CNS pathology lecture 7

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Lectures 7 :neurodegenerative diseases part 1

ILOS

- 1. List types of neurodegenerative diseases and understand their pathogenesis.
- 2. List causes of dementia
- 3. Define dementia
- 4. Describe the pathogenesis of Alzheimer disease
- 5. Recognize the morphologic changes related to Alzheimer disease

Neurodegenerative disorders

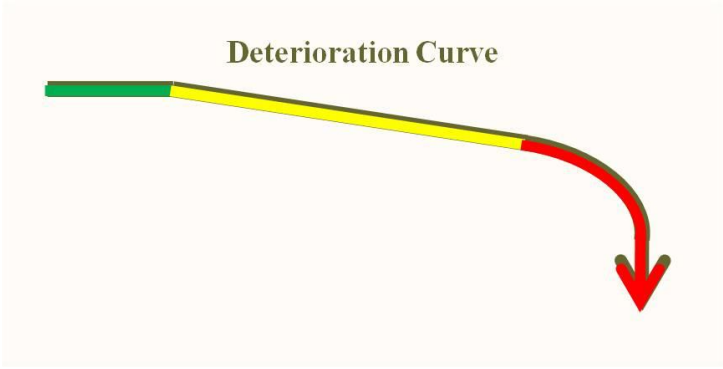
- These are a group of diseases that are caused by **accumulation of abnormal proteins** causing a **slow** deterioration in a certain neurological function depending on where the abnormal protein has accumulated.

Note;

Degeneration means decline or deterioration. إرْتِكاس؛ إنْتِكَاس؛ تَدَهْوُر

Degeneration

- All degenerative diseases show slow deterioration. They are chronic diseases. The process needs time to fully develop into a clinically recognised disease and the symptoms worsen slowly.



Neurodegenerative diseases

- =Disorders characterised by cellular degeneration of functionally related neurones.
- Many of them related to accumulation of abnormal proteins.
- Involved proteins are widely expressed in the CNS but they only accumulate in certain areas causing certain disease… we don't know the reason for this bias!

Abnormal protein aggregates in neurodegenerative diseases

- so: in all these diseases there is abnormal protein accumulation.
- how does the abnormal protein affect the brain and cause disease?
- 1. the abnormally aggregated proteins often are directly toxic to neurons.
- 2. ALSO: There is loss of function as more and more protein is shunted into the aggregates rather than performing its normal physiologic functions.

Why do these proteins aggregate?

Aggregates may arise because of :

1. mutations that alter the protein's conformation

2. or that disrupt pathways involved in processing or clearance of the proteins.

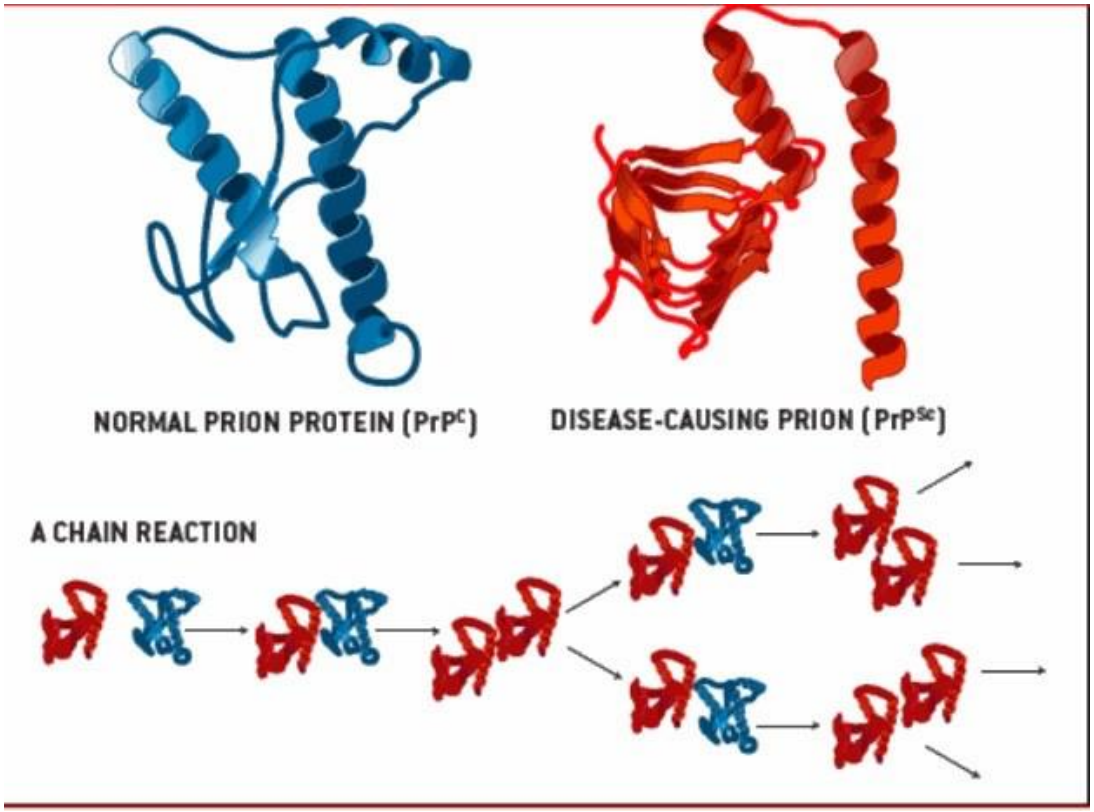
3. or there may be a subtle imbalance between protein synthesis and clearance (due to genetic or environmental factors) that allows gradual accumulation of proteins.

IMPORTANT NOTE

-It is thought that these protein aggregates behave like prions; so aggregates derived from one cell are taken up by another, giving rise to more aggregates. (as if they “infect” other cells)

-The data supporting this concept are largely derived from experimental animal studies, but some case studies of patients who died with Alzheimer disease suggest that the disease spreads from one site in the brain to another in the same individual.(NOT INFECTIOUS FROM PERSON TO PERSON)

Prions are abnormally folded proteins that cause a chain of reactions: one abnormally folded protein causes abnormal folding of another and so on..



Remember: one “rotten” protein will affect adjacent ones.. the more abnormal proteins accumulate, the worse the symptoms. That's why these diseases are progressive.

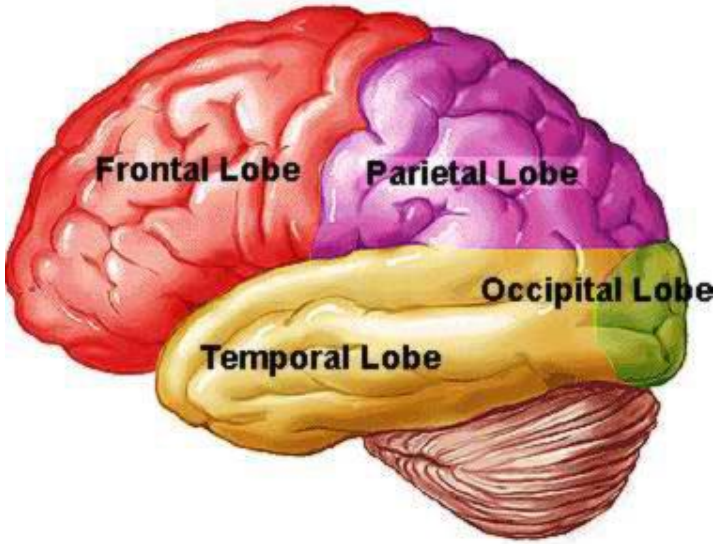
Types of neurodegenerative diseases

- they are divided according to what part of the brain is affected (where the abnormal protein accumulates)

- So we divide them into diseases affecting the
- 1. Cortex,
- 2. Basal nuclei,
- 3. Spino-cerebellum,
- 4. motor neurones.

