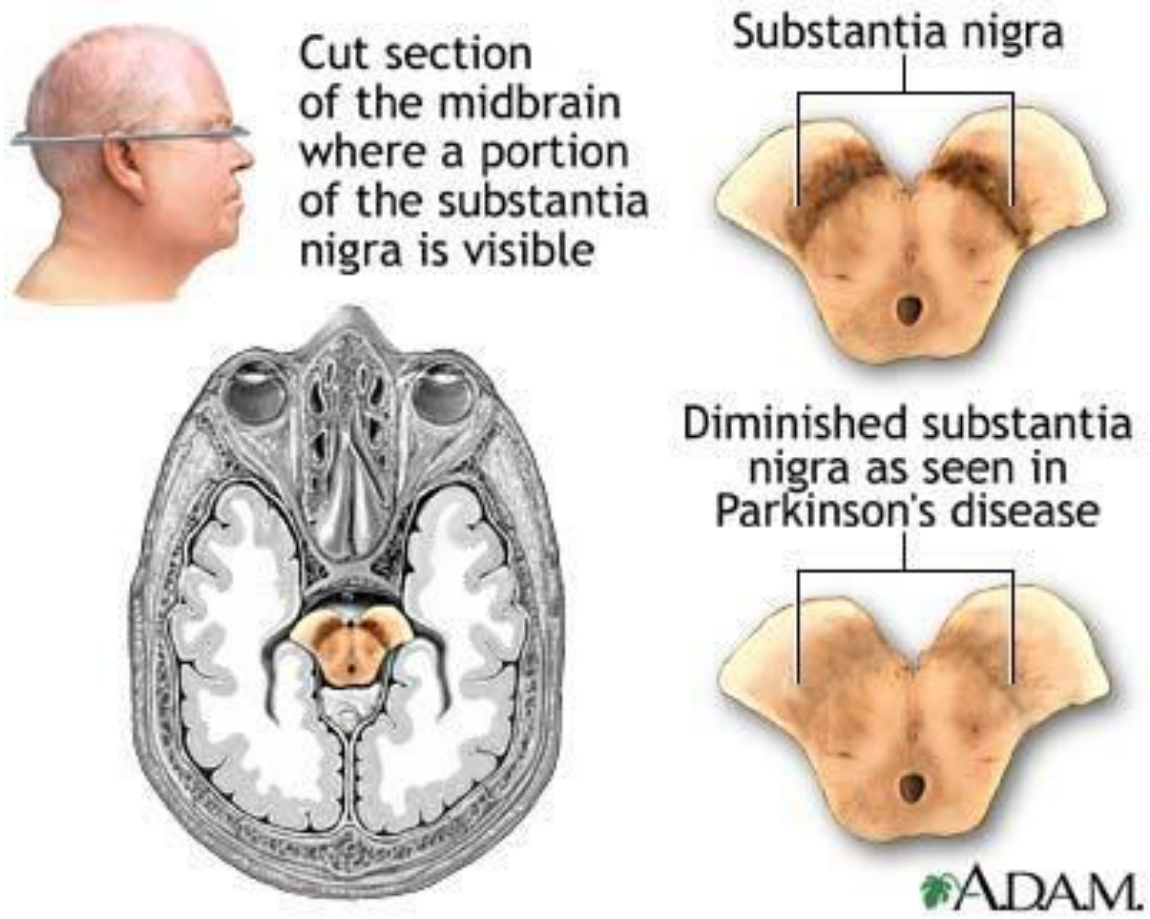
-BUT Treatment does not reverse the morphologic changes or arrest the progress of the disease

-ALSO with progression drug therapy tends to become less effective and symptoms become more difficult to manage.

