CNS lecture 5

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Neurodegenerative diseases

- Cellular degeneration of functionally related neurones. → not anatomically-related
- Many of them related to accumulation of abnormal proteins. ⇒ problems
- 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!

accumulate in certain areas + neurons ⇒ functional problems

Neurodegenerative diseases

1. Alzheimer
2. Frontotemporal lobar degeneration
3. Parkinson disease
4. Huntington disease
5. Spinocerebellar ataxia
6. Amyotrophic lateral sclerosis

Dementia = memory loss + cognitive impairment that affect normal daily life
→ completely changed lifestyle

1 Alzheimer disease

- Most common cause of dementia

First:
- Gradual onset of impaired higher intellectual function + altered mood and behaviour.

Later:
- Progresses to disorientation, memory loss, aphasia (problem in language communication)
- Then.. Over 5-10 years, become disabled, mute and immobile → more predisposed to infections
- Death due to infections, mainly pneumonia

→ swallowing is also affected → might die of chocking

Incidence ↑ dramatically with age (mainly after 80)

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

pathogenesis

one of the chemical types of amyloid

- Beta amyloid (AB) accumulate in the brain. abnormally
- Transmembrane protein: amyloid precursor protein (APP) cleaved by ① beta amyloid converting enzyme and ② gamma secretase... generates beta amyloid. → aggregates + accumulates
- Mutations in APP or components of gamma secretase .. Increased beta amyloid.... → ↑ accumulation Resulting in familial Alzheimer ↓ earlier onset

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

Accumulation of β-amyloid:

① Compresses tissues → affecting function

② Toxic effect of amyloid on neurons + synapses → kills neurons which cannot be replaced → ↓ neural mass → atrophy of brain

③ Hyper-phosphorylation of Tau

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.

So β-amyloid → primary

Abnormal Tau → secondary to β-amyloid

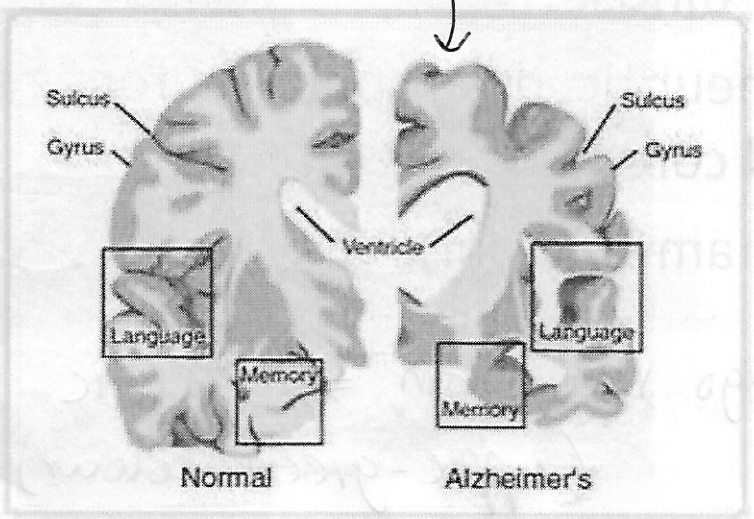
morphology

Gross:

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

*Mainly affecting language and memory areas

Wider sulci + enlarged ventricles



Microscopic changes → masses of misfolded proteins (accumulations)

- Amyloid plaques (A) and neurofibrillary tangles (B).
- 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.

Any aging person will have amyloid plaques, but will not necessarily have dementia or Alzheimer's