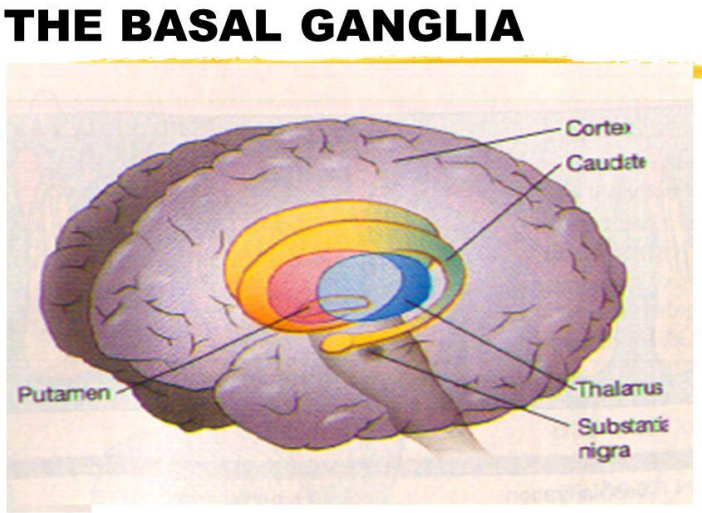
Type1: those affecting the cortex

- If affecting the **cortex**, neurodegenerative diseases will cause **dementia**. Disease entities in this category include:
- *Alzheimer disease* (Alzheimer's, both are correct)
- *Frontotemporal dementia* (FTD)
- *Pick disease* (a subtype of FTD)



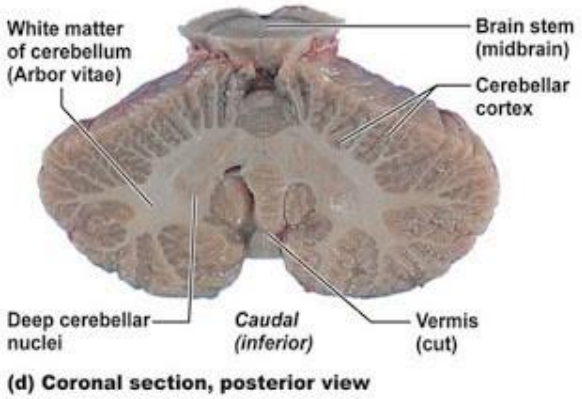
Type 2: affecting basal ganglia

- Neurodegenerative diseases affecting **basal ganglia** (basal nuclei) will cause motor problem; **either decreased or increased movement**. Diseases in this category include
- 1. *Parkinson disease*
- 2. *Huntington Chorea*



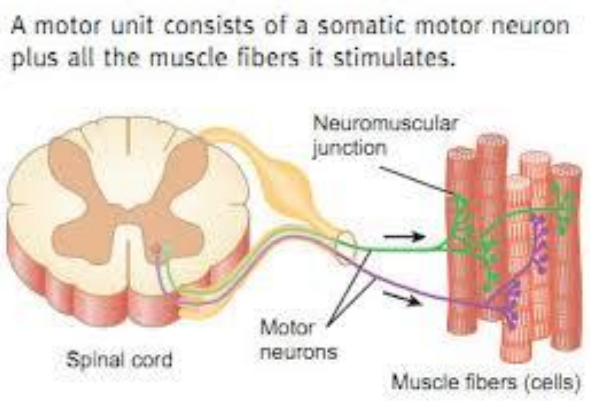
Type 3. Diseases affecting spinocerebellum

- These will cause *ataxia* and they include
- .1Spinocerebellar ataxia
- .2Friedrich ataxia
- .3Ataxia telengiectasia



Type 4. Affecting motor neurones

- these will cause muscle weakness and the main disease is ALS = <u>amyotrophic lateral sclerosis.</u>



A recap

The Clinical picture is dictated by the pattern of neuron dysfunction.

- 1. if neurons of cerebral cortex affected= loss of memory, language, insight and planning.(all these are components of dementia)
- 2. if neurons of basal ganglia affected: results in movement disorder.
- 3. if cerebellar neurons… ataxia
- 4. motor neurons.. Muscle weakness

Note

- Basal nuclei are traditionally called basal ganglia.
- The correct term is basal nuclei because they are aggregates of neurones within the CNS
- However, many books uses the old name: basal ganglia.

- in this lecture we will start talking about neurodegenerative diseases that affect the cortex.. the ones that cause dementia
- So what is dementia…..

dementia

- *Development of memory impairment and other cognitive deficits severe enough to decrease the person's capacity to function at **his previous** level **despite** normal level of consciousness.*
- note from this definition that the cognitive deficit *must affect the person's performance in his daily life activities* to be called dementia.
- Also note that you have to *compare* the cognitive function of this person to ***his*** *previous cognition.*. there is no standard level considered normal cognition.

Dementia- symptoms

Cognitive changes

- Memory loss, which is usually noticed by a spouse or someone else
- Difficulty communicating or finding words
- Difficulty reasoning or problem-solving
- Difficulty handling complex tasks
- Difficulty with planning and organizing
- Difficulty with coordination and motor functions
- Confusion and disorientation

Psychological changes

- Personality changes
- Depression
- Anxiety
- Inappropriate behavior
- Paranoia
- Agitation
- Hallucinations

Causes of dementia

Progressive, irreversible dementia:

- Alzheimer's disease.
- Lewy body dementia.
- Frontotemporal dementia.

Other causes of dementia 1

- **Infections.** Dementia-like symptoms can result from infections.
- **Metabolic problems and endocrine abnormalities:** thyroid problems, hypoglycemia, sodium or calcium imbalance,
- **Nutritional deficiencies.** dehydration; thiamin (vitamin B-1) deficiency,
- **Reactions to medications.**
- **Subdural hematomas.**
- **Poisoning**: heavy metals, pesticides, alcohol abuse. Symptoms might resolve with treatment.
- **Brain tumors.** Rarely, dementia can result from damage caused by a brain tumor.
- **Anoxia.**

Complications of dementia

- **Inadequate nutrition.** Many people with dementia eventually reduce or stop their intake of nutrients.
- **Pneumonia.** Difficulty swallowing increases the risk of choking or aspirating food into the lungs
- **Inability to perform self-care tasks.** As dementia progresses, it can interfere with bathing, dressing, brushing hair or teeth, using the toilet independently and taking medications accurately.
- **Personal safety challenges.** Some day-to-day situations can present safety issues for people with dementia, including driving, cooking and walking alone.
- **Death.** Late-stage dementia results in coma and death, often from infection

Alzheimer disease (AD)

- Alzheimer disease is the most common cause of dementia
- It is characterised by 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

- The most commonly recognised **symptom** of Alzheimer is an inability to acquire **new memories** and difficulty in recalling recently observed facts.
- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.

pathogenesis

- Alzheimer is a neurodegenerative disease, so it's caused by accumulation of abnormal proteins.
- In fact, two proteins accumulate in Alzheimer: AB amyloid and tau
- These accumulate in the *cortex*.
- And they accumulate due to overproduction and decreased removal.
- Both protein aggregates cause neural death and dysfunction.
- The initial event is the AB accumulation.

AB amyloid deposition

-The AB amyloid that accumulates in Alzheimer is derived from a large protein in the brain called **Amyloid precursor protein (APP)**

- APP is a cell surface protein with a single transmembrane domain

-The Aβ portion of the protein extends from the extracellular region into the transmembrane domain

-Processing of APP begins with cleavage in the extracellular domain, followed by an intra-membranous cleavage.

APP

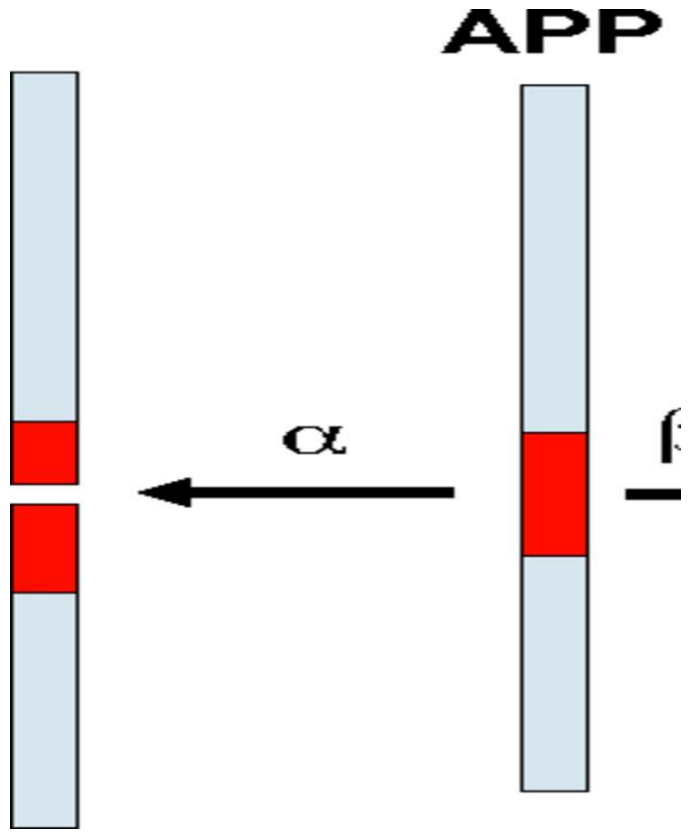
Amyloid precursor protein (**APP**) is an integral membrane portion that is expressed in many tissues including the synapses of neurones.

Its primary function is not known, but it has been implicated as a regulator of synapse formation and iron export.

Cleavage of APP

- APP is a large protein that is cleaved at two sites. The first cleavage site has two possibilities:
- If the first cut occurs at the α-secretase site within the Aβ sequence, then Aβ is not generated (the non-amyloidogenic pathway).
- The alpha secretase cuts in the middle of AB so soluble protein fragments are formed. No complete AB protein is produced; hence no aggregation
- see next slide for more explanation.

- the red colour is the AB protein which is a component of the APP.
- Alpha secretase cuts through the AB so complete AB fragments are not formed.