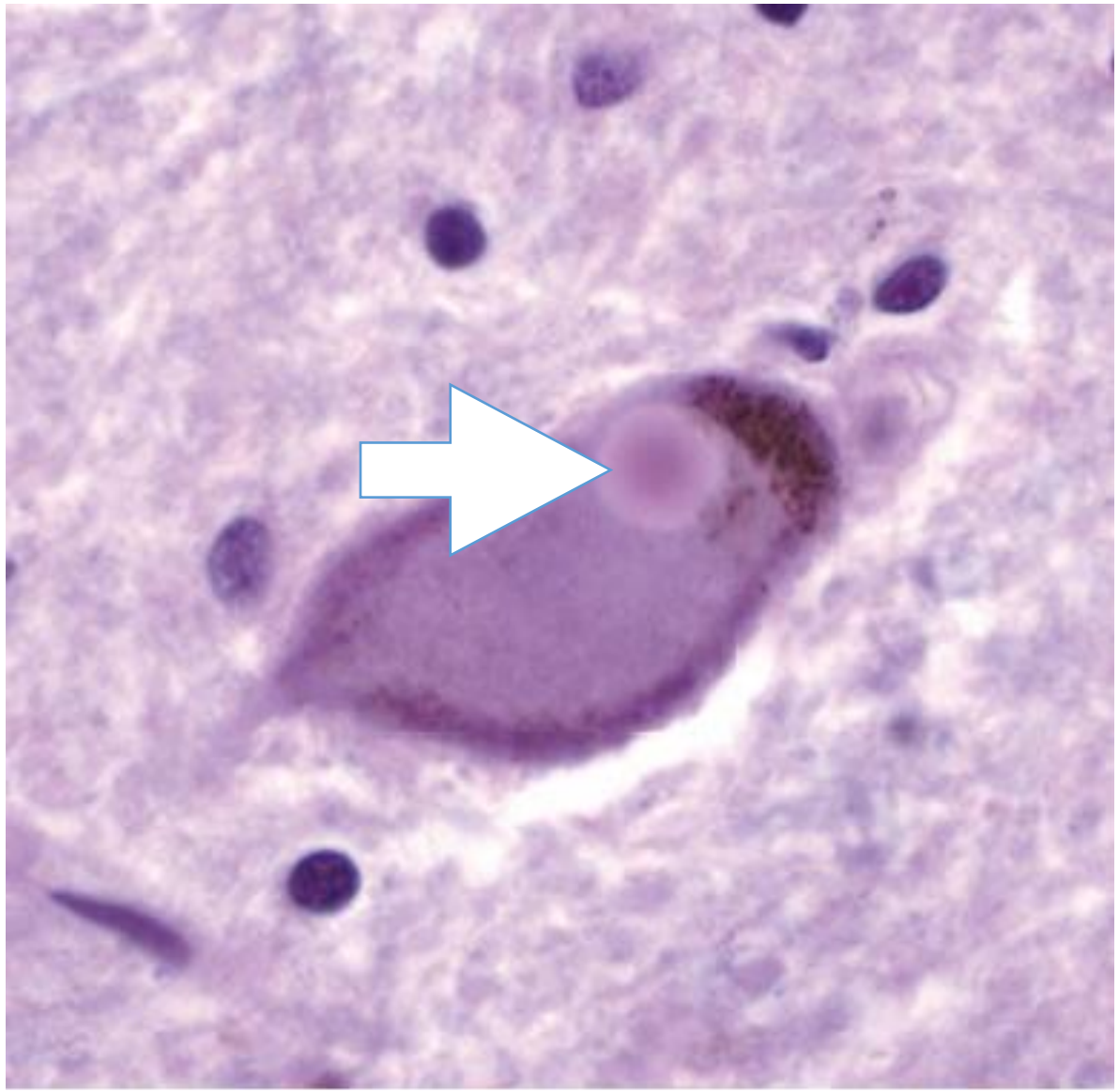
morphology

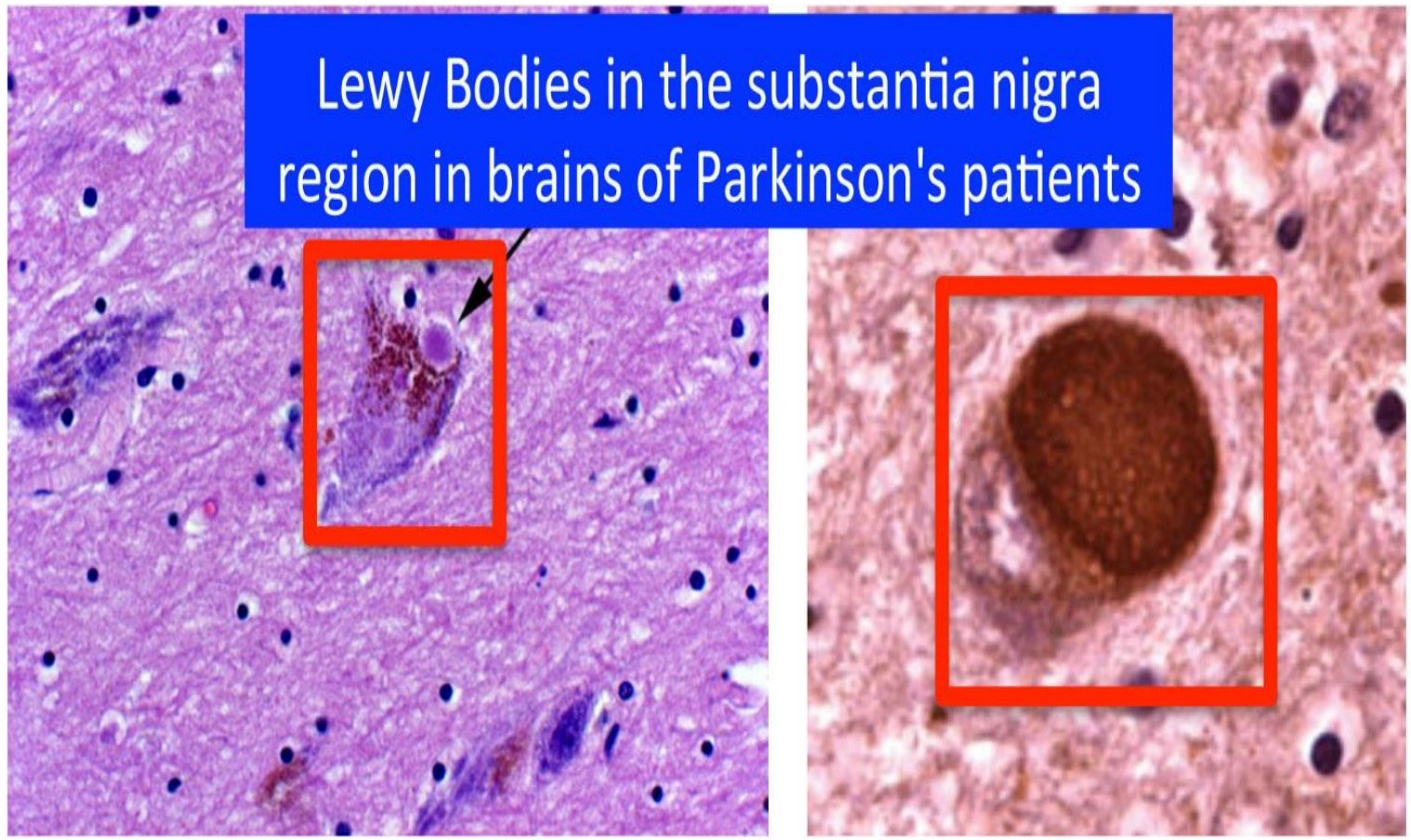
- Pale substantia nigra and locus ceruleus
- Loss of pigmented neurones with associated gliosis
- Lewy bodies seen in the remaining neurones in these regions
- Lewy body: **intracytoplasmic eosinophilic round to elongated** inclusions that have a **dense core surrounded by a pale halo**

