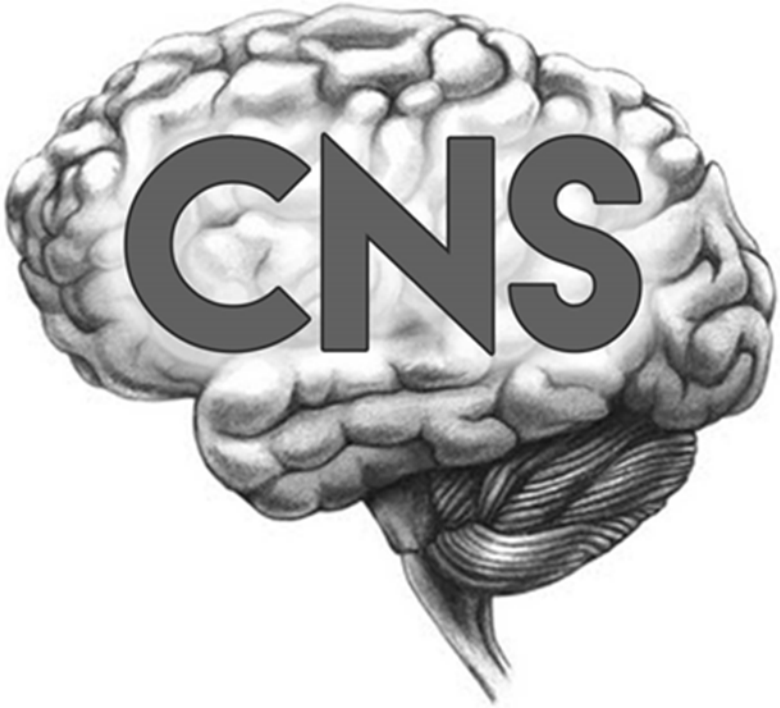


PATHOLOGY

○ Sheet ✓ Slide ○ Handout

Number

7

Subject

Neurodegenerative disorders / part 2

Doctor

Heyam Awad

Date: **00/00/2016**

Price:

