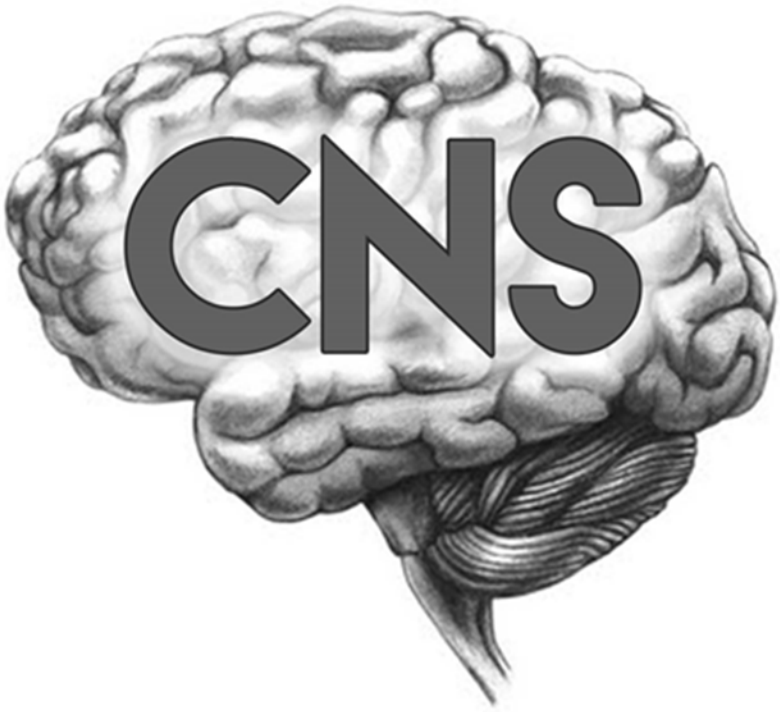


PATHOLOGY

○ Sheet ☑ Slide ○ Handout

Number

6

Subject

Neurodegenerative disorders / part 1

Doctor

Heyam Awad

Date: **00/00/2016**

Price:

CNS pathology
Third year medical students

Dr Heyam Awad

FRCPath

2017

LECTURE 6

Neurodegenerative disorders / part 1

Note;

Degeneration means decline or deterioration.
إرْتِكاس؛ إنْتِكَاس؛ تَدَهْوُر

ILOS

- 1. lists types of neurodegenerative diseases
- 2. lists causes of dementia
- 3. defines dementia
- 4. understands pathogenesis of Alzheimer disease
- 5. recognizes morphologic changes related to Alzheimer disease

Neurodegenerative diseases

- = Disorders characterized 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 accumulate in certain areas causing certain disease… we don’t know the reason for this bias!

Abnormal protein aggregates in neurodegenerative diseases

- Abnormally aggregated proteins often are directly toxic to neurons.
- ALSO: There is loss of function m as more and more protein is shunted into the aggregates rather than performing normal physiologic functions.

IMPORTANT NOTE

Recently, it has become clear that these protein aggregates are capable of behaving like prions; that is, aggregates derived from one cell are taken up by another, thereby giving rise to more aggregates. 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 but there is no evidence that these diseases are transmissible

Neurodegenerative diseases

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

Neurodegenerative diseases

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

- WE WILL DISCUSS ALL THESE IN THIS AND THE COMING LECTURES>

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.

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.
- Vascular dementia.
- Lewy body dementia.
- Frontotemporal dementia.
- Mixed dementia. Autopsy studies of the brains of people 80 and older who had dementia indicate that many had a combination of Alzheimer's disease, vascular dementia and Lewy body dementia.

Other causes of dementia 1

- **Infections.** Dementia-like symptoms can result from fever or infection
- **Metabolic problems and endocrine abnormalities.** thyroid problems, hypoglycemia), sodium or calcium imbalance, or an impaired ability to absorb vitamin B-12 can develop dementia-like symptoms or other personality changes.
- **Nutritional deficiencies.** dehydration; thiamin (vitamin B-1) deficiency, which is common in people with chronic alcoholism; B-6 and B-12 deficiency can cause dementia-like symptoms.
- **Reactions to medications.**
- **Subdural hematomas.**.