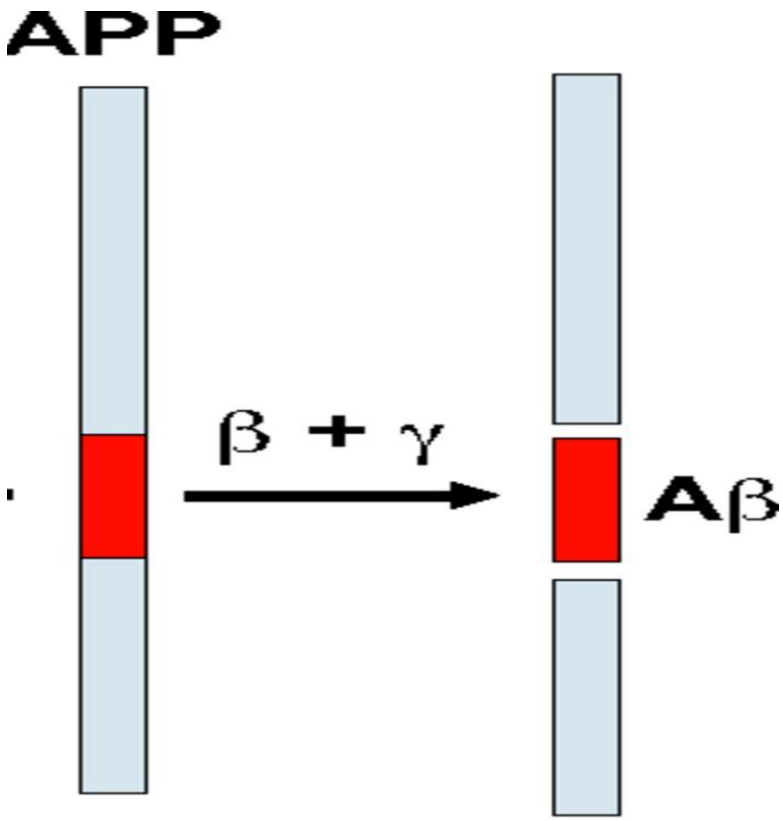


The other cleavage pathway

- IF APP is cleaved by β-secretase, which cuts at the N-terminal region of the Aβ sequence then AB is formed (the amyloidogenic pathway).

.see next slide

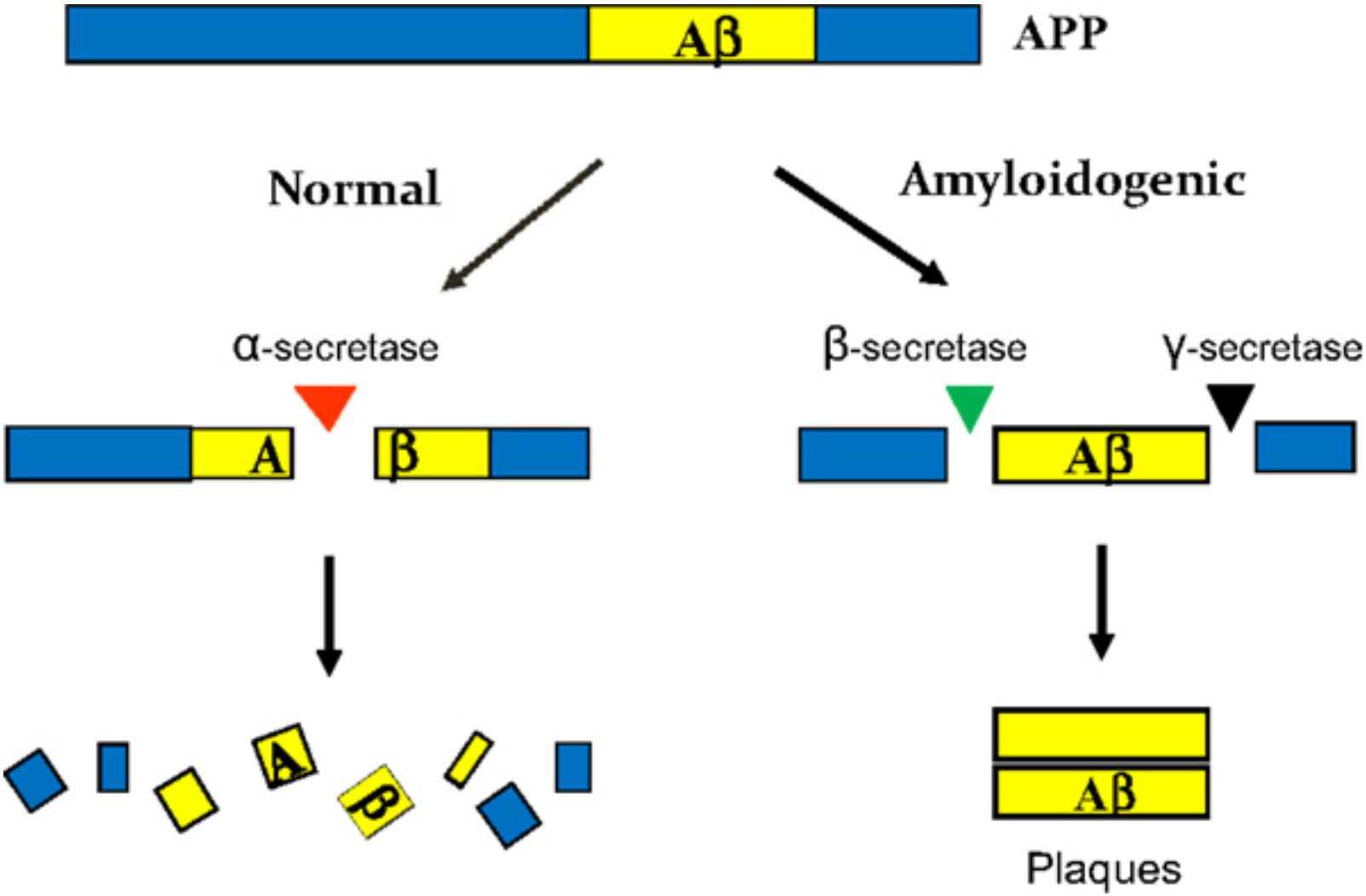
- Here the Beta secretes is cleaving at the one end of the AB amyloid and the gamma secretes is cleaving at the other end. So complete AB fragments are formed which can aggregate.



Note

Following cleavage of APP by alpha or beta secretase, the γ-secretase complex performs an intramembranous cleavage

When paired with a first cut by α-secretase, it produces a soluble fragment, but when paired with β-secretase cleavage, it generates Aβ .


Aβ
APP
Normal
Amyloidogenic
α-secretase
β-secretase
γ-secretase
A
β
Aβ
A
β
Aβ
Plaques

Once generated, Aβ is highly prone to aggregation—first into small oligomers (which maybe the toxic form responsible for neuronal dysfunction), and eventually into large aggregates and fibrils.

Role of inflammation

Both small aggregates and larger deposits of Aβ elicit an inflammatory response from microglia and astrocytes. This response probably assists in the clearance of the aggregated peptide, but may also stimulate the secretion of mediators that cause damage.

- Additional consequences of the activation of these inflammatory cascades may include alterations in **tau phosphorylation, along with oxidative injury to the neurons.**

Tau protein

- So : the main protein that aggregates in AD is AB amyloid. but later in the diseases anther protein accumulates: Tau protein.
- Tau is a **microtubule-associated protein** present in axons in association with the microtubular network.
- In AD Tau becomes hyperphosphorylated, and loses the ability to bind to microtubules.
- Remember that Tau hyperphosphorylation is secondary to inflammation caused by AB amyloid aggregation, so Tau accumulation occurs later in the disease and is not the primary abnormality.

effects of aggregated AB amyloid and tau

- Aggregation of beta amyloid alter neurotransmission
- AB amyloid is toxic to neurones and synapses
- Large deposits cause neuronal death and cause inflammatory response
- Aggregates of Tau cause neuronal damage
- loss of normal tau affects microtubule stability.

genetic factors in AD

The genetic locus on chromosome 19 that encodes apolipoprotein E (ApoE) has a strong influence on the risk of developing AD. Certain polymorphisms in this locus increase risk of sporadic AD.

APP mutations can cause familial Alzheimer disease(AD)

Point mutations in APP are a cause of familial AD.