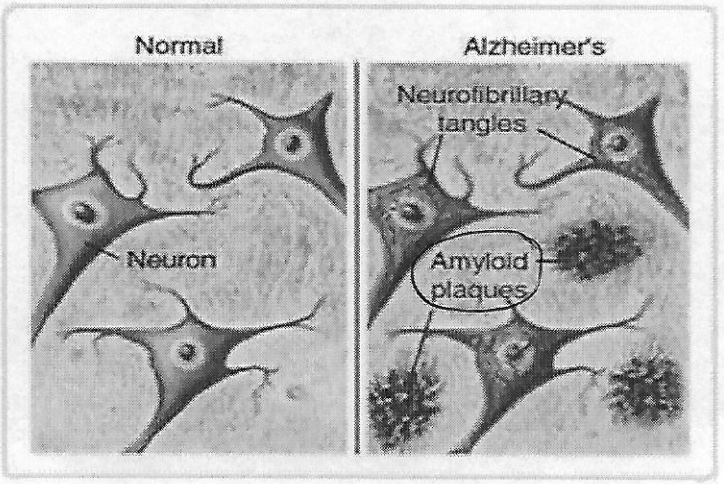
(A) plaques → amyloid → extracellularly

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

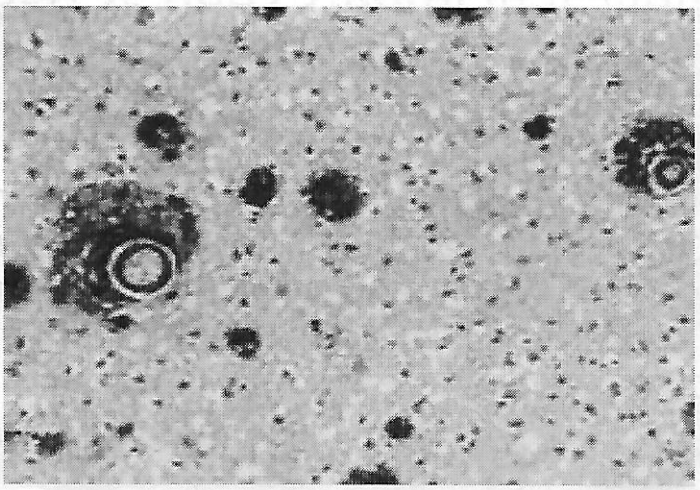
*Congo red stain ⇒ specific (apple-green colour)

*Amyloid is specific to Alzheimer's

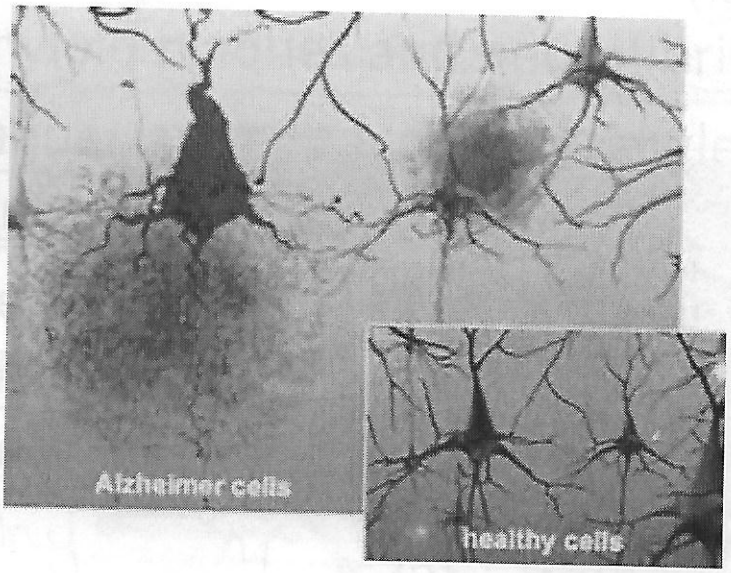
morphology



amyloid



amyloid



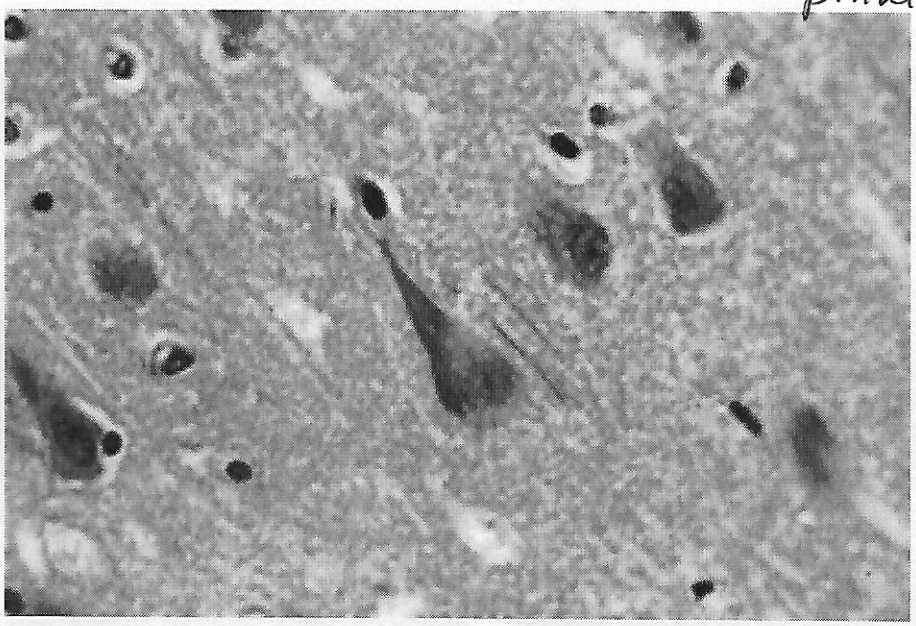
ⓑ Neurofibrillary tangles (NFT)

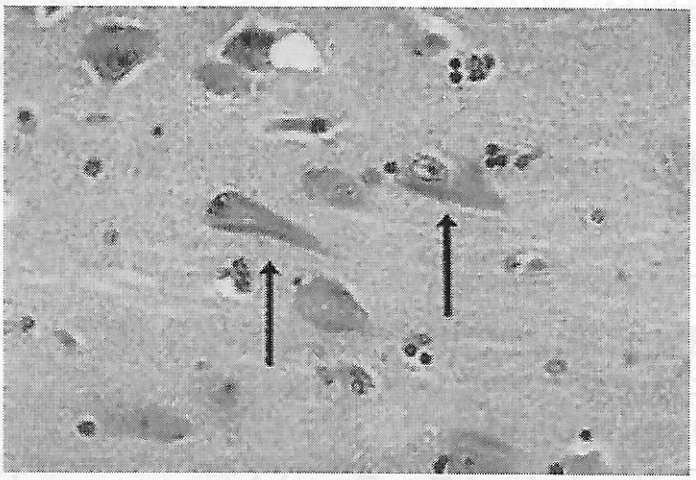
= Misfolded Tau accumulated intracellulary