CNS pathology
Third year medical students

Dr Heyam Awad

FRCPath

2017

LECTURE 7

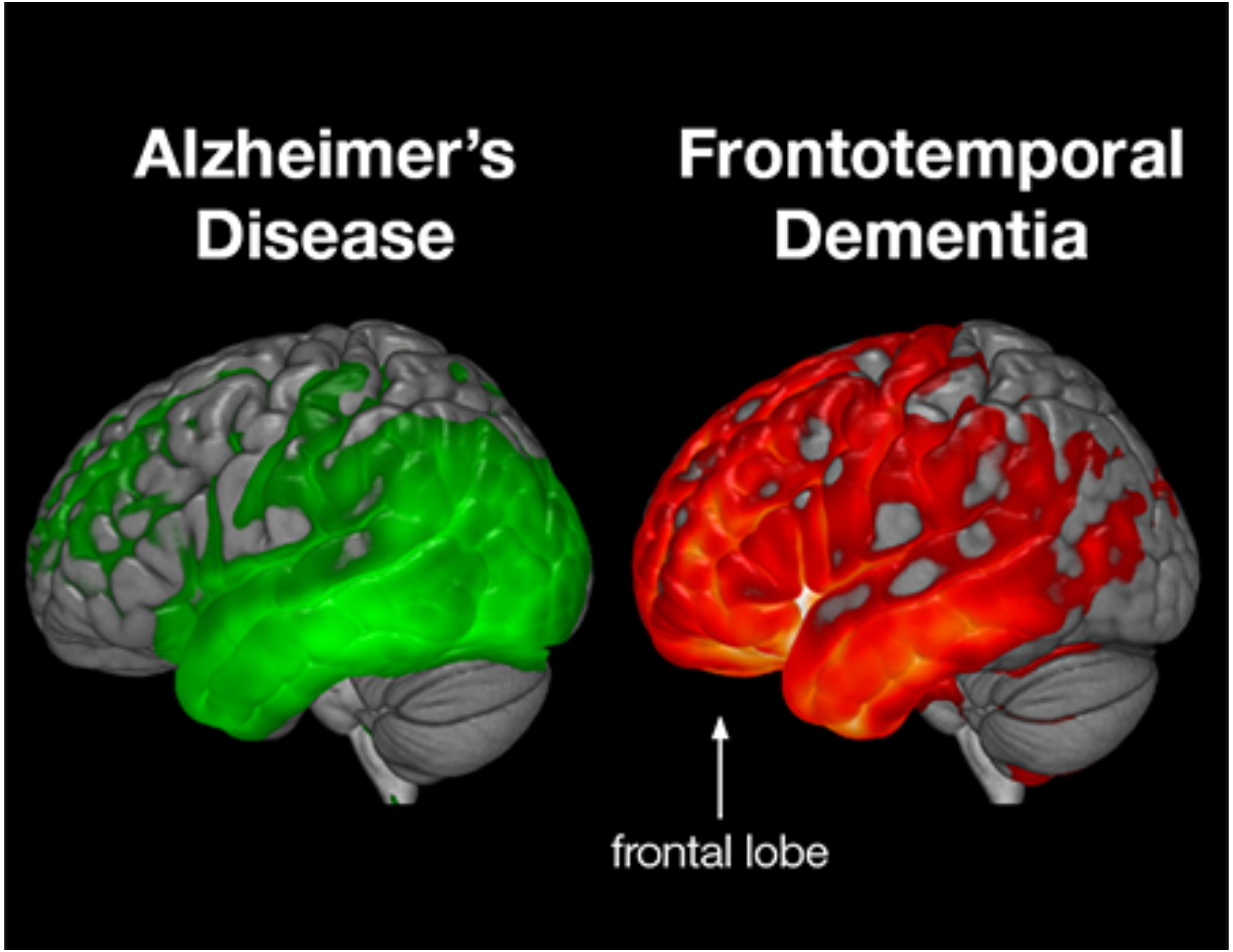
Neurodegenerative disorders / part 2

Topics to be covered:

1. Frontotemporal lobar degeneration (FTLD)
2. Pick disease (subtype of FTLD)
3. Parkinson disease
4. Huntington chorea

Fronto-temporal lobar degeneration (FTLD)

- Heterogeneous group of diseases associated with focal degeneration of frontal and/or temporal lobe.
- Differ from Alzheimer by : changes in personality and language precede memory loss .
- With time.. The disease progresses and dementia occurs.


Alzheimer's Disease
Frontotemporal Dementia
frontal lobe

etiology

- Accumulation of abnormal Tau protein.

Tau in FTLD accumulates in two forms:

- 1. **neurofibrillary tangles**; like those seen in Alzheimer (but in FTLD there is only Tau and no amyloid aggregates)
- 2. smooth inclusions = **Pick bodies**.. This subtype of FTLD is called Pick disease.

Tau protein

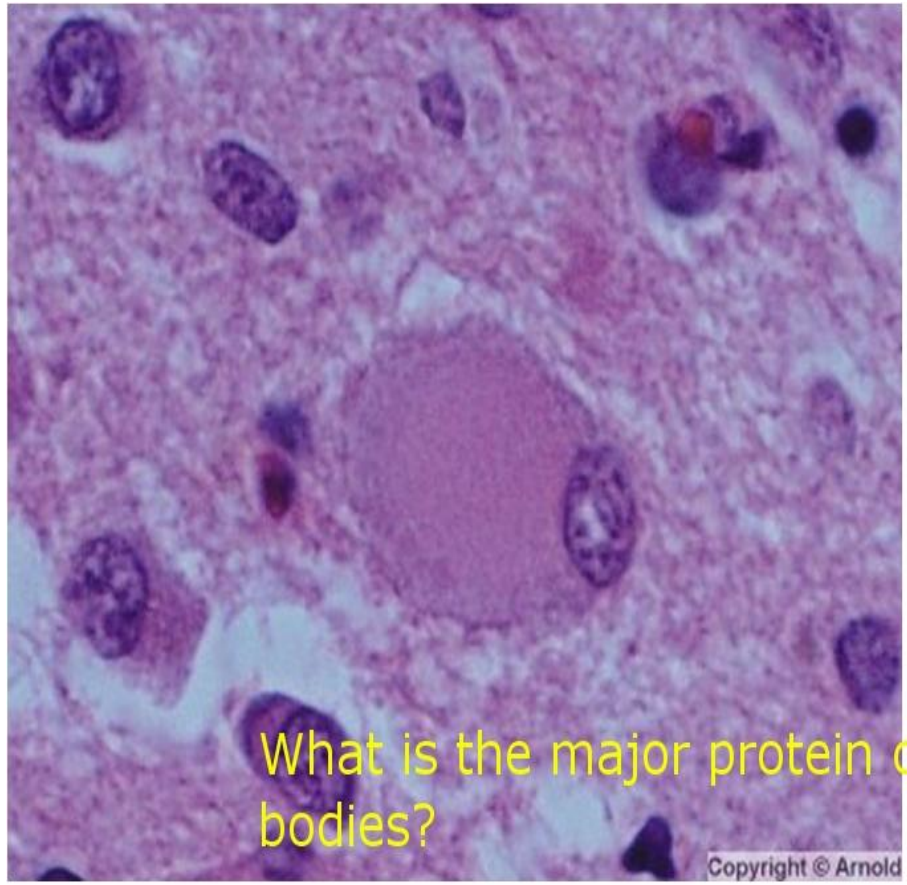
- Is a phosphoprotein that interacts with microtubules and stabilizes them.
- When Tau is hyperphosphorylated two changes occur: 1) its ability to bind with microtubules decreases and 2) its ability to aggregate increase.