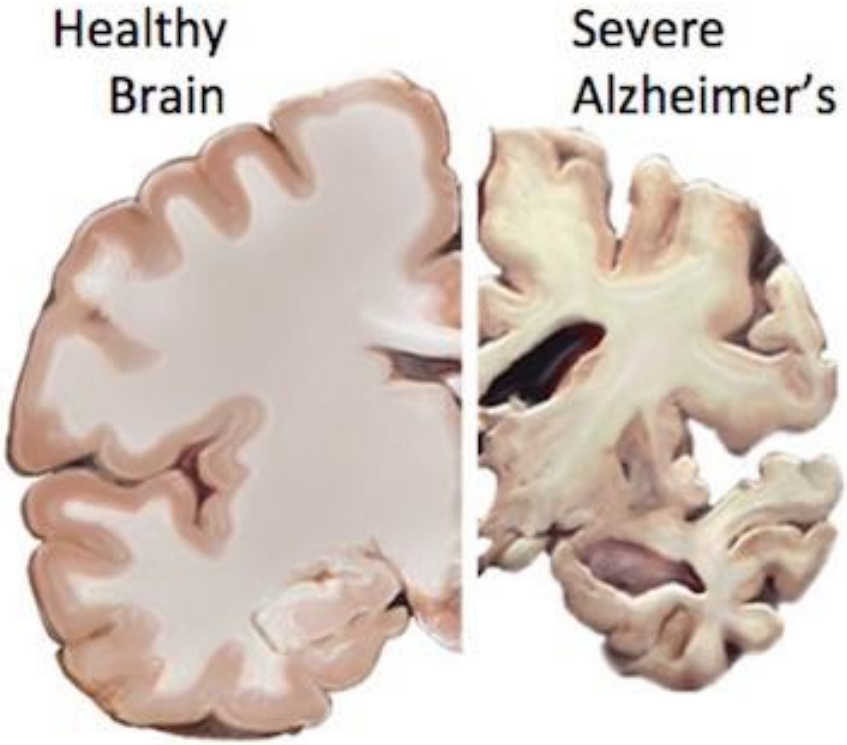
Some mutations lie near the β-secretase and γ-secretase cleavage sites, and others sit in the Aβ sequence and increase its ability to aggregate.

Genetic factors.. continuation

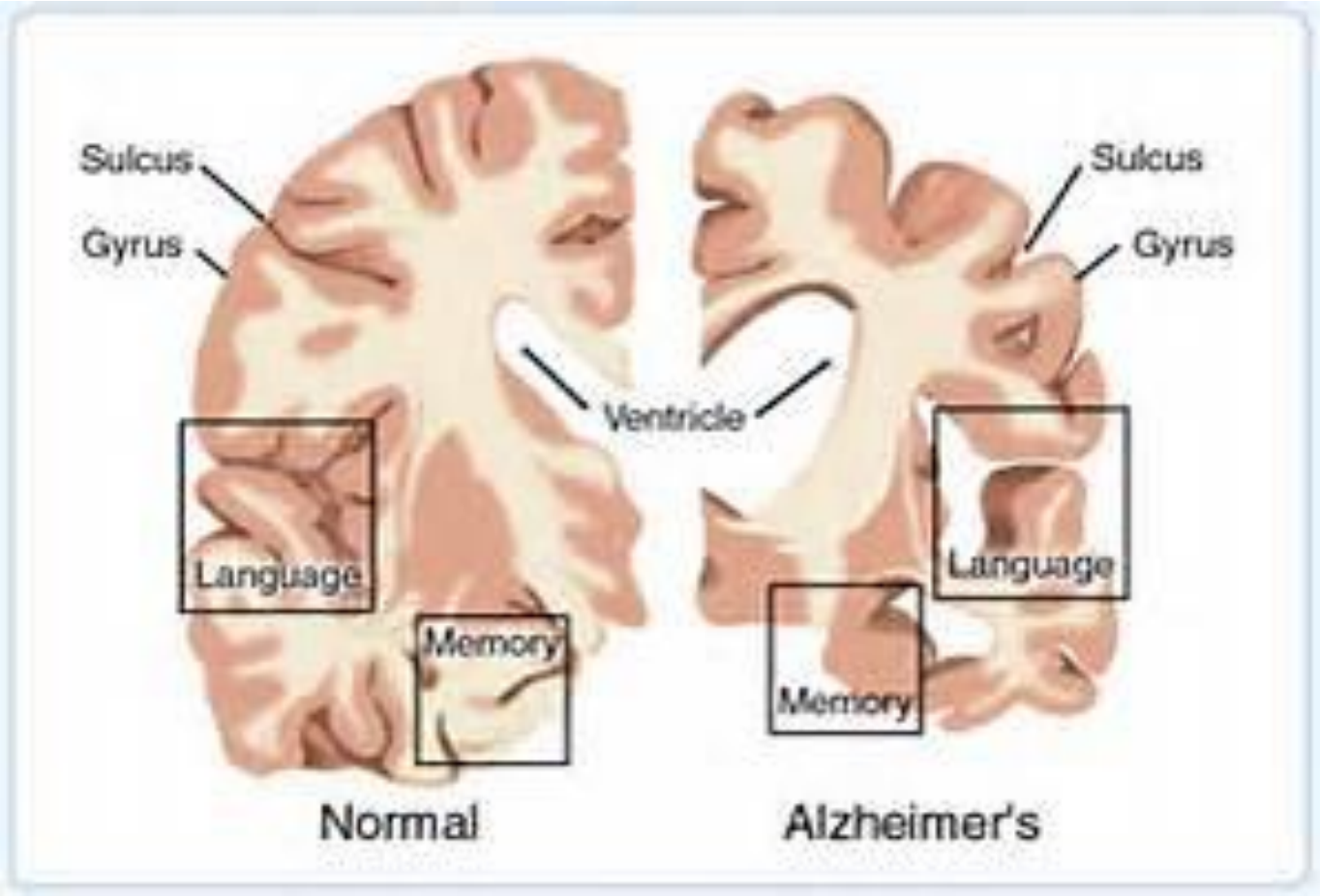
- APP gene present on chromosome 21.
- Trisomy 21 (Down syndrome) have increased risk of Alzheimer because there is an extra copy of APP gene.

morphology

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



Neuronal cell loss leading to extensive shrinkage in an Alzheimer's brain (right), as compared to a healthy human brain (left).


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

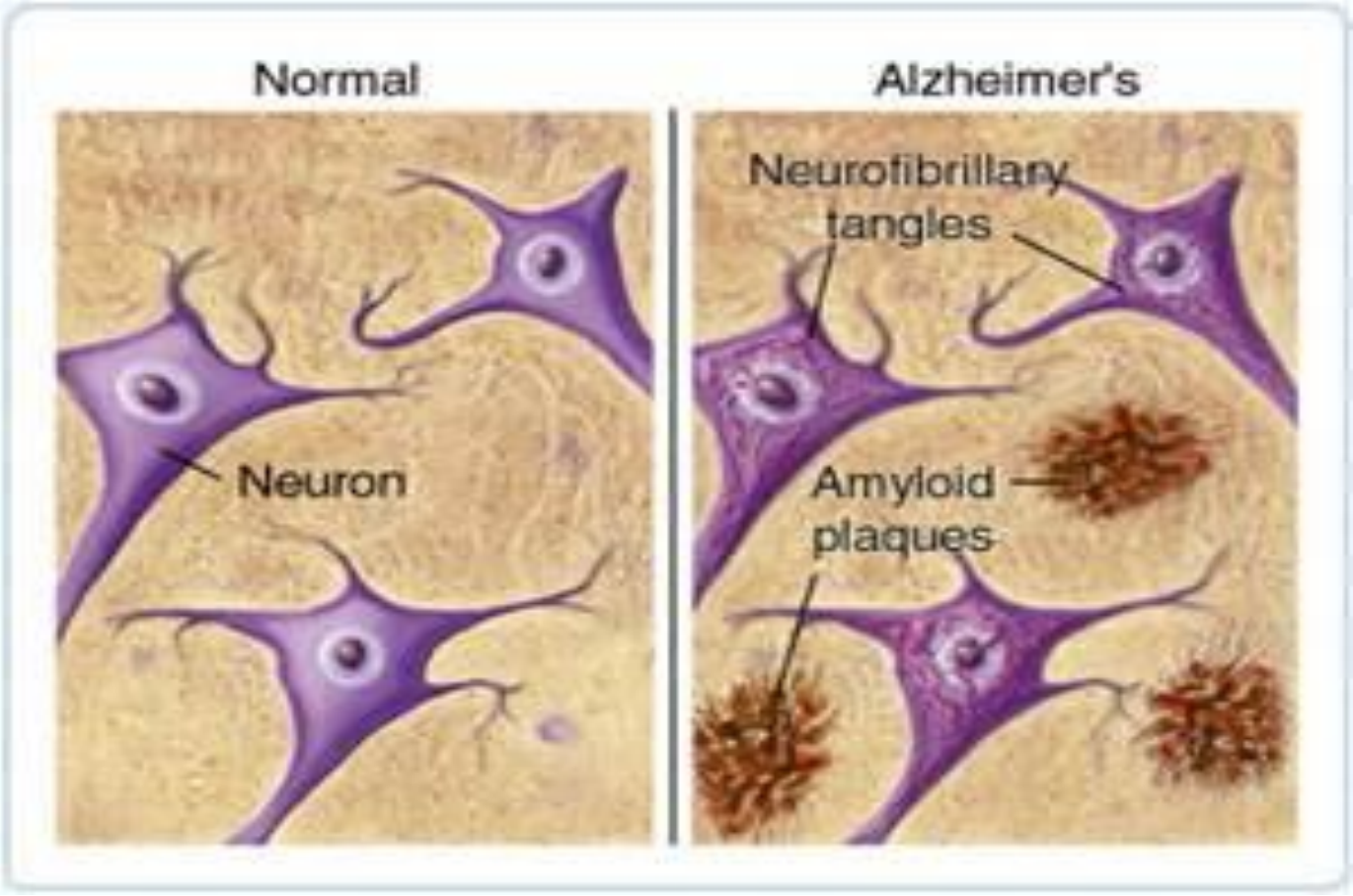
Microscopic changes

- Amyloid plaques (due to accumulation of AB amyloid) and neurofibrillary tangles (due to Tau accumulation).
- 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.*

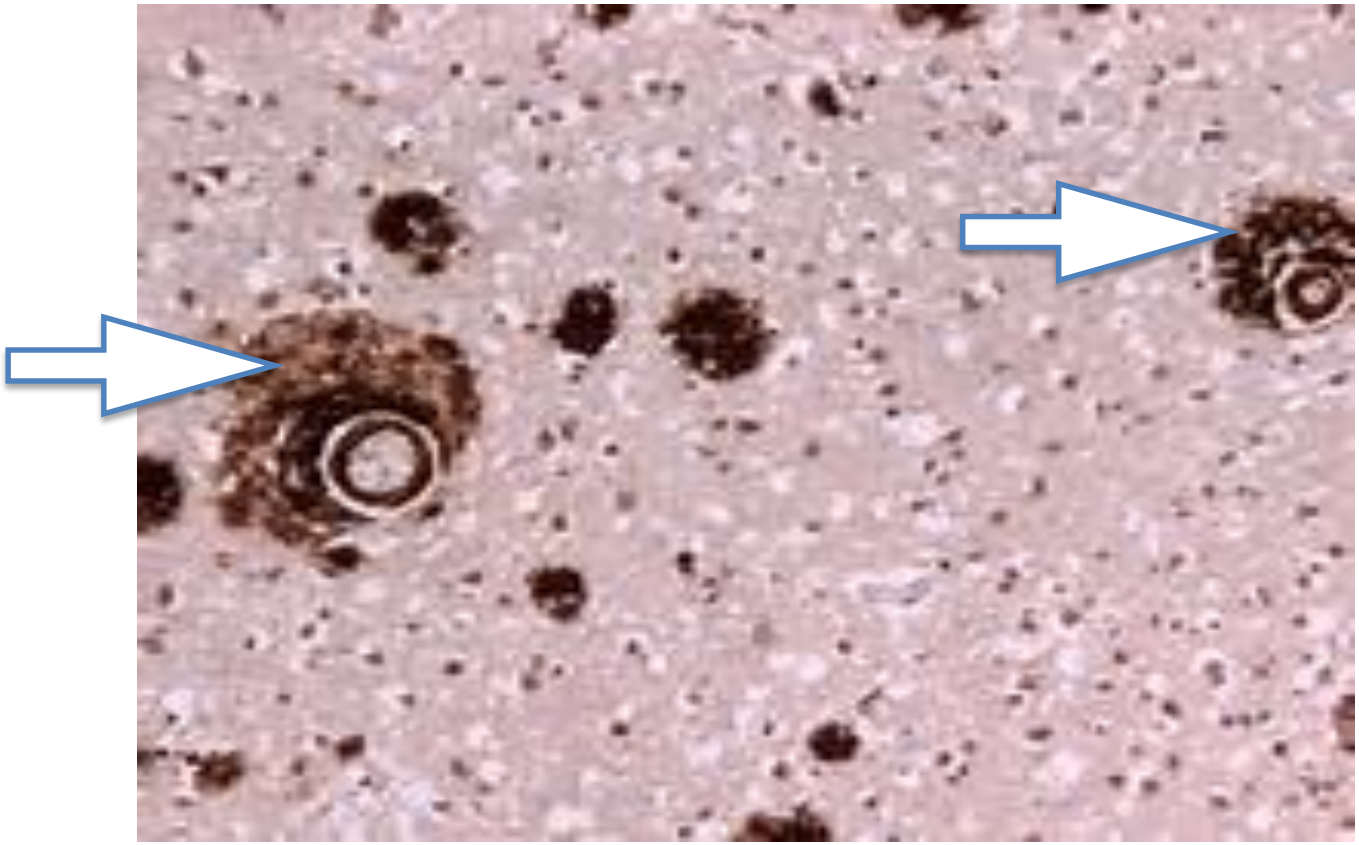
plaques

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

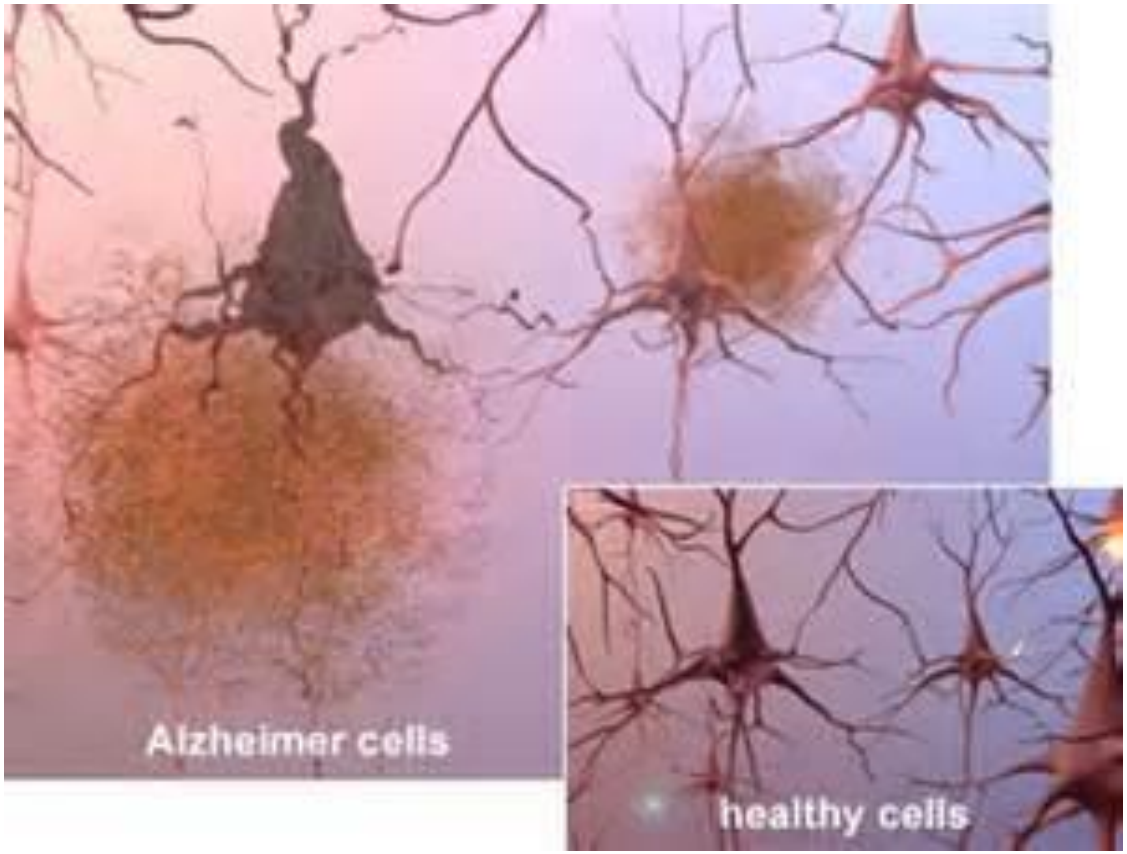
morphology


Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

amyloid plaques



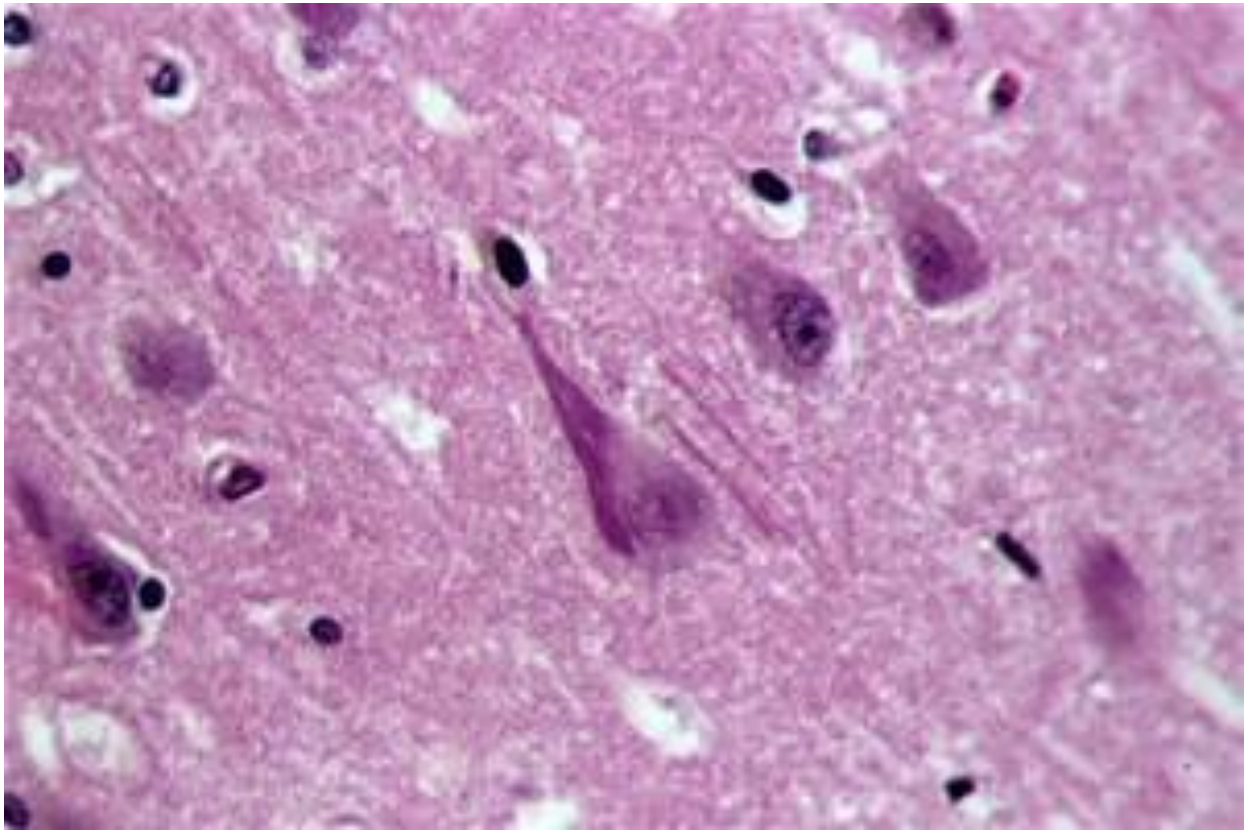
amyloid



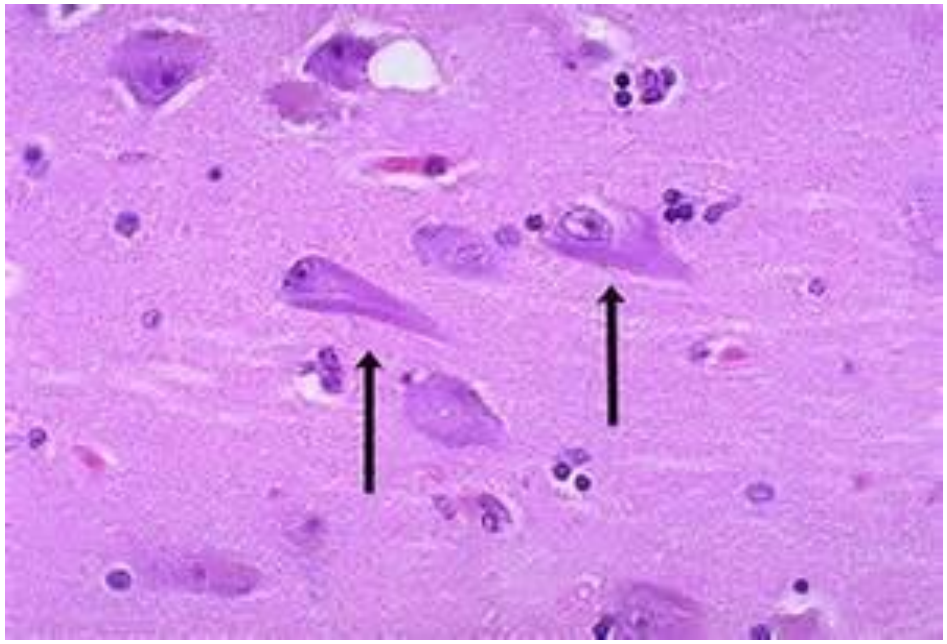
Neurofibrillary tangles

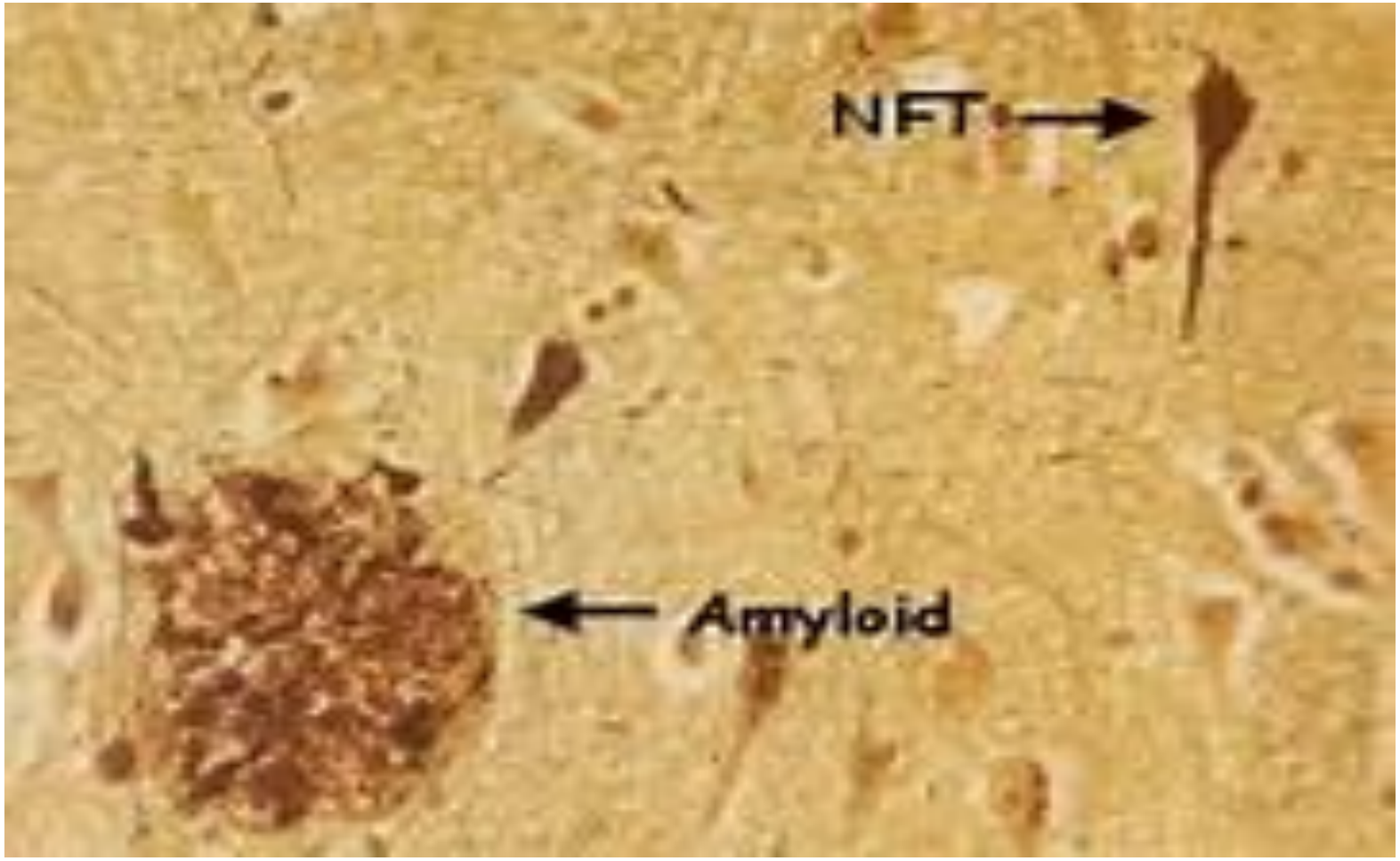
