CNS lecture 5

DR Heyam Awad

FRCpath

Neurodegenerative diseases

- Cellular degeneration of functionally related neurones.
- Many of them related to accumulation of abnormal proteins.
- Involved proteins are widely expressed in the CNS but accumulate in certain areas causing certain disease… we don’t know the reason for this bias!

Neurodegenerative diseases

- Alzheimer
- Frontotemporal lobar degeneration
- Parkinson disease
- Huntington disease
- Spinocerebellar ataxia
- Amyotrophic lateral sclerosis

Alzheimer disease

- Most common cause of dementia
- Gradual onset of impaired higher intellectual function + altered mood and behaviour.
- Progresses to disorientation , memory loss, aphasia
- Then.. Over 5-10 years, become disabled, mute and immobile
- Death due to infections, mainly pneumonia

- Age is the most important risk factor
- Mostly sporadic but familial in 5-10% of cases
- Some heritable forms: early onset; before 50

pathogenesis

- Beta amyloid (AB) accumulate in the brain.
- Transmembrane protein: amyloid precursor protein (APP) cleaved by beta amyloid converting enzyme and gamma secretase… generates beta amyloid.
- Mutations in APP or components of gamma secretase .. Increased beta amyloid…. Resulting in familial Alzheimer

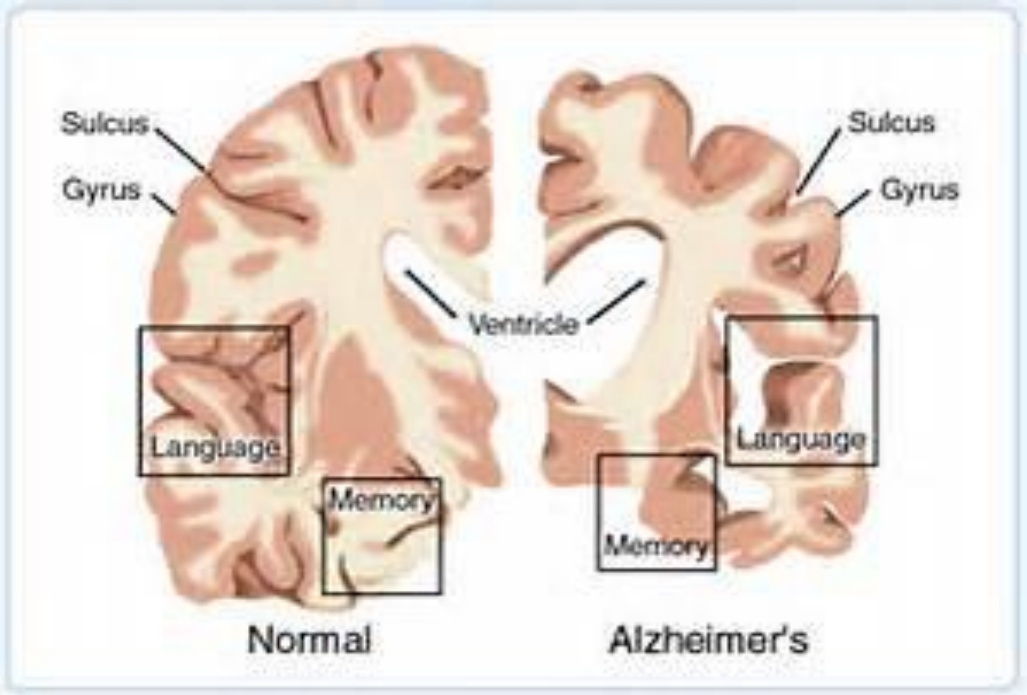
- APP gene present on chromosome 21.
- Trisomy 21 (Down syndrome) have increased risk of Alzheimer
- Other genetic mutations can also cause Alzheimer

pathogenesis

- Aggregation of beta amyloid alter neurotransmission and are toxic to neurones and synapses
- Large deposits cause neuronal death and cause inflammatory response
- AB amyloid also causes hyperphosphorylation of tau protein.. Aggregates and causes neuronal damage
- Tau.. Important for microtubule stability.

morphology

- Cortical atrophy
- Wide sulci mainly in frontal, temporal and parietal lobes
- Compensatory ventricular enlargement