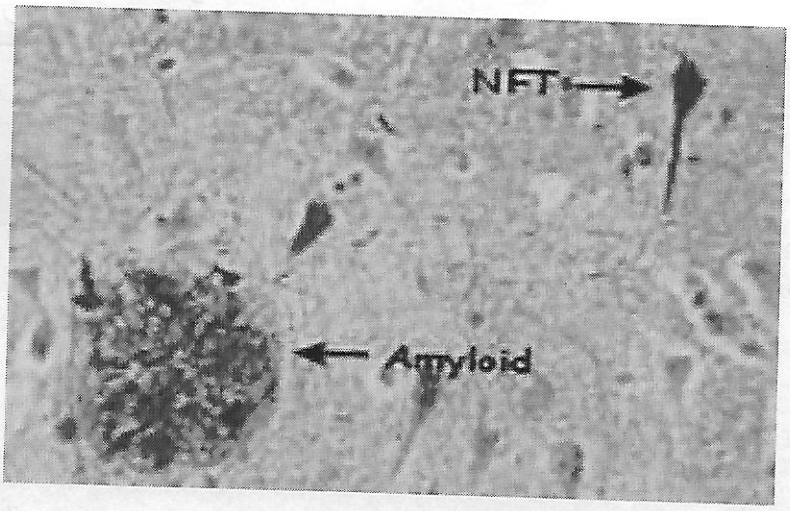
- Bundles of helical filaments seen as basophilic fibrillary structures in the cytoplasm of neurones
- Major component: hyper phosphorylated tau
- Tangles are seen in other degenerative diseases (not specific to Alzheimer's)

Neurofibrillary tangles

Triangular shape, pinkish colour







2 Frontotemporal lobar degeneration= frontotemporal dementia

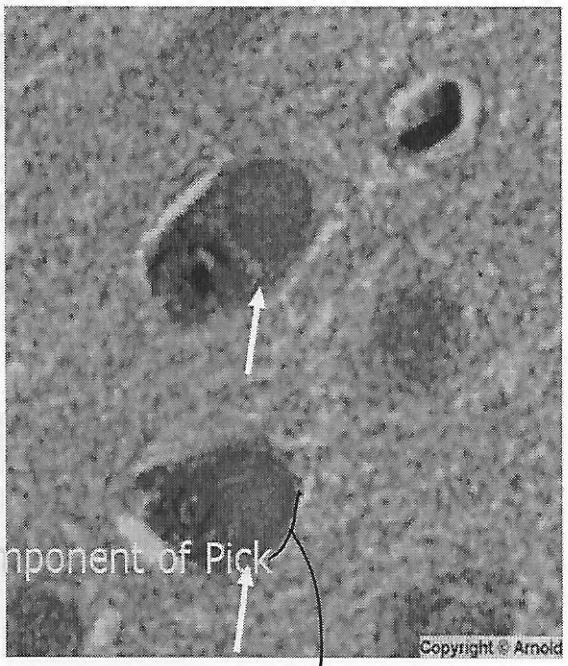
- Progressive deterioration of language and changes in personality
- Atrophy of temporal and frontal lobes
- Memory loss follows
- Tau tangles present
- Pick disease is a subtype: smooth round inclusions: pick bodies

Signs and symptoms are similar to Alzheimer's but only affect frontal and temporal lobes

not like NFT

only in frontal & temporal lobes ←

Pick bodies = Smooth, round Tau inclusions in cytoplasm



Smooth outer surface

3 Parkinson disease — relatively common

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

Damage of dopaminergic neurons of substantia nigra → loss of pigment → no longer black

Parkinson disease

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

pathogenesis

- Majority: sporadic
- Autosomal dominant and recessive forms exist

Due to mutations of genes coding for alpha synuclein (mutations in protein itself)

- 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

Neurons die
↳ those that remain ⇒ Lewy bodies in region of Substantia Nigra

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

⇒ These are responsible for the neurologic deficit (ex: dementia)

Clinical features

- Movement disorder. Starts as motor problems
- Progresses over 10-15 years.. Severe motor slowing → ↑ susceptibility due to immobility
- Death: infections and trauma due to falls (instability) → especially pneumonia
- Dementia can develop
- If dementia within first year of diagnosis: lewy body dementia. → happening early in Parkinson's (it is called ↓)

Summary:

* Alzheimer's → B-amyloid → Plaques
  → Hyperphosphorylated Tau → Neurofibrillary tangles
* Pick disease (frontotemporal lobar degeneration) → Tau → Pick bodies
* Parkinson's → α-synuclein → Lewy bodies