- Two forms of FTLD: sporadic and inherited
- Inherited forms have mutations in Tau protein causing increased accumulation
- Tau accumulation causes toxic damage to the nurons + loss of their normal function…. Both cause neuronal damage

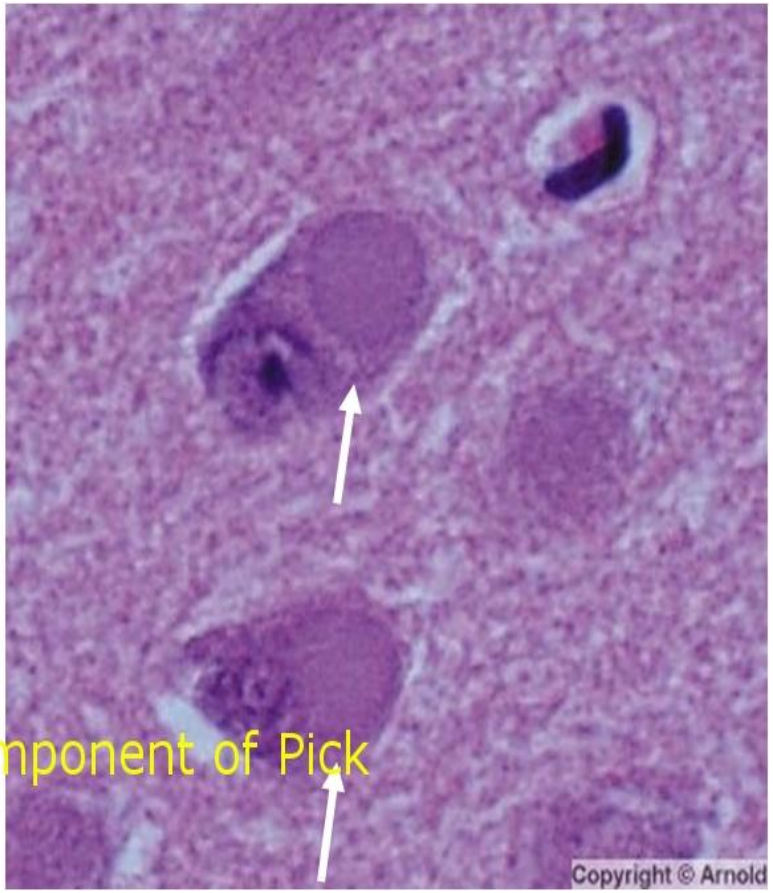
Pick disease

- Subtype of FTLD
- Charectarized by the presence of Pick inclusions

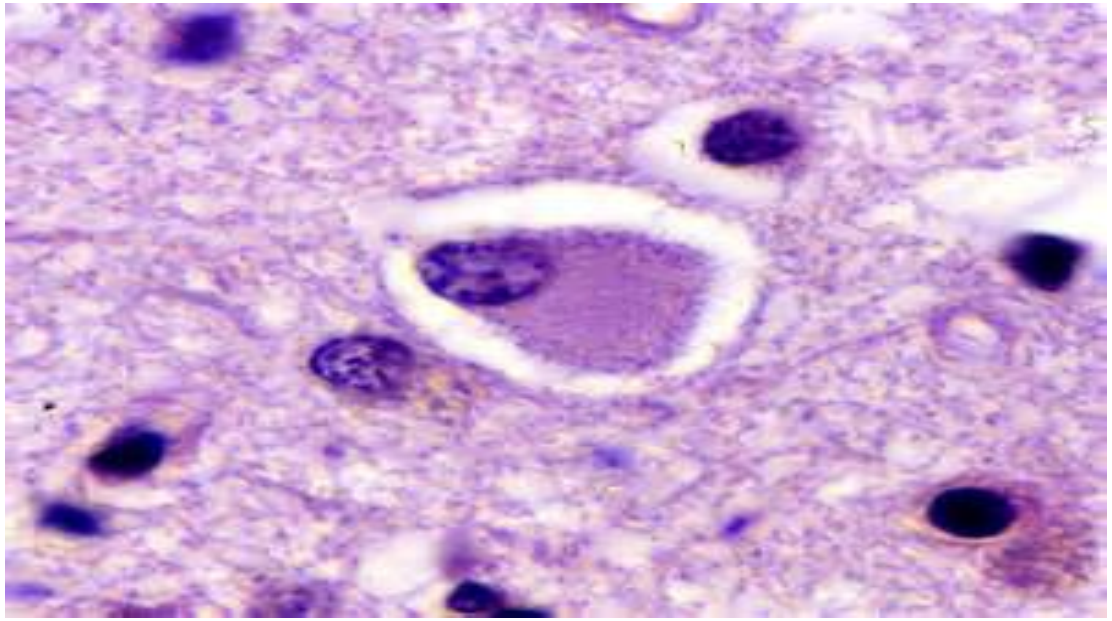
Pick bodies



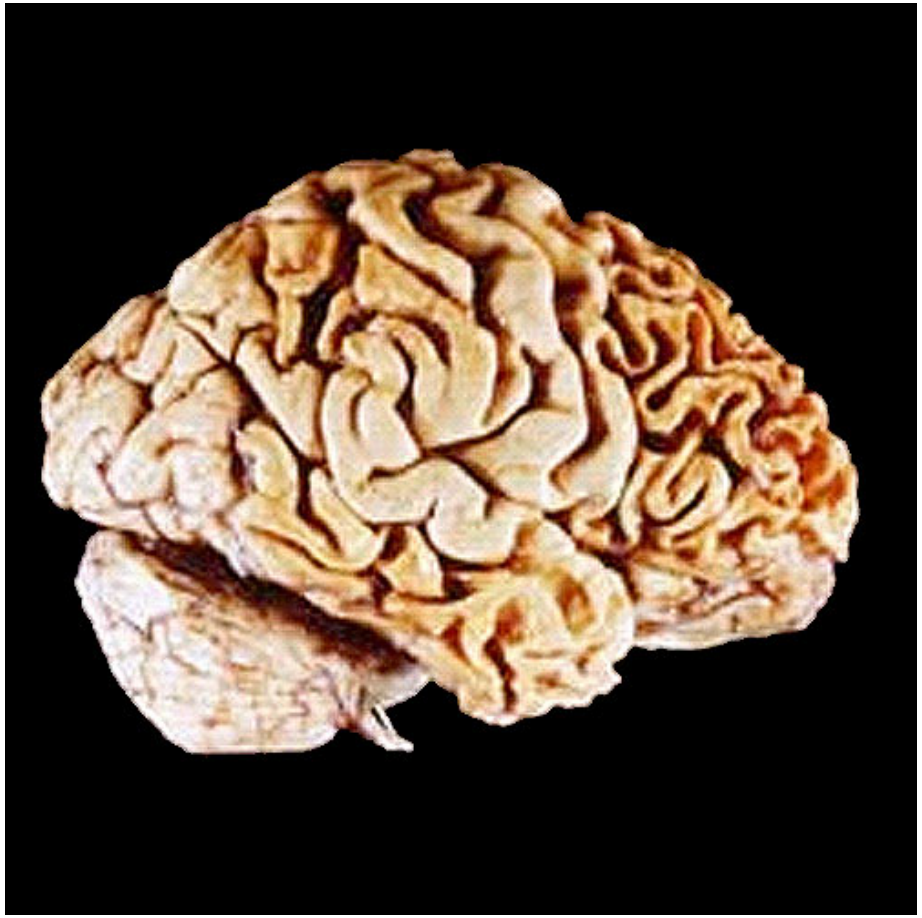
What is the major protein component of Pick bodies?



Pick bodies



Morphology of FTLD: atrophy of the frontal and temporal lobes



Other diseases caused by Tau accumulation:

- **Repetitive mild traumatic brain injury(TBI**), now recognized as a central component of brain injury in contact sports, especially American football, and the concussive force of military blasts, can lead to chronic traumatic encephalopathy (CTE) that is characterized by fibrillar tangles of hyperphosphorylated tau.