Sulcus
Gyrus
Ventricle
Language
Memory
Sulcus
Gyrus
Language
Memory
Normal
Alzheimer's

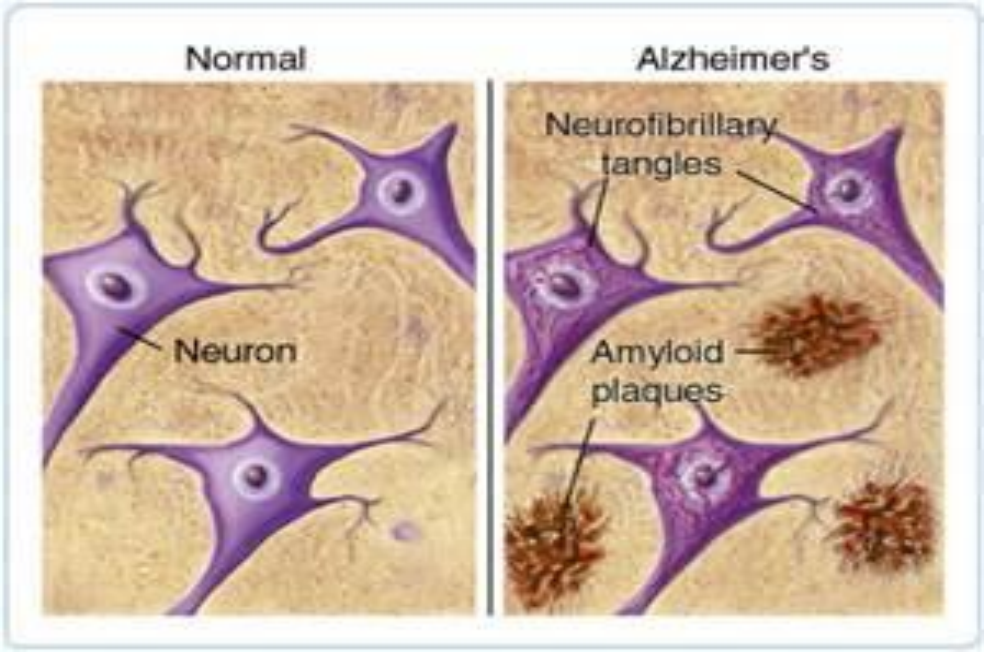
Microscopic changes

- Amyloid plaques and neurofibrillary tangles.
- Plaques are extracellular; tangles are intracellular
- These can be found(to a lesser extent) in elderly non-demented brain… so diagnosis needs both clinical and histological findings.

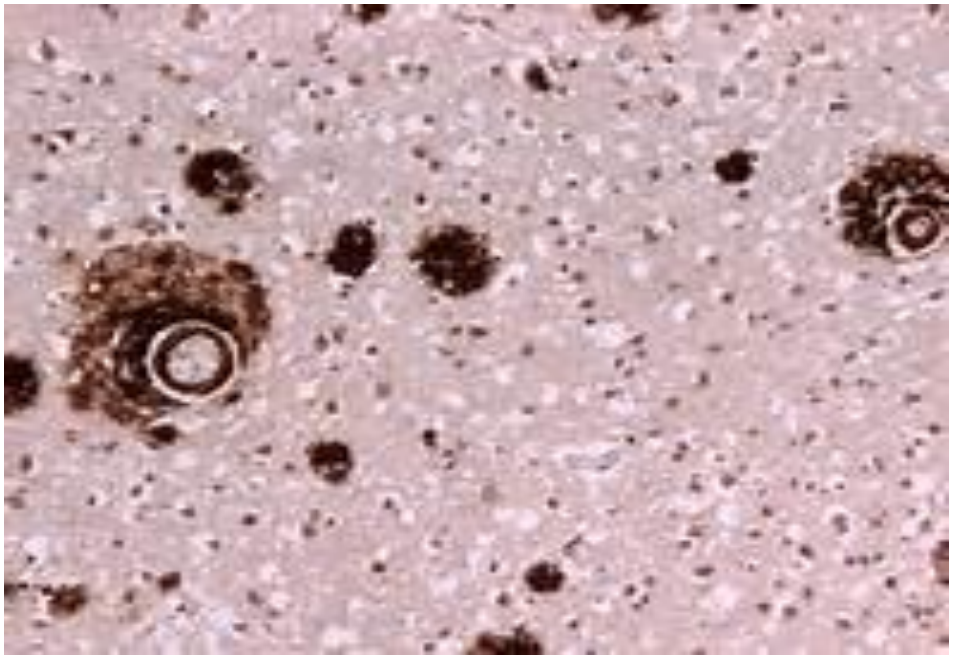
plaques

- Focal or diffuse.
- Focal= neuritic, dystrophic neurones around amyloid core
- Diffuse: amyloid only