Morphology: pale substantia nigra



Lewy body




Lewy Bodies in the substantia nigra region in brains of Parkinson's patients

Huntington Chorea

Chorea is a Greek word that means circle dance

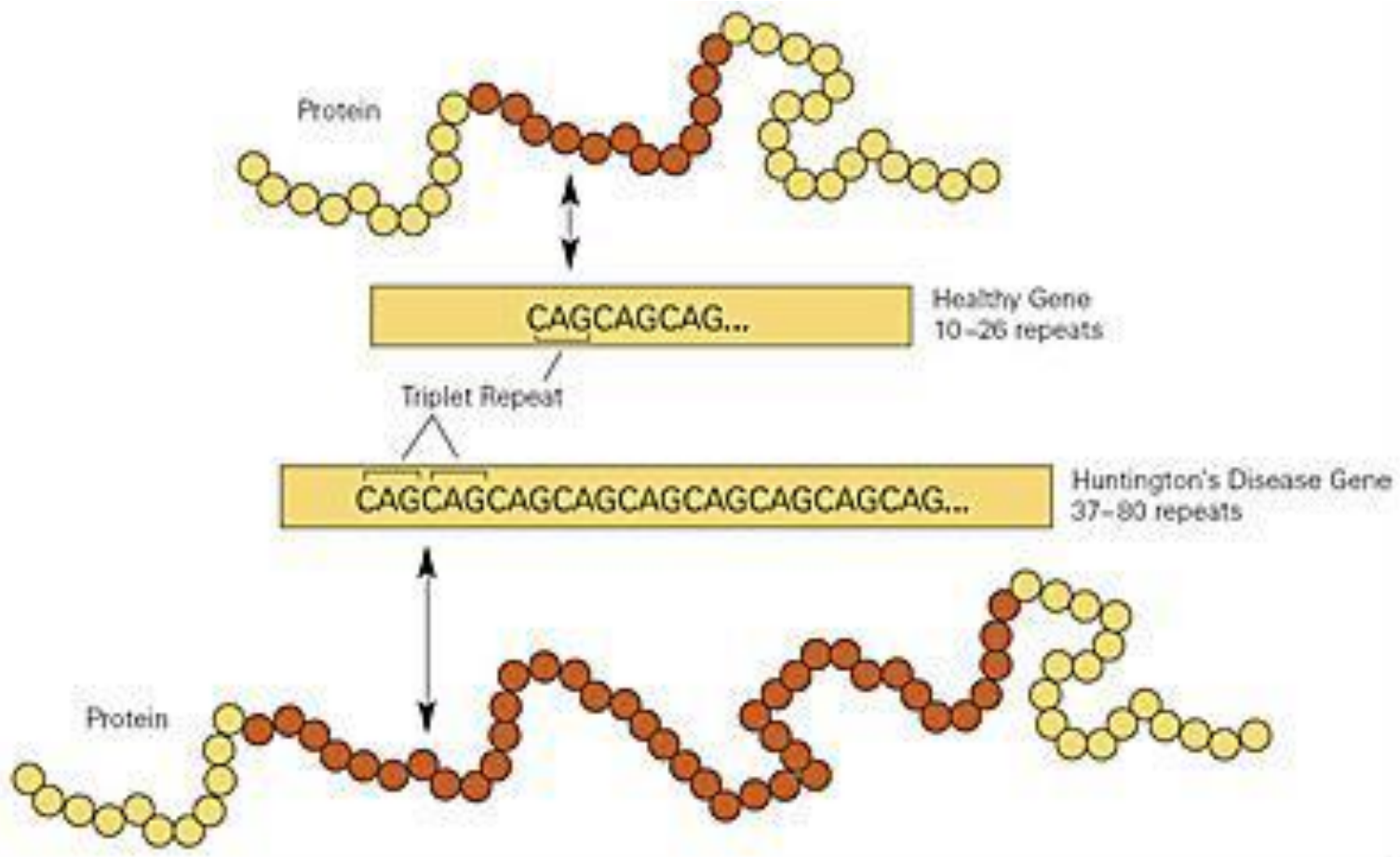
Huntington disease

- ***Autosomal dominant disease. (no sporadic cases)***
- Movement disorder which is chorieform =dancelike Involuntary jerky movements of all parts of the body
- Degeneration of caudate and putamen

pathogenesis

- Huntington disease is inherited in an autosomal dominant fashion.
- It is caused by a trinucleotide repeat mutation.
- CAG(cytosine-adenine-guanine) trinucleotide repeat expansions in the gene that encodes huntingtin protein.
- CAG codes for glutamine
- Huntingtin protein is thought to play a role in long term memory storage