Vascular dementia(this is not a neurodegenerative disorder but a cause of dementia mentioned here to complete the subject of dementia)

- Vascular dementia, also known as multi-infarct dementia (MID) and vascular cognitive impairment (VCI), is dementia caused by problems in the supply of blood to the brain, typically a series of minor stokes, leading to worsening cognitive decline that occurs step by step. The term refers to a syndrome consisting of a complex interaction of cerebrovascular disease and risk factors that lead to changes in the brain structures due to strokes and lesions, and resulting changes in cognition. The temporal relationship between a stroke and cognitive deficits is needed to make the diagnosis.

Neurodegenerative diseases that cause motor dysfunction

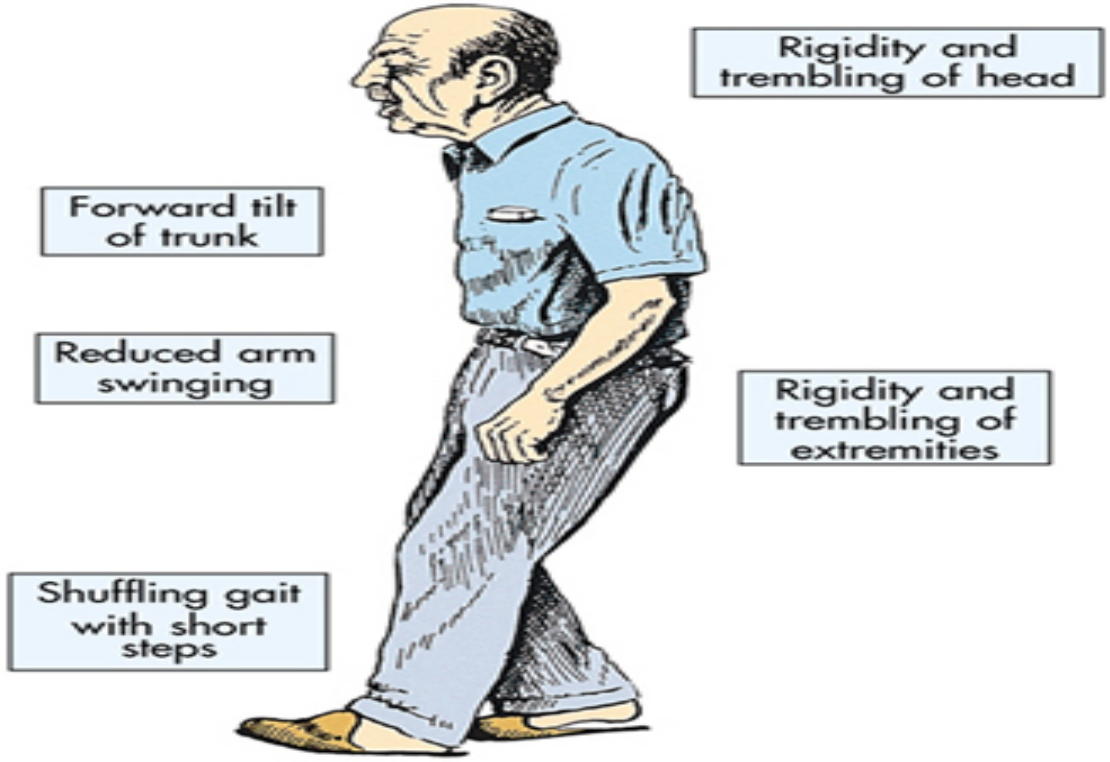
- 1. Parkinson disease
- 2. Huntington chorea