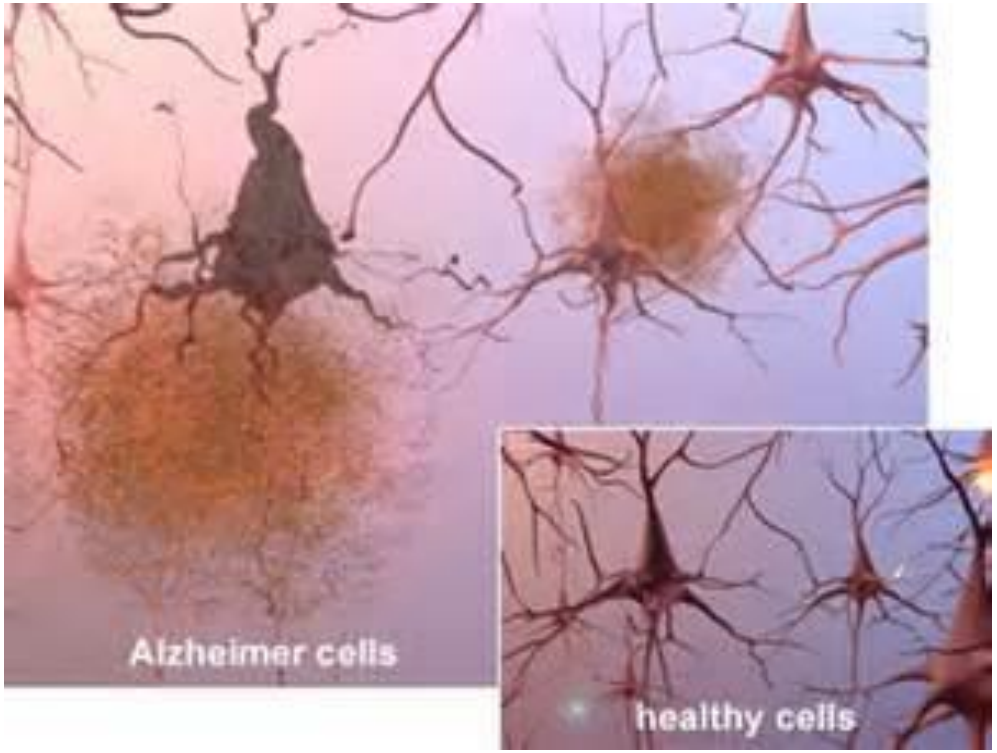
morphology


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

amyloid



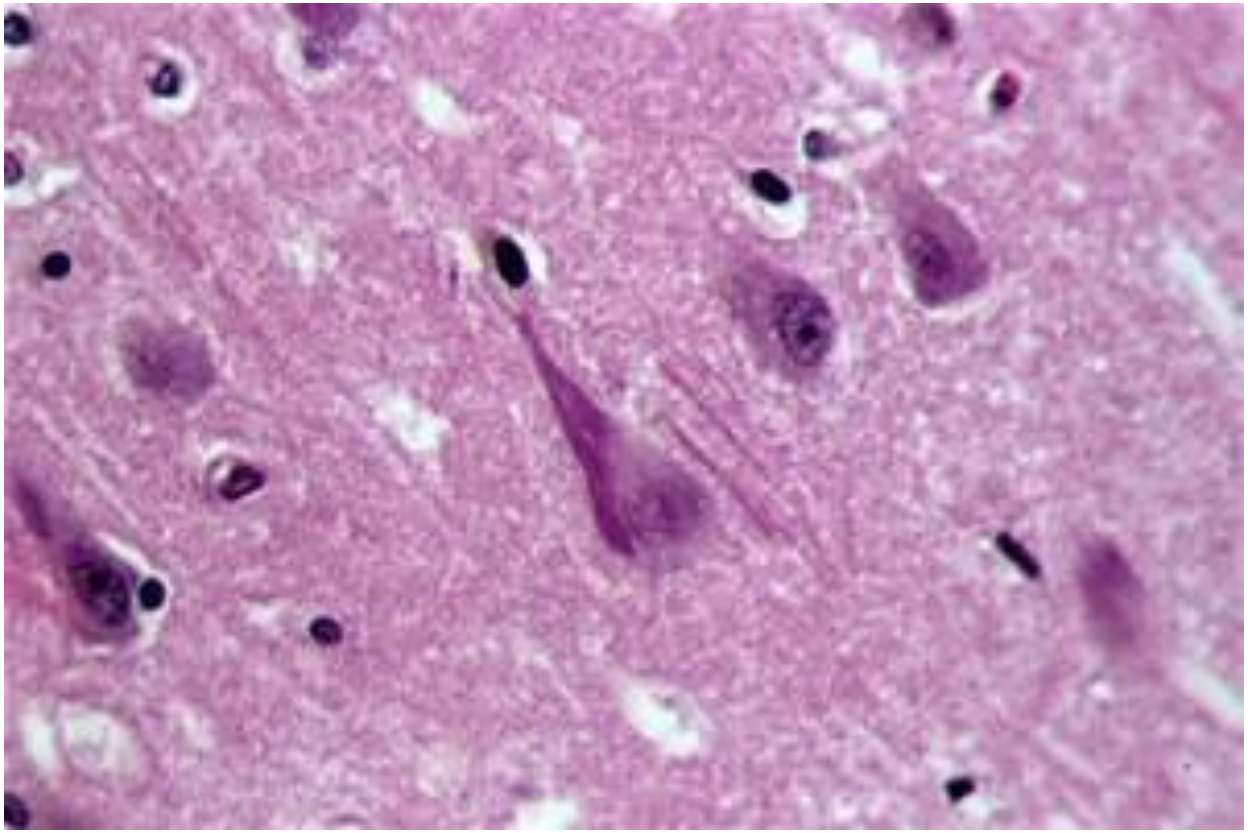