Other causes of dementia 2

- **Poisoning.** Exposure to heavy metals, such as lead, and other poisons, such as pesticides, as well as alcohol abuse or recreational drug use can lead to symptoms of dementia. 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. Ultimately, they may be unable to chew and swallow.
- **Pneumonia.** Difficulty swallowing increases the risk of choking or aspirating food into the lungs, which can block breathing and cause pneumonia.
- **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)

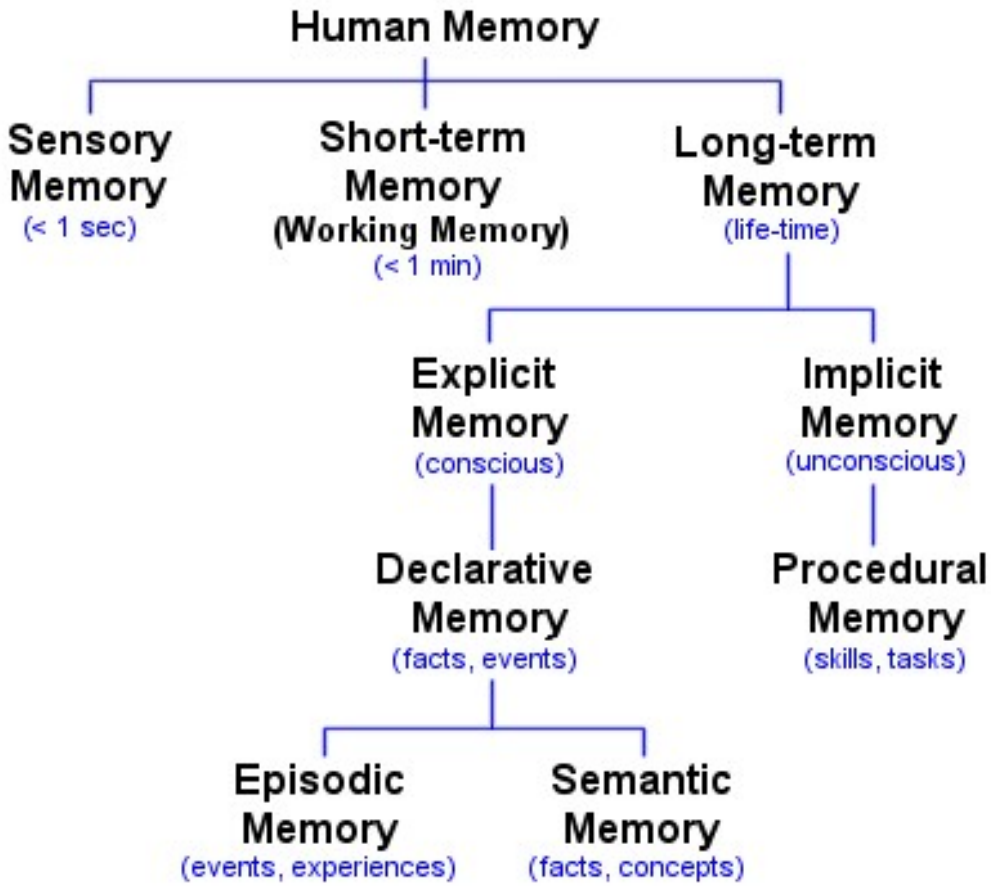
- Most common cause of dementia
- Gradual onset of impaired higher intellectual function + altered mood and behaviour.
- Progresses to disorientation , memory loss, aphasia
- Then.. Over 5-10 years, become disabled, mute and immobile
- Death due to infections, mainly pneumonia

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

NOTE

- SLIDE 17-26 are for your information and interest
- NOT FOE EXAM PURPOSES but please read them, they are interesting and will help you in your clinical years

Memory loss in Alzheimer types of memory



Sensory memory

- **Sensory memory** is the shortest-term element of memory. It is the ability to retain impressions of sensory information after the original stimuli have ended. It acts as a kind of **buffer** for stimuli received through the **five senses** of sight, hearing, smell, taste and touch, which are retained accurately, but very briefly. For example, the ability to look at something and remember what it looked like with just a second of observation is an example of sensory memory.