Parkinson disease

- Parkinsonism: Tremors, rigidity, bradykinesia and instability.
- 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)

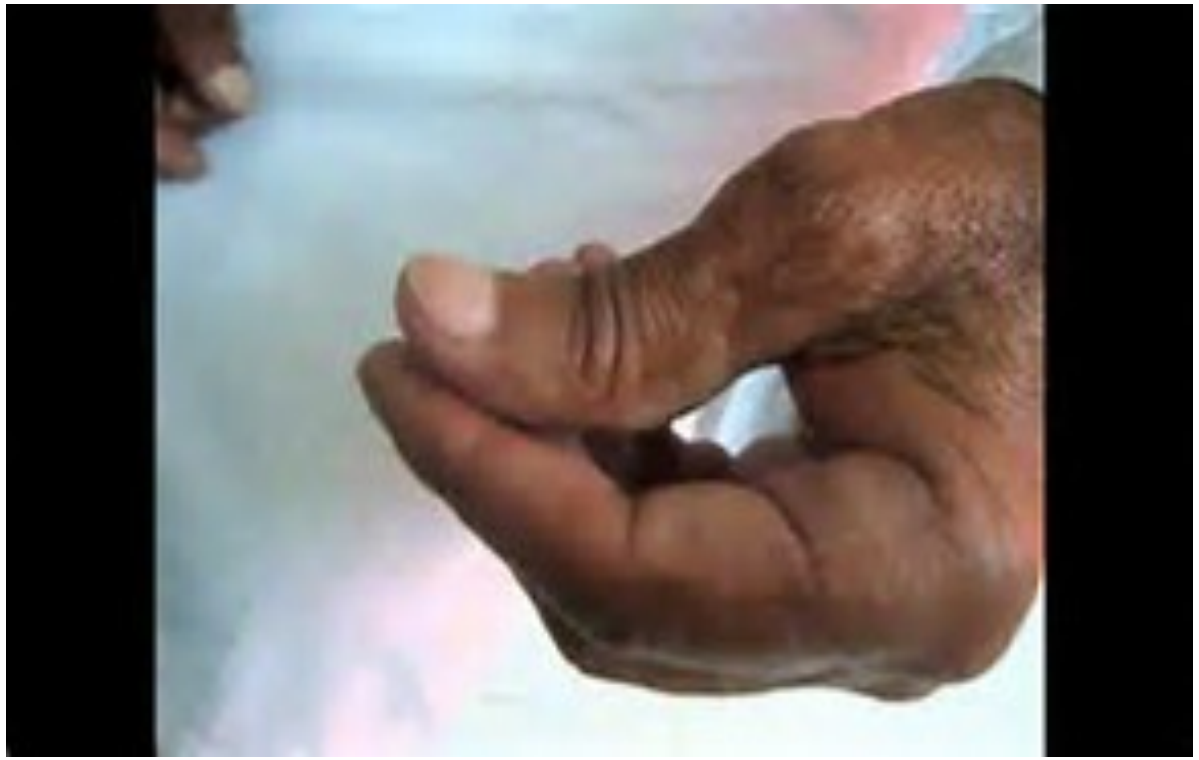
Parkinson disease
signs and symptoms

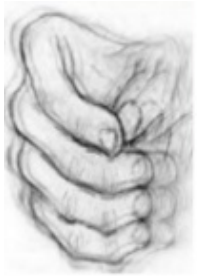
- Diminished facial expressions (Masked facies)
- Stooped posture
- Slow voluntary movement
- Rigidity
- Pill rolling tremor
- Festinating gait= progressively shortened accelerated steps.