- Bundles of helical filaments seen as basophilic fibrillary structures in the cytoplasm of neurones
- Major component: hyper phosphorylated tau
- Tangles are seen in other degenerative diseases

Neurofibrillary tangles



Neurofibrillary tangles

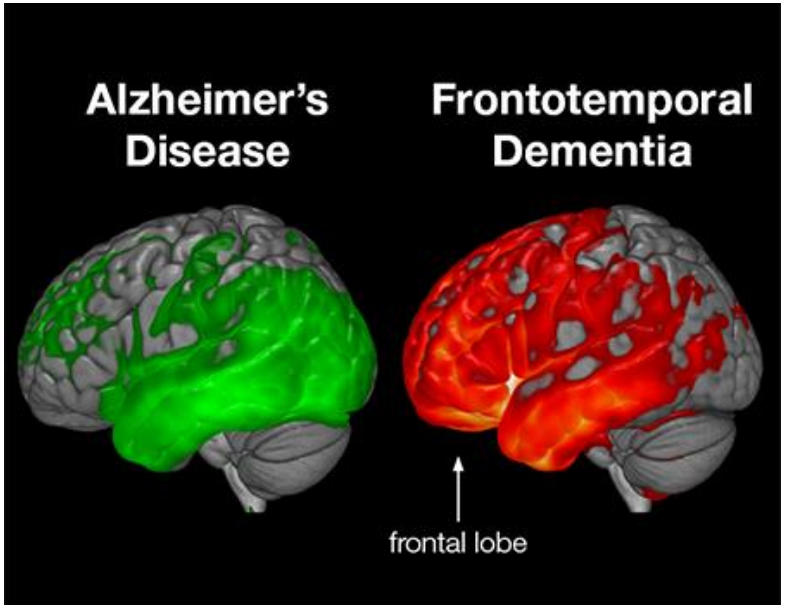



NFT
Amyloid

Fronto-temporal lobar degeneration (FTLD)

- These are a 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.

- Remember that in Alzheimer memory loss comes first.
- In FTLD patients at the beginning have good memory, but there personality and language skills are affected. this is because frontal and temporal lobes are important for these two functions.



- this pic shows where the abnormal proteins accumulate in Alzheimer and in FTLD.
- In AD 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 .

Symptoms of FTD include

- Aggressive behaviour.
- Loss of interest in everyday activities
- Irritability and agitation
- drastic and quick mood swings
- Having trouble with unplanned activities
- Increasingly inappropriate social behavior
- Loss of empathy and other interpersonal skills, such as having sensitivity to another's feelings
- Lack of judgment
- Lack of interest (apathy), which can be mistaken for depression
- Repetitive compulsive behavior, such as tapping, clapping or smacking lips
- Changes in eating habits, usually overeating or developing a preference for sweets and carbohydrates
- Eating inedible objects

Problems with language usually happen early in the disease resulting in problems with:

- Recalling names of common objects
- Copying simple shapes with pencil and paper
- Understanding written words

aetiology

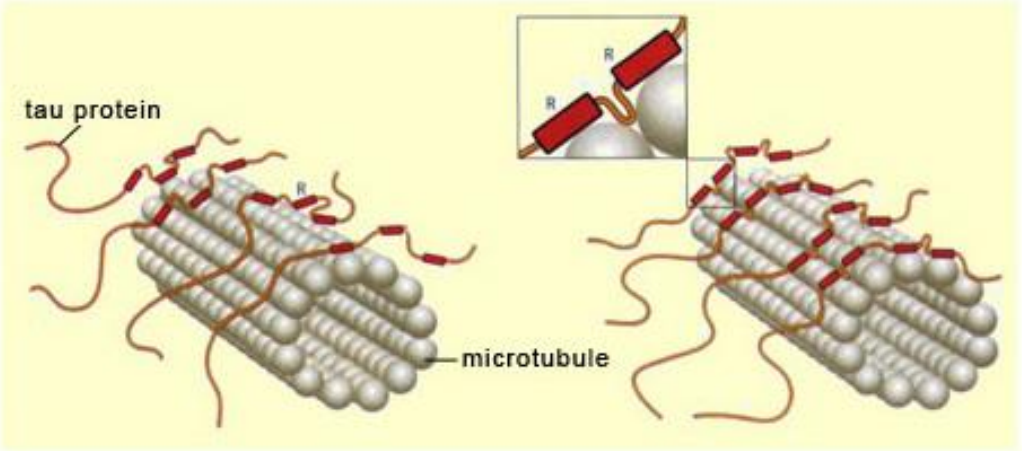
- Accumulation of abnormal Tau protein.

Tau in FTLD accumulates in two forms:

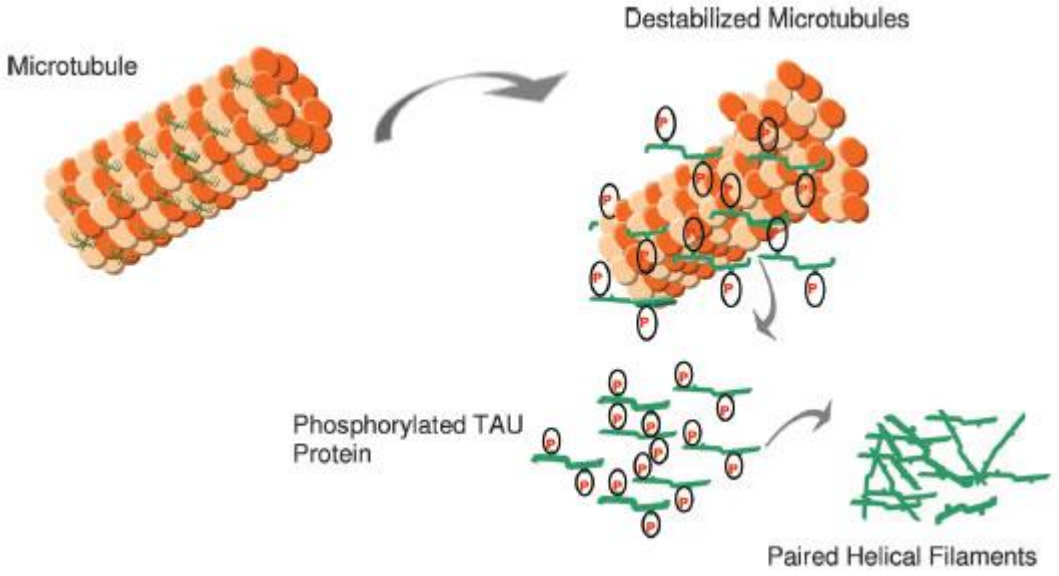
- .1**neurofibrillary tangles** ni nees esoht ekil ;
  on dna uaT ylno si ereht DLTF ni tub) remiehzlA
  (setagergga diolyma
- .2smooth inclusions = **Pick bodies** fo epytbus sihT ..
  .esaesid kciP dellac si DLTF

Tau protein

- Is a phosphoprotein that interacts with microtubules

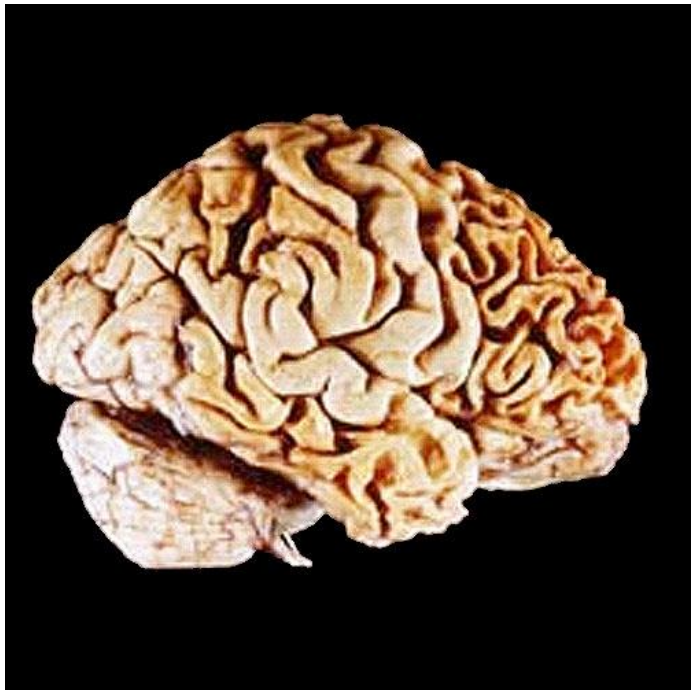


- When Tau is hyperphosphorylated two changes occur: 1) its ability to bind with microtubules decreases and 2) its ability to aggregate increases.

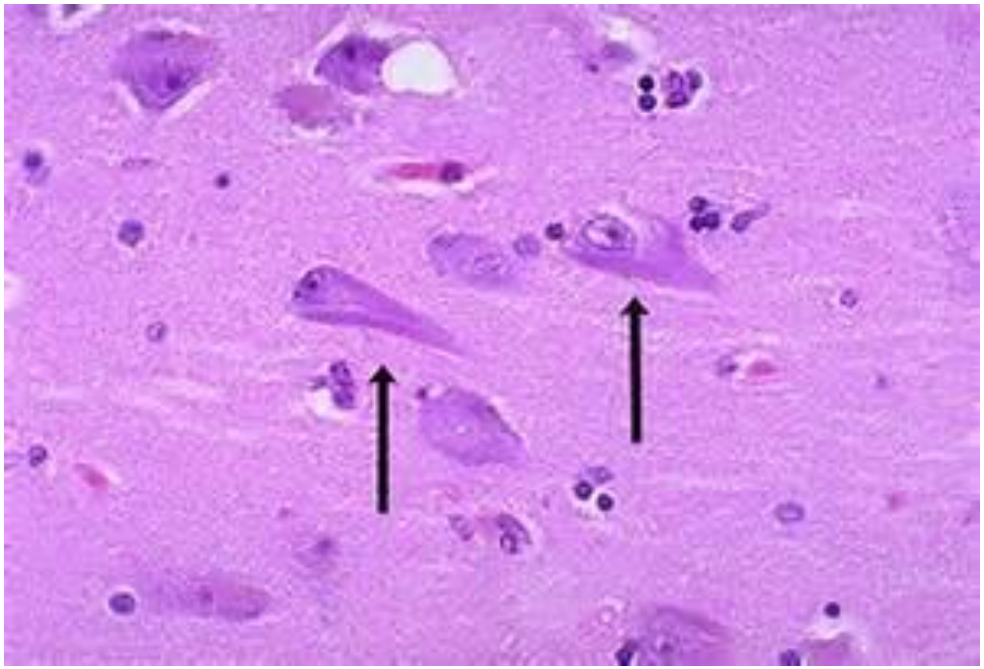


- Two forms of FTLD: sporadic and inherited
- Inherited forms have mutations in Tau protein causing increased accumulation
- Tau accumulation causes toxic damage to the neurones + loss of their normal function…. Both cause neuronal damage