Short term memory

- **Short-term memory** acts as a kind of **“scratch-pad”** for temporary recall of the information which is being processed at any point in time, and has been refered to as "the brain's Post-it note". It can be thought of as the ability to **remember** and **process information** at the same time. It holds a small amount of information (typically around 7 items or even less) in mind in an active, **readily-available** state for a short period of time (typically from 10 to 15 seconds, or sometimes up to a minute).

Short term memory

- For example, in order to understand this sentence, the beginning of the sentence needs to be held in mind while the rest is read, a task which is carried out by the short-term memory. Other common examples of short-term memory in action are the holding on to a piece of information temporarily in order to complete a task (e.g. “carrying over” a number in a subtraction sum, or remembering a persuasive argument until another person finishes talking), and simultaneous translation (where the interpreter must store information in one language while orally translating it into another). What is actually held in short-term memory, though, is not complete concepts,but rather links or pointers (such as words, for example) which the brain can flesh out from it's other accumulated knowledge.

Long term memory

- **Long-term memory** is, obviously enough, intended for storage of information over a long period of time. Despite our everyday impressions of **forgetting**, it seems likely that long-term memory actually decays very little over time, and can store a seemingly **unlimited** amount of information **almost indefinitely**. Indeed, there is some debate as to whether we actually ever "forget" anything at all, or whether it just becomes increasingly difficult to access or retrieve certain items from memory.

- Long-term memory is often divided into two further main types: **explicit** (or **declarative**) memory and **implicit** (or **procedural**) memory.
- **Declarative memory** (“knowing what”) is memory of facts and events, and refers to those memories that can be **consciously** recalled (or "declared"). It is sometimes called **explicit memory**, since it consists of information that is explicitly stored and retrieved, although it is more properly a subset of explicit memory. Declarative memory can be further sub-divided into episodic memory and semantic memory.
- **Procedural memory** (“knowing how”) is the **unconscious** memory of skills and how to do things, particularly the use of objects or movements of the body, such as tying a shoelace, playing a guitar or riding a bike. These memories are typically acquired through repetition and practice, and are composed of automatic sensorimotor behaviours that are so deeply embedded that we are no longer aware of them. Once learned, these "body memories" allow us to carry out ordinary motor actions more or less automatically. Procedural memory is sometimes referred to as **implicit memory**, because previous experiences aid in the performance of a task without explicit and conscious awareness of these previous experiences, although it is more properly a subset of implicit memory.

- The most commonly recognized **symptom** of Alzheimer is an inability to acquire **new memories** and difficulty in recalling recently observed facts, but it is by no means the only sympto. 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.

- Alzheimer's does not affect all memory capacities equally: short-term memory (the ability of hold information in mind in an active, readily-available state for a short period of time) is the first to go; next comes episodic memory (memory of autobiographical events); then semantic memory (memory of the meanings of words and facts about the world); and finally procedural memory (how to perform tasks and skills). As the disease advances, parts of memory which were previously intact also become impaired, and eventually all reasoning, attention, and language abilities are disrupted.
- Alzheimer patients tend to display a loss of knowledge of the specific characteristics of **semantic categories**. Initially, they lose the ability to distinguish **fine categories**, such as species of animals or types of objects, but, over time, this lack of discrimination extends to broader, more **general categories**. Thus, at first, an AD patient may see a spaniel and say, “that is a dog”; later, they may just say, “that is an animal”.

- END OF SLIDES NOT NEEDED FOR THE EXAM!!!!

pathogenesis

- Alzheimer is caused by accumulation of two proteins: AB amyloid and tau in specific brain regions due to overproduction and decreased removal.
- Both protein aggregates cause neural death and dysfunction.
- The initial event is the AB accumulation.

AB amyloid deposition

-Amyloid precursor protein (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 intramembranous cleavage.

-There are two potential pathways, determined by the type of initial proteolytic enzyme.

- If the first cut occurs at the α-secretase site within the Aβ sequence, then Aβ is not generated (the non-amyloidogenic pathway).