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

Global StemGenn
Therapy & Research

PARKINSON'S DISEASE

- Onset usually gradual, after age 50. (Slowly progressive)
- Mask-Like, Blank Expression
- Stooped Posture
- Pill Rolling Tremors

Bradykinesia
- Loss of normal arm swing while walking
- ↓ Blinking of the eyelids
- Loss of ability to swallow
- Blank expression
- Difficulty initiating movement

- Possible Mental Deterioration
- Depression

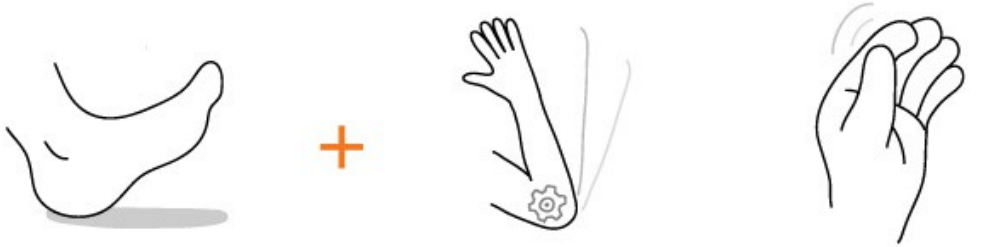
Tremor
- Commonly in hands and arm
- Pill rolling motion with the fingers
- Occurs most often at rest
- May involve diaphragm, tongue, lips and jaw
- Increases with stress

Muscle Rigidity
- ↑ Resistance to passive movement
- Cog wheel, jerky slow movement

- Rarely Occurs In Black Population
- Shuffling, Propulsive Gait

©2007 Nursing Education Consultants, Inc.

Parkinson's Disease



Bradykinesia
(as seen in toe tapping)

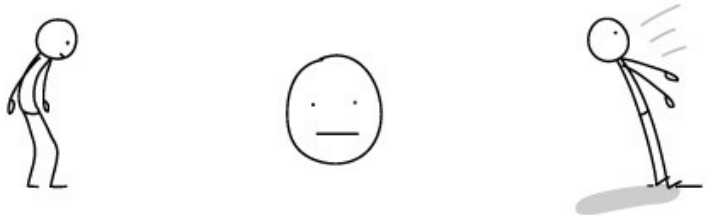
+

Cogwheel Rigidity

Resting Tremor
(pill rolling tremor)

sketchymedicine.com

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

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

- 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 (which results in the motor symptoms 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 and Lewy neurites) 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.

L DOPA

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

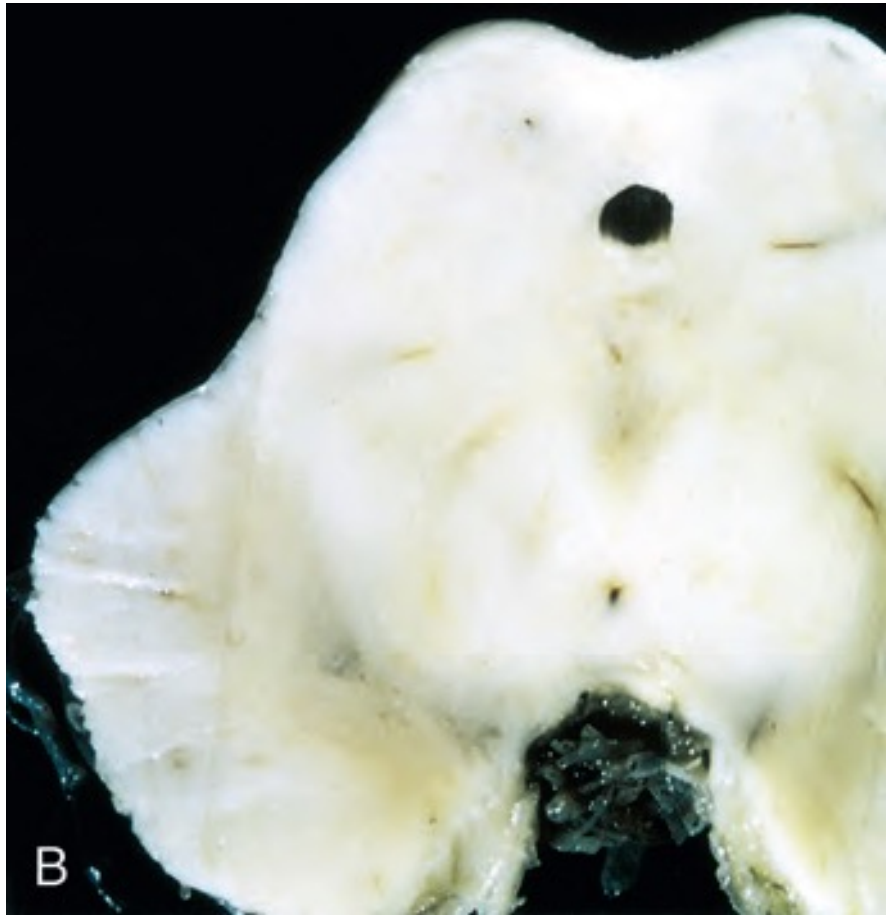
-BUT Treatment does not reverse the morphologic changes or arrest the progress of the disease

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

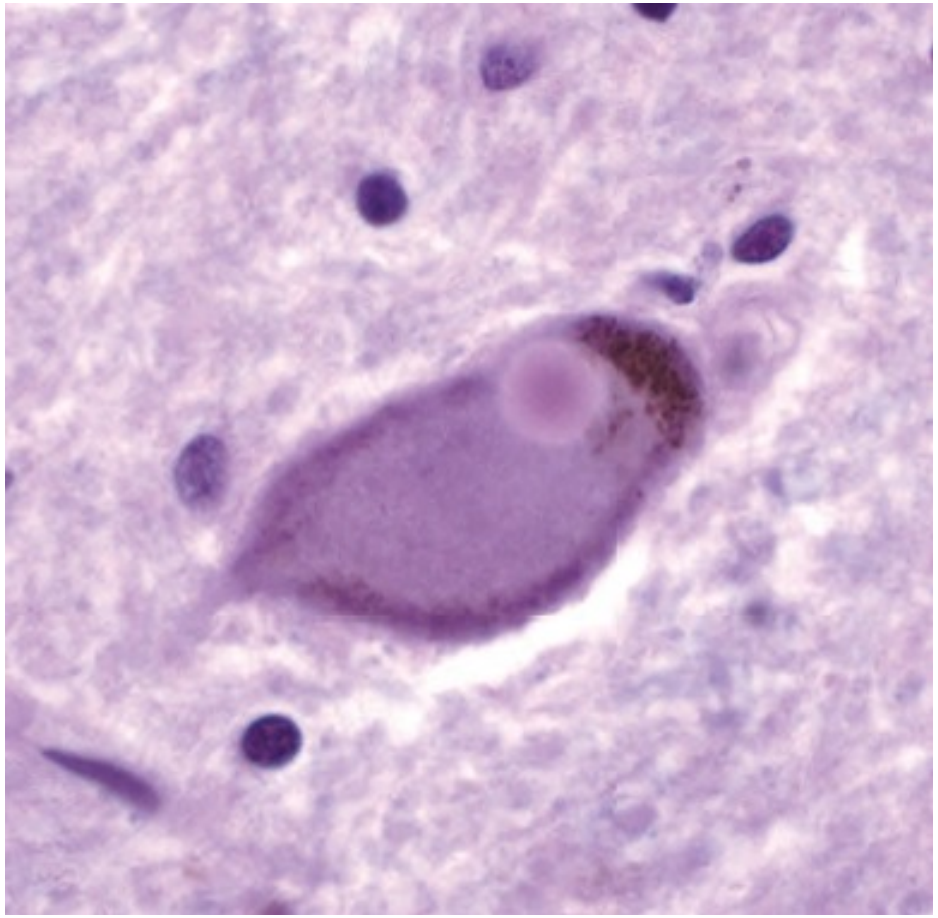
morphology

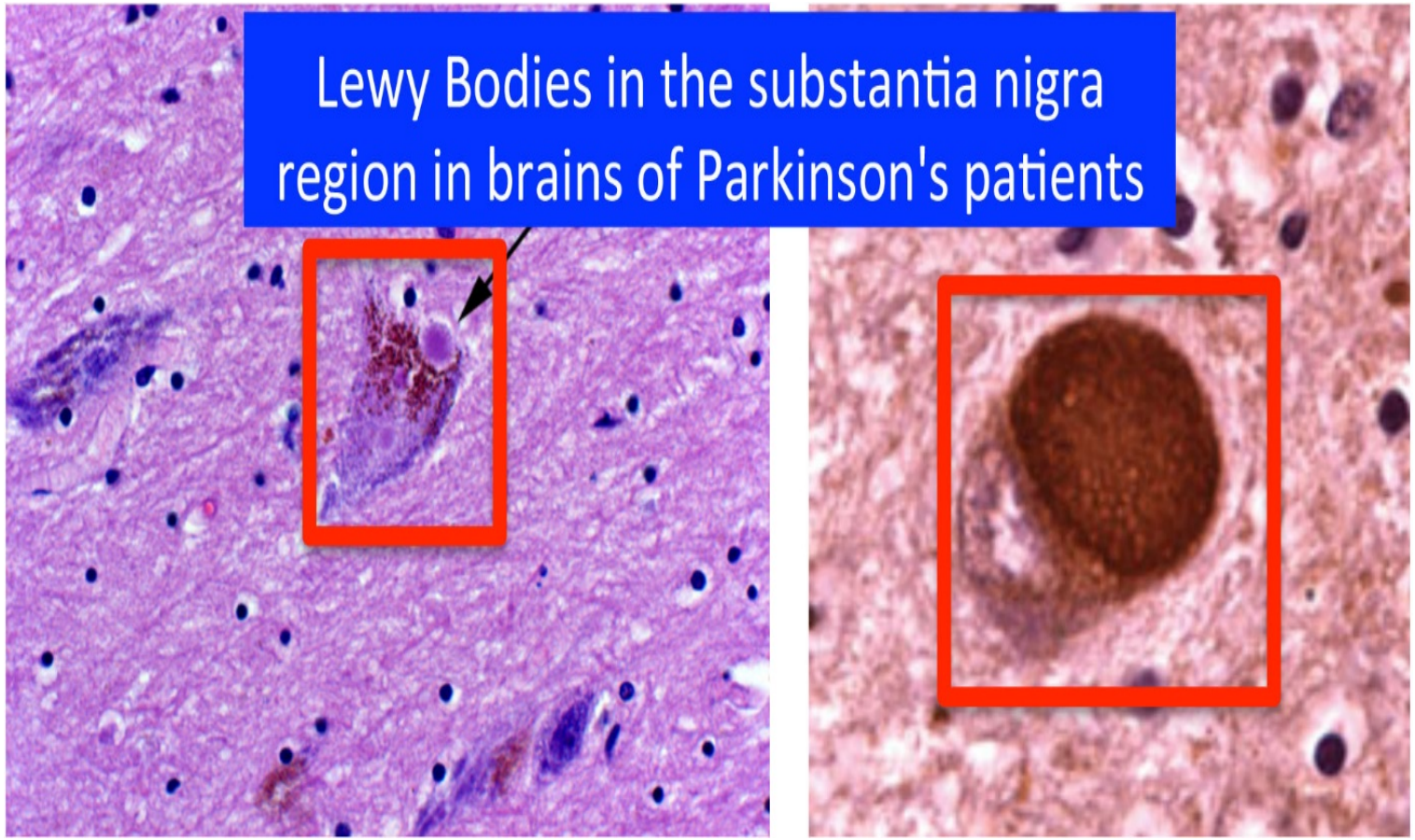
- Pale substantia nigra and locus ceruleus
- Loss of pigmented neurones with associated gliosis
- Lewy bodies seen in the remaining neurones in these regions
- Lewy body: intracytoplasmic eosinophilic round to elongated inclusions that have a dense core surrounded by a pale halo

Pale substantia nigra



Lewy body




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

Huntington disease

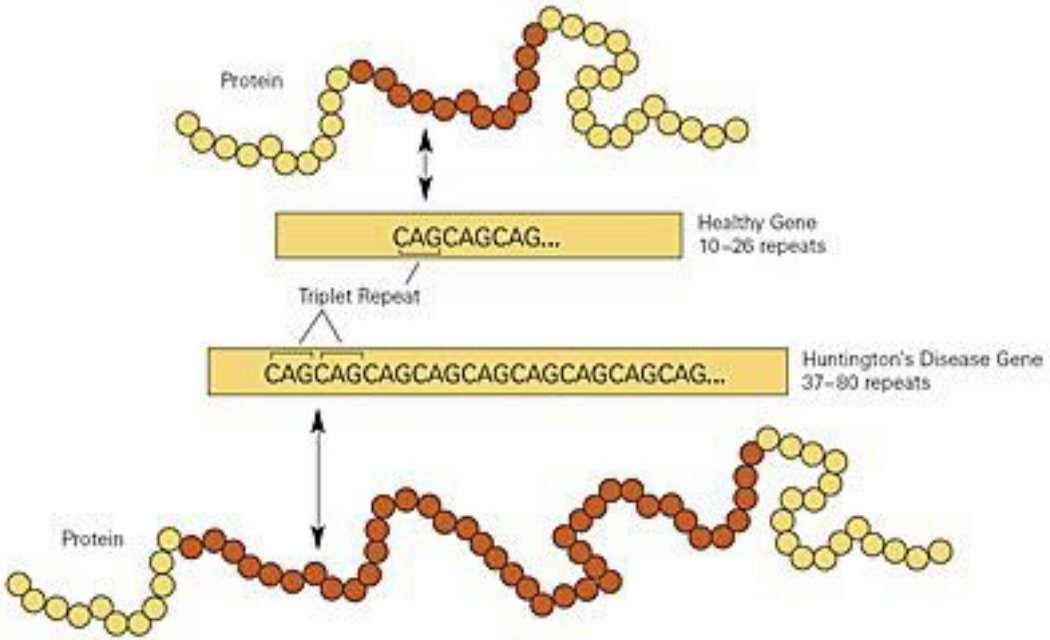
- Autosomal dominant disease. (no sporadic cases)
- Movement disorder which is chorieform =dancelike Involuntary jerky movements of all parts of the body
- Degeneration of caudate and putamen

Chorei = Greek word = circle dance

pathogenesis

- 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


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

- 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

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

Clinical course

- Age of onset:40-50 years of age; related to the length of CAG repeats(more repeats; earlier age of onset)
- First symptoms are motor disturbances and choreiform movements

Clinical course

- Progressive
- Memory loss can develop and progresses to severe dementia
- Behavioral changes.. Risk of suicide

LoveOfLifeQuotes.com