- Normally CAG repeated between 11-35 times
- Huntington disease, repeats more than 35
- The more number of the repeats, the earlier the onset of symptoms
- Course of disease not affected by number of repeats

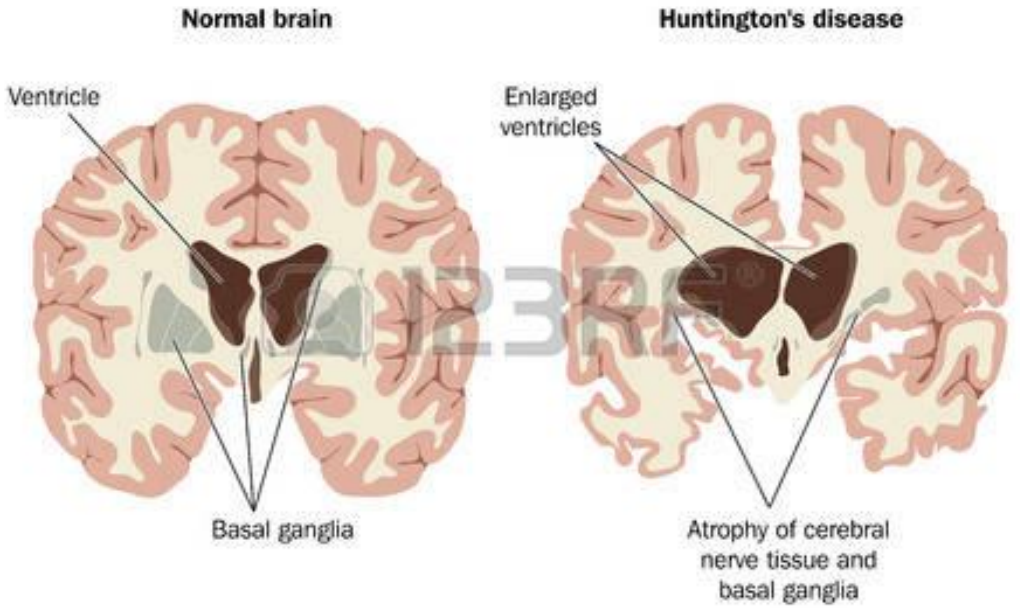

Protein
CAGCAGCAG...
Healthy Gene
10–26 repeats
Triplet Repeat
CAGCAGCAGCAGCAGCAGCAGCAGCAG...
Huntington's Disease Gene
37–80 repeats
Protein

pathogenesis

- The abnormal huntingtin protein.. Contains polyglutamine tract
- it forms large intra-nuclear aggregates
- These aggregates cause functional problems leading to the symptoms of Huntington disease