SEE PICS IN COMING SLIDES

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

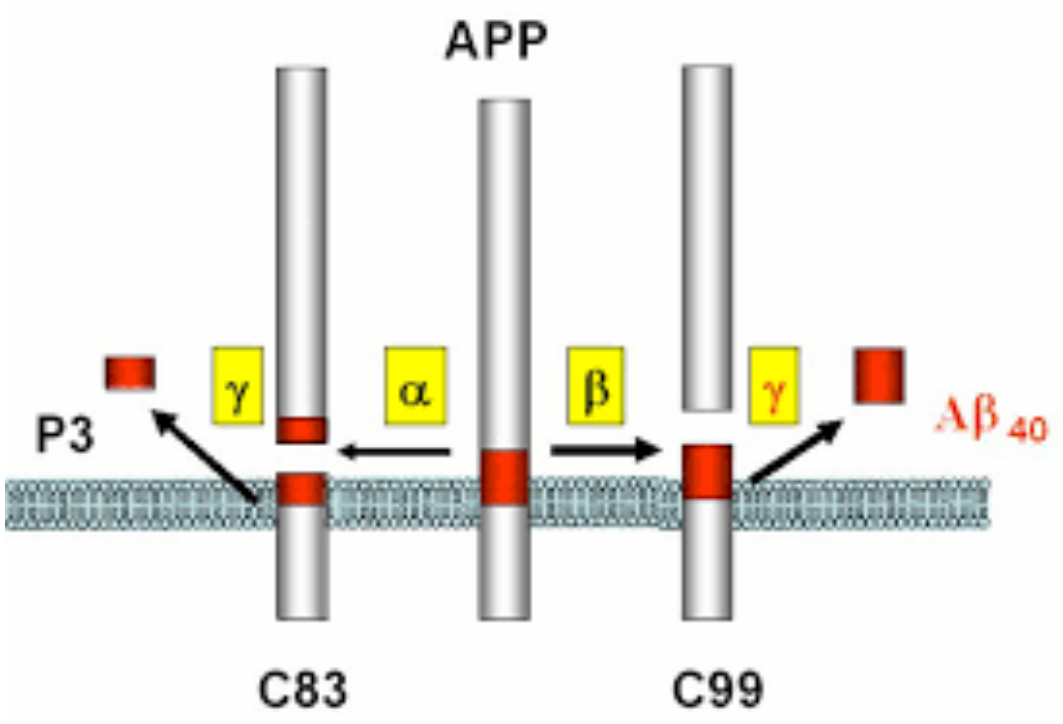
.

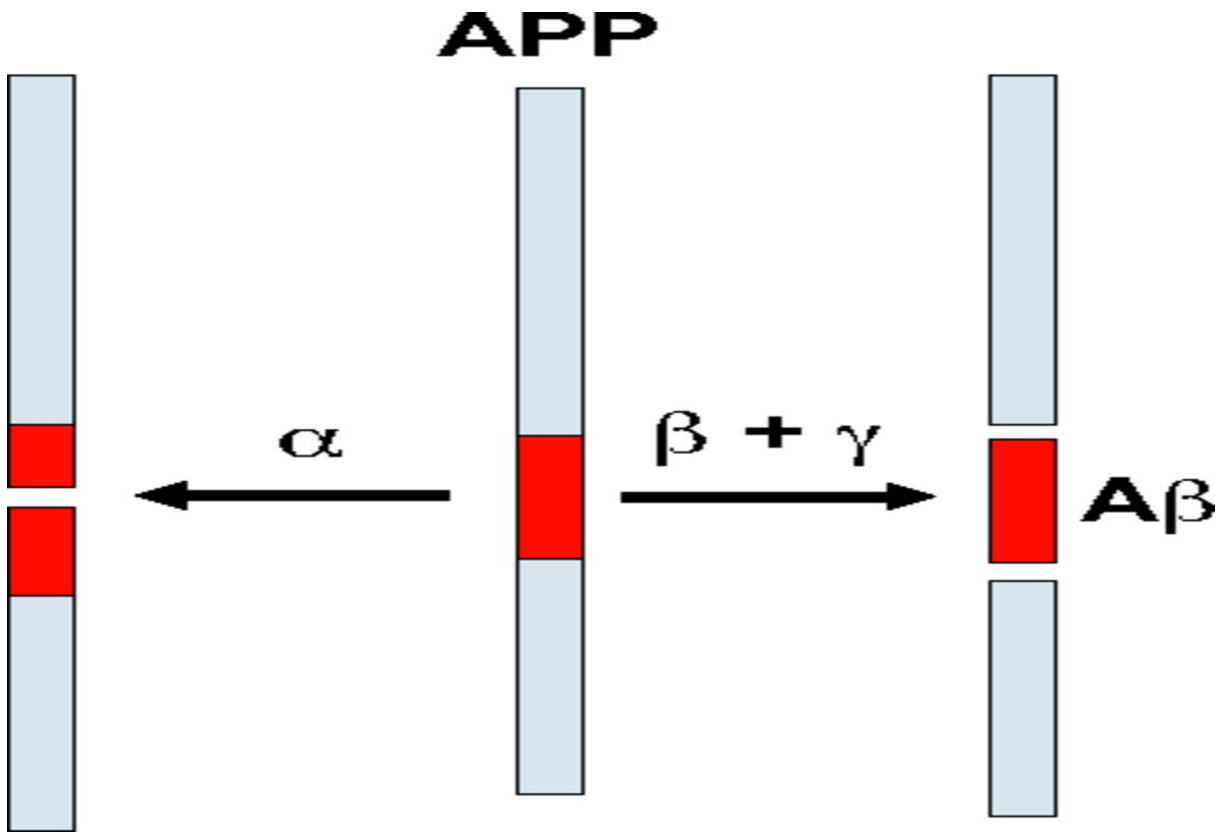
Following cleavage of APP at either of these sites, the γ-secretase complex performs an intramembranous cleavage