Morphology of FTLD: atrophy of the frontal and temporal lobes

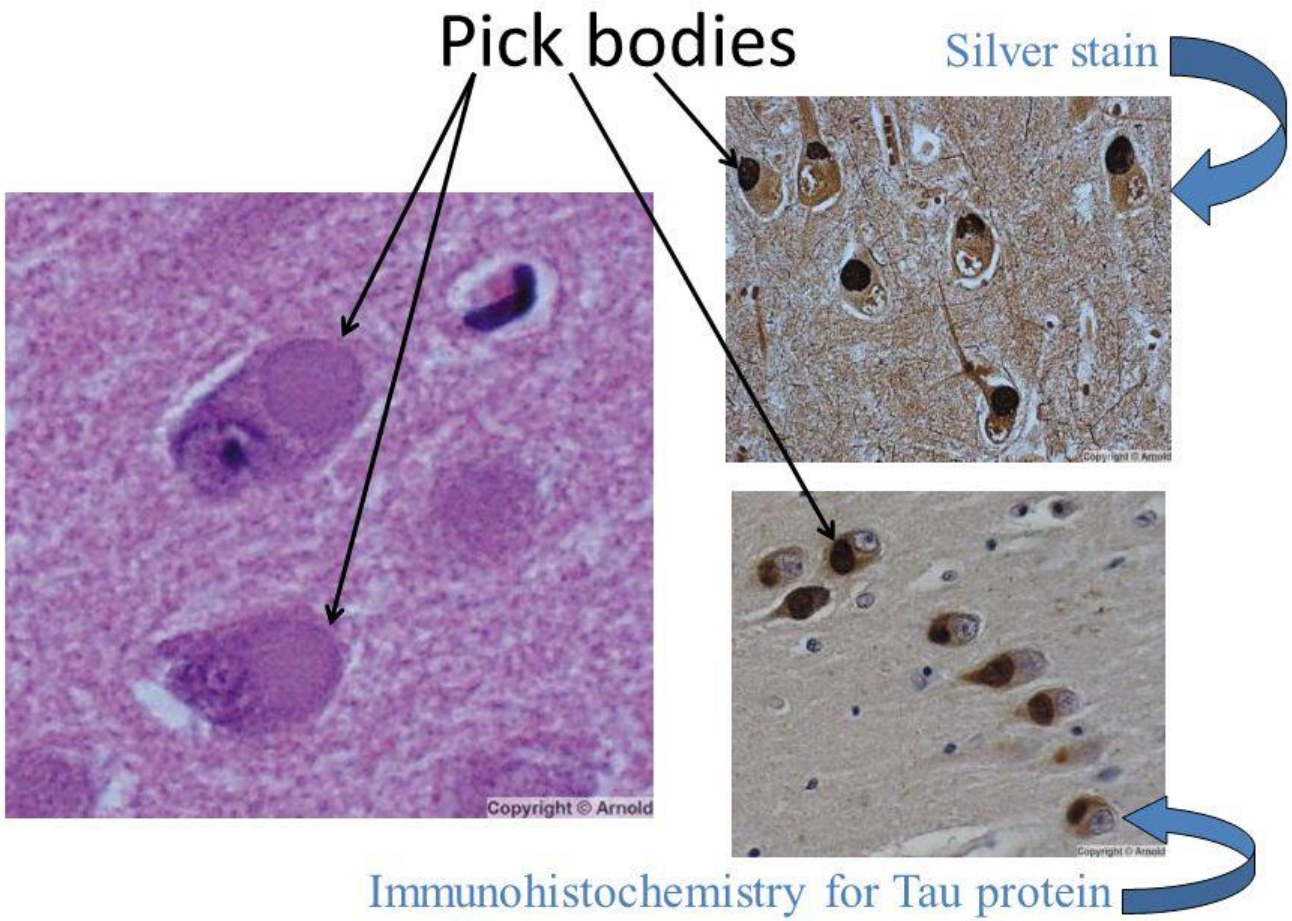


Neurofibrillary tangles: Tau in FTLD

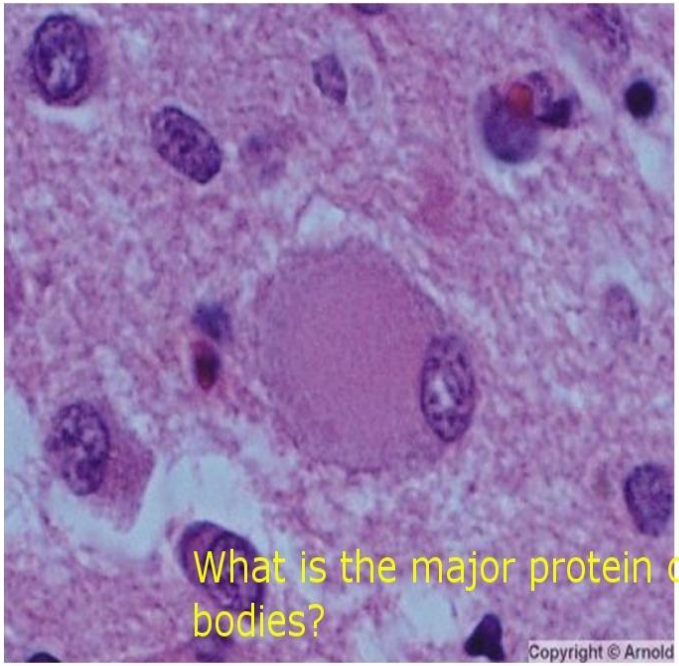


Pick disease

- it is a subtype of FTLD
- Characterised by the presence of Pick inclusions, which are **intracellular Tau** but instead of forming neurofibrillary tangles (the triangular shaped inclusions) , it forms **rounded, well circumscribed inclusions**, which are also intracellular.


Pick bodies
Silver stain
Copyright © Arnold
Immunohistochemistry for Tau protein

Pick bodies


What is the major protein component of Pick bodies?
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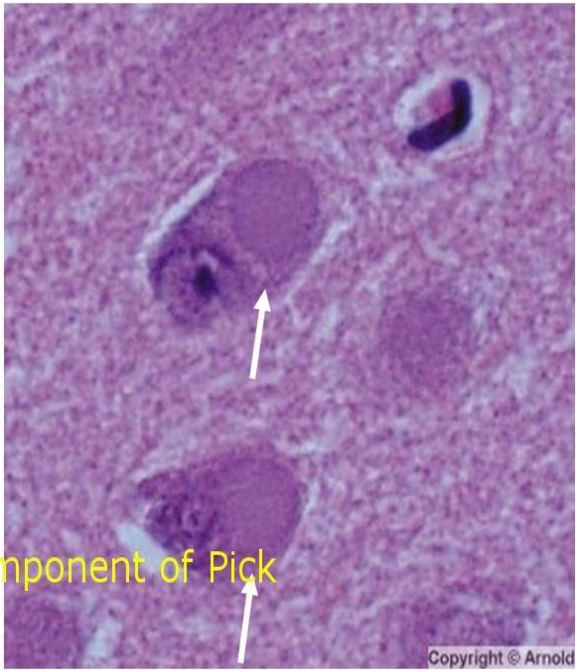
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Summary 1/3

- Neurodegenerative diseases are a group of disorders having in common: deterioration of neurological function is gradual and caused by accumulation of certain proteins in certain parts of the brain.
- each disease in this group is characterised by accumulation of a different protein.
- Proteins accumulate in *functionally* related areas.
- There are four types of neurodegenerative diseases: dementia; caused by accumulated proteins in the cortex, ataxia caused by cerebellar accumulation, muscle weakness if the accumulation is in the motor neurones, and movement disorders f the problem is in the basal nuclei.
- Protein aggregates, whatever their type, cause neurological deficit by: toxic damage to neurones, and by loss of their normal function.

Summary 2/3

- Alzheimer (AD) is the most common cause of dementia.
- AD is characterised by cognitive impairment followed by disability, immobility and death; mainly due to pneumonia.
- AD is caused by accumulation of AB amyloid which is formed from APP cleavage by Beta secrtase.
- As an effect of AB aggregation, Tau protein is hyperphosphorylated and it also accumulates causing more damage.
- AB amyloid accumulates as extracellular amyloid plaques, Tau accumulates as intracellular neurofibrillary tangles.
- Genetic factors that play a role in AD are: ApoE (certain polymorphisms increase risk) , secretase ,and trisomy 21 (APP encoded on chromosome 21).

Summary 3/3

- FTLD is a neurodegenerative disease where the primary abnormality is in the Tau protein.
- Abnormal Tau aggregates as intracytoplasmic neurofibrillary tangles or as Pick bodies which are also intracytoplasmic but are rounded.
- If Pick bodies are prominent the disease is called Pick disease, which is a subtype of FTLD.
- In FTLD patients have personality and memory problems followed by memory loss, which is the reverse of what happens in Alzheimer.


Thank
you!