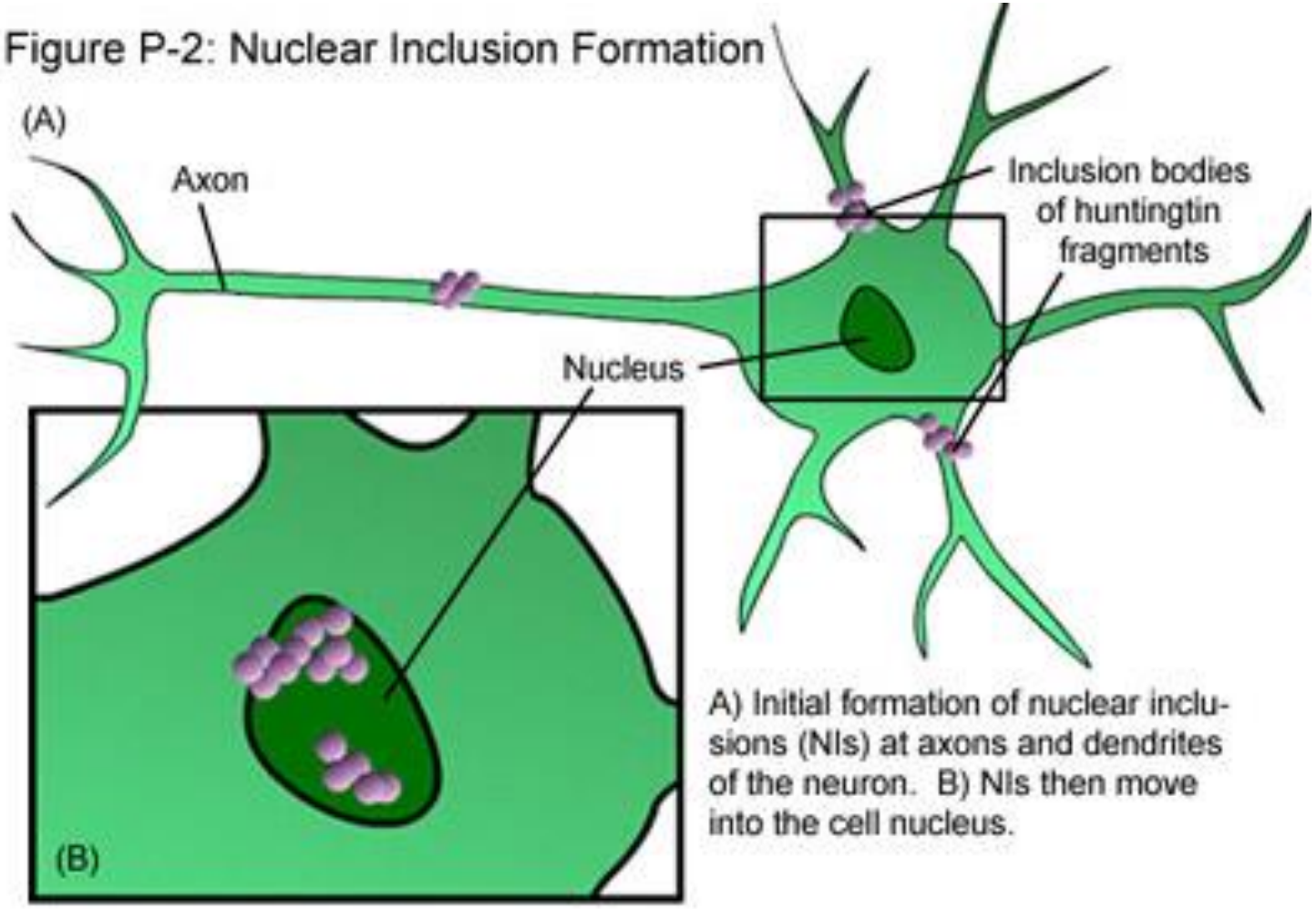
morphology

- Small brain
- Atrophy of caudate and putamen
- Severe loss of neurons



- abnormal huntington protein is cleaved by caspases.
- the cleaved fragments move to the nucleus and form **intranuclear inclusions.**

Huntingtin protein aggregates as intranuclear inclusions.