amyloid

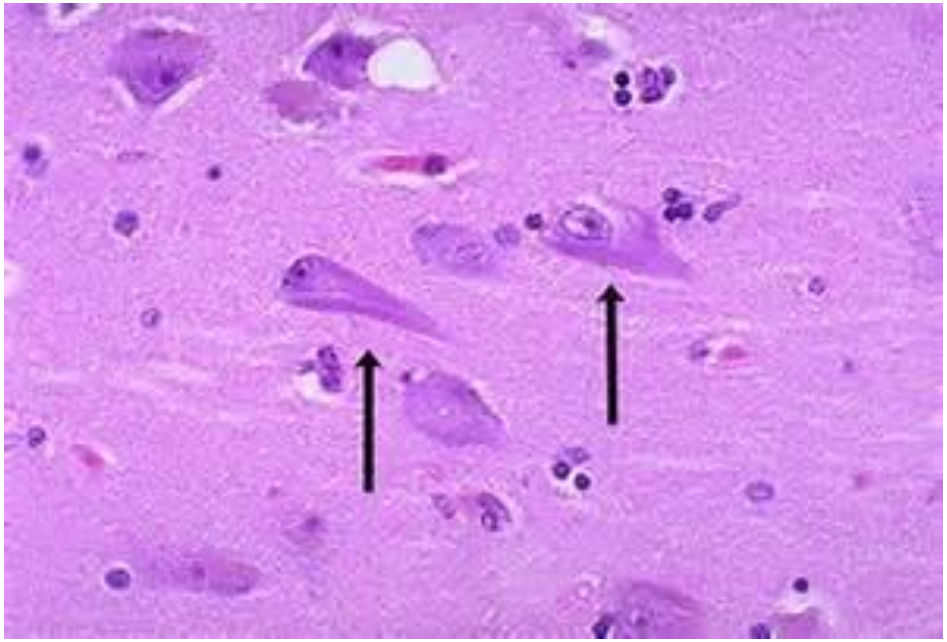


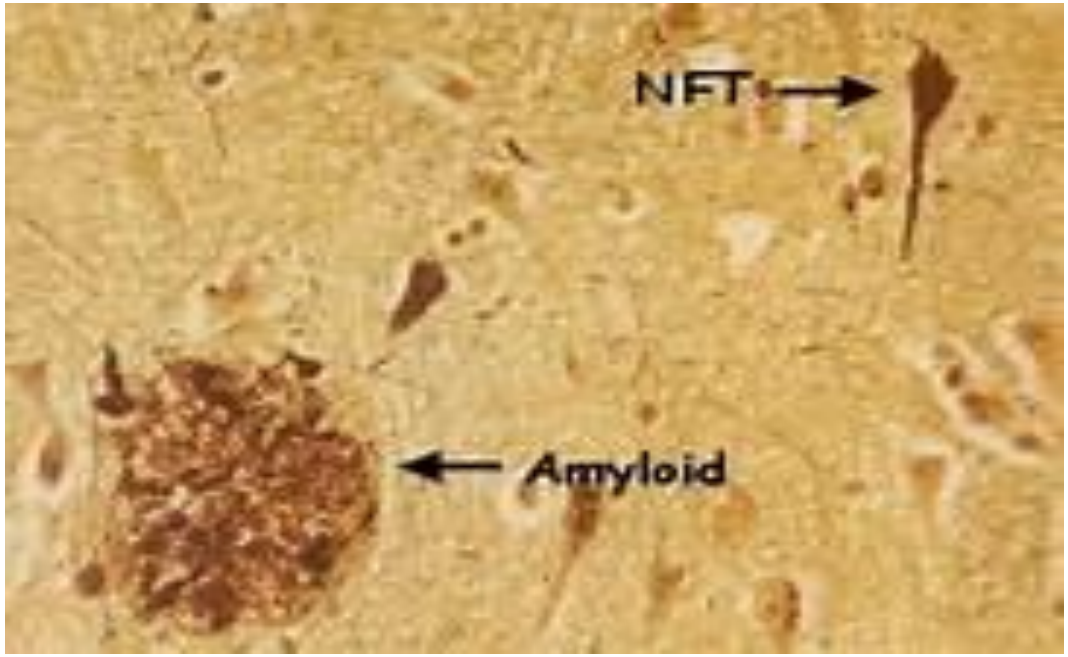
Neurofibrillary tangles

- Bundles of helical filaments seen as basophilic fibrillary structures in the cytoplasm of neurones
- Major component: hyper phosphorylated tau
- Tangles are seen in other degenerative diseases