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

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.

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 propensity to aggregate.


APP
γ
α
β
γ
P3
Aβ 40
C83
C99


APP
α
β + γ
Aβ

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.

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.

genetic risk factors

The genetic locus on chromosome 19 that encodes apolipoprotein E (ApoE) has a strong influence on the risk of developing AD.

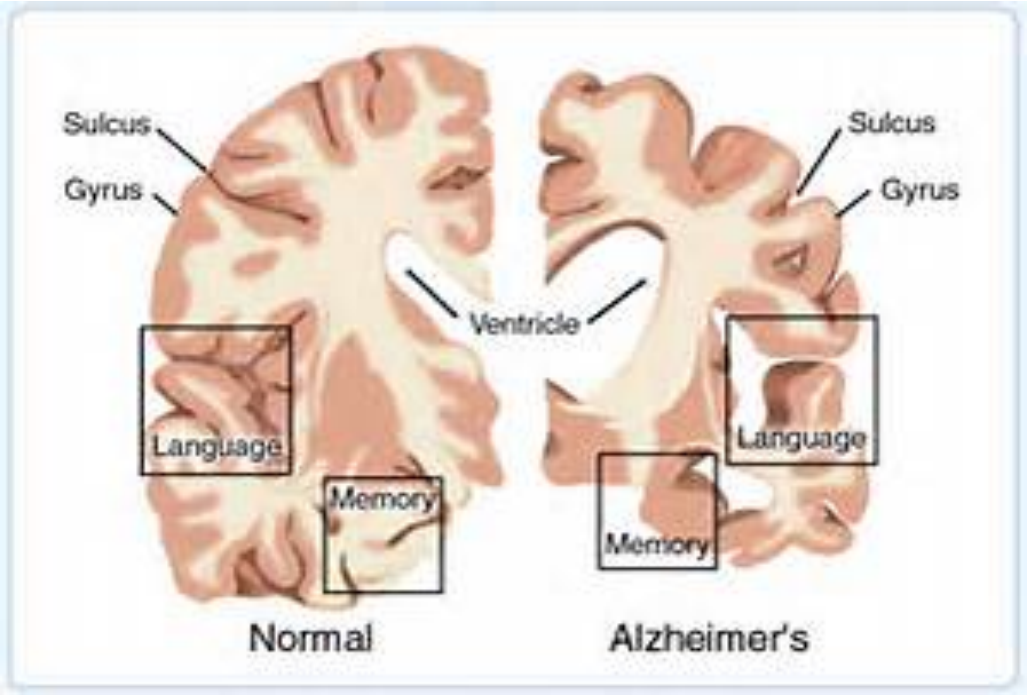
- APP gene present on chromosome 21.
- Trisomy 21 (Down syndrome) have increased risk of Alzheimer
- Other genetic mutations can also cause Alzheimer

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

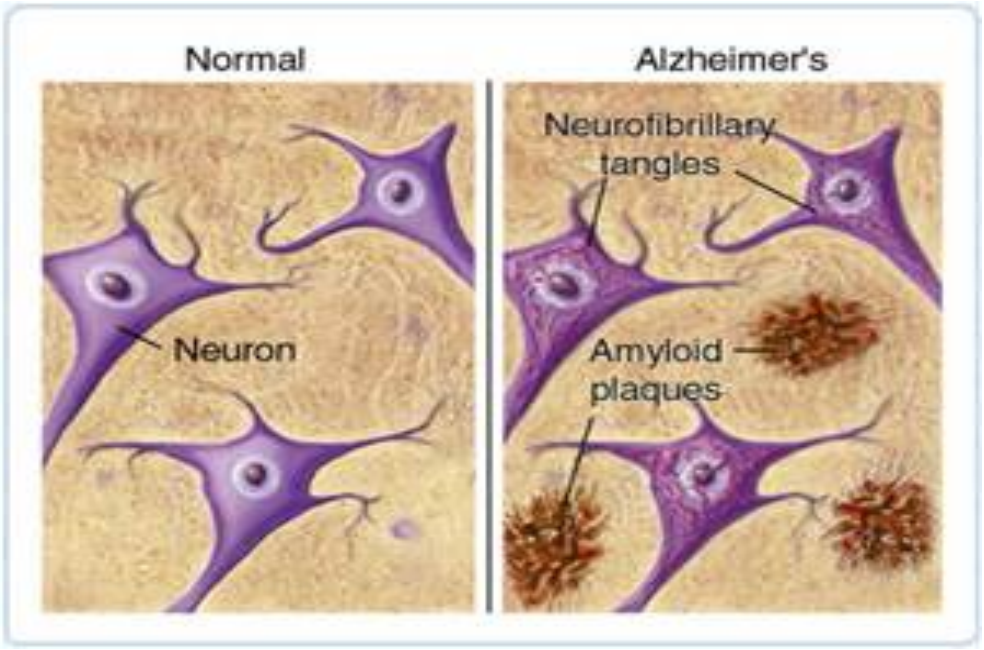
Microscopic changes

- 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.

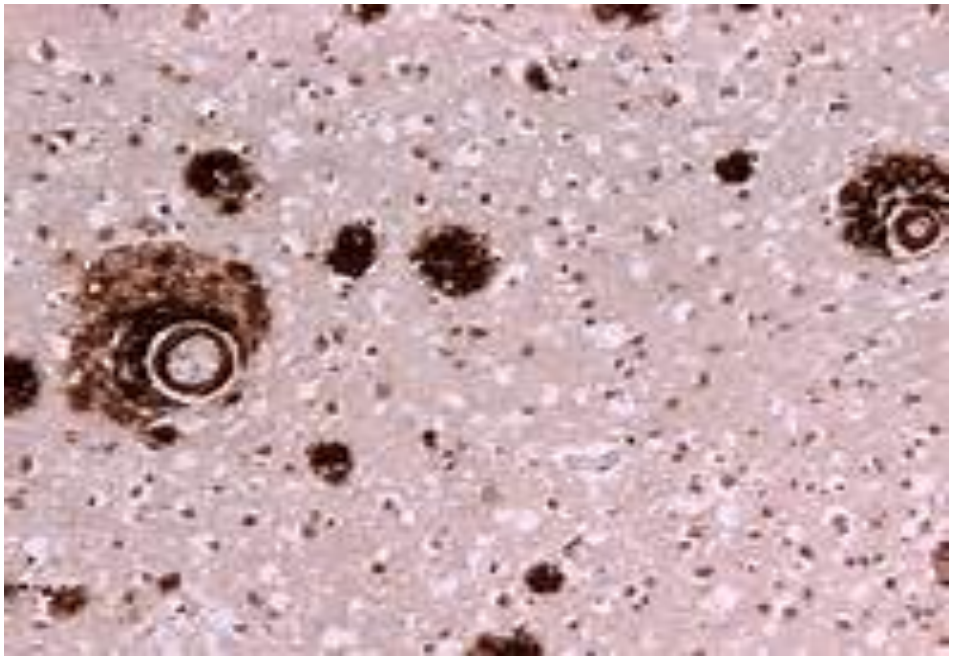
plaques

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