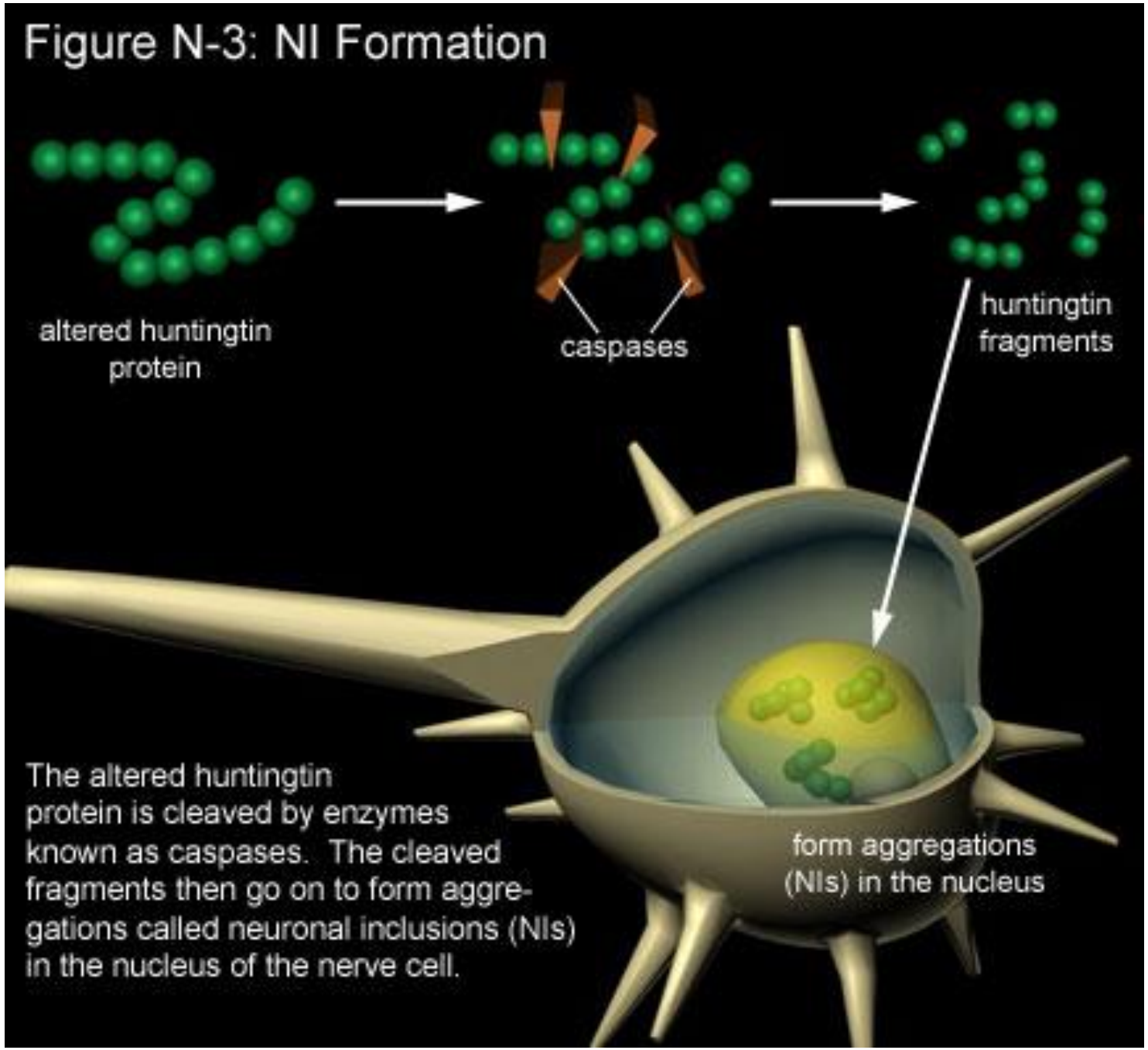


Figure N-3: NI Formation
altered huntingtin protein
caspases
huntingtin fragments
The altered huntingtin protein is cleaved by enzymes known as caspases. The cleaved fragments then go on to form aggregations called neuronal inclusions (NIs) in the nucleus of the nerve cell.
form aggregations (NIs) in the nucleus

Clinical course

- Age of onset:40-50 years of age; related to the length of CAG repeats(more repeats; earlier age of onset)
- Symptoms : motor disturbances and choreiform movements
- Memory loss can develop and progresses to severe dementia
- Behavioural changes.. Risk of suicide

SUMMARY 1/1

- In Parkinson, there is loss of dopaminergic neurones due to accumulation of alpha synculein, which accumulates mainly in the substantial nigra as Lewy bodies.
- In parkinson patients have decreased motor function but later they might have dementia.
- If dementia occurs within the first year of diagnosing Parkinson disease, it is called Lewy body dementia.
- Huntington disease is inherited in an autosomal dominant fashion. It is caused by a tri-repeat mutation causing abnormality in Huntington protein which is cleaved by caspases , the cleaved fragments are translocated to the nucleus where they form intranuclear inclusions

Question:

A 67 year old male presents with tremors, rigidity and slow movement. You notice that he had stooped posture and diminished facial expressions. He seems to have good cognitive function and no memory loss. All of the following play a role in his disease except:

A. accumulation of alpha synculein

B. accumulation of protein that acts as a prion protein

C. lewy bodies

D. loss of pigmented neurons in substantia nigra

E. **accumulation of a protein important for long term memory storage**

LoveOfLifeQuotes.com