Neurofibrillary tangles



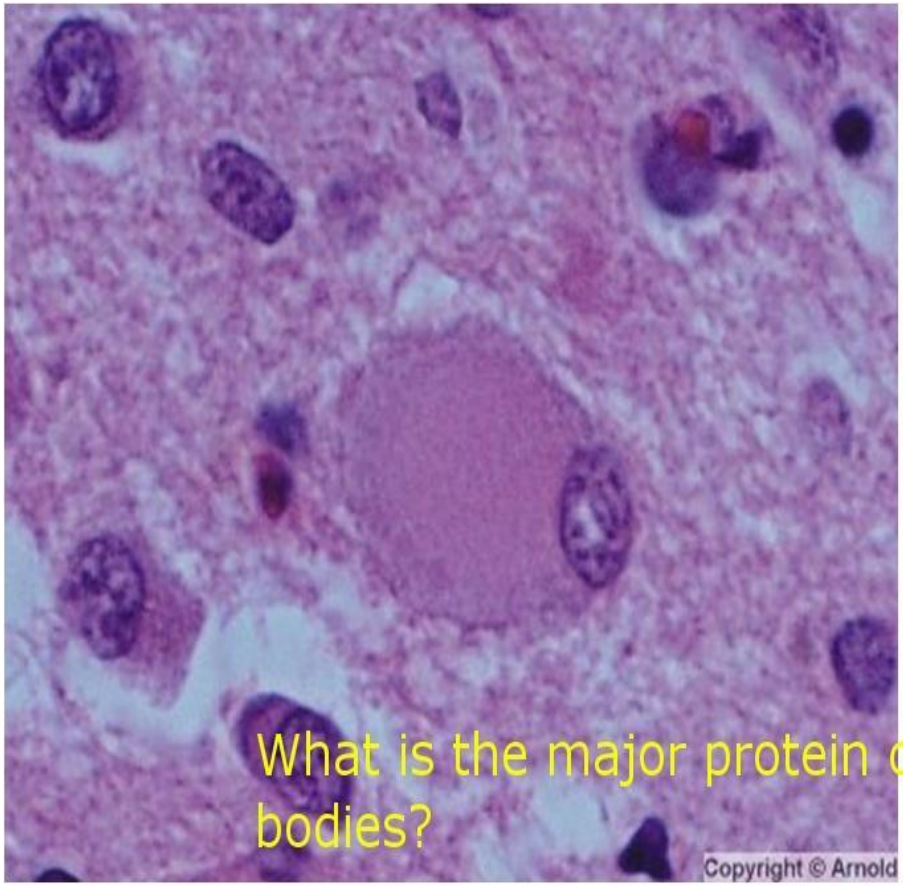



NFT
Amyloid

Frontotemporal lobar degeneration= frontotemporal dementia

- Progressive deterioration of language and changes in personality
- Atrophy of temporal and frontal lobes
- Memory loss follows
- Tau tangles present
- Pick disease is a subtype: smooth round inclusions: pick bodies

Pick bodies


What is the major protein component of Pick bodies?
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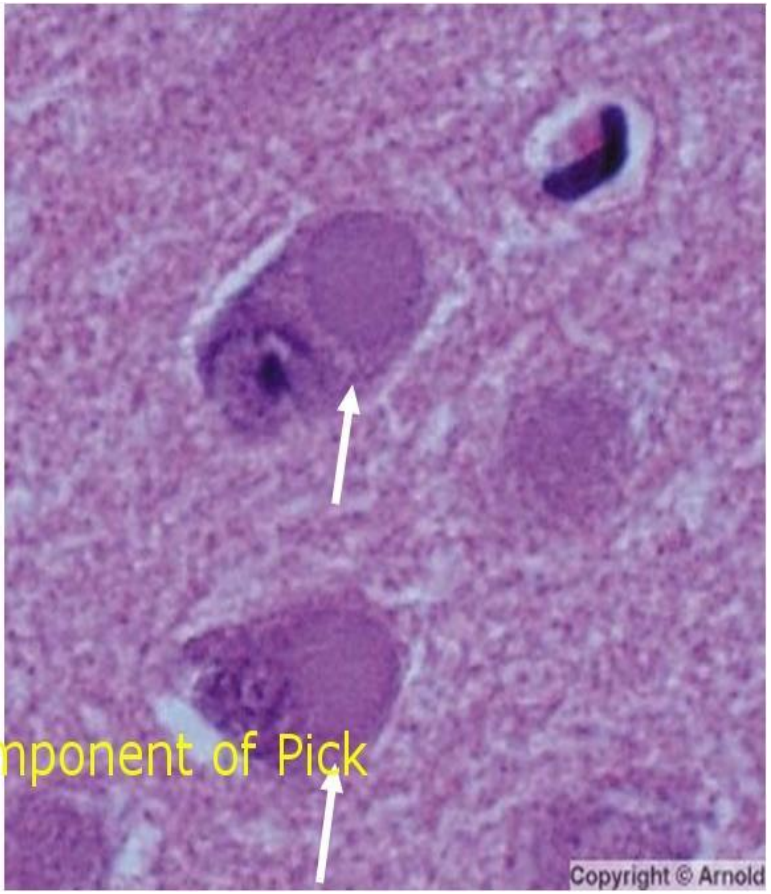
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Parkinson disease

- Parkinsonism: Tremors, rigidity, bradykinesia and instability.
- Damaged dopaminergic neurones that project from substantia nigra
- Parkinsonism can be due to dopamine antagonists or toxins
- Or: can be caused by Parkinson disease

Parkinson disease

- Neural inclusions containing alpha synuclein; a protein involved in synaptic transmission.
- These inclusions= Lewy bodies

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

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

- Subtle Lewy bodies are present in other areas than substantia nigra.. E:g in cerebral cortex

These ae responsible for the neurologic deficit

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 f diagnosis: lewy body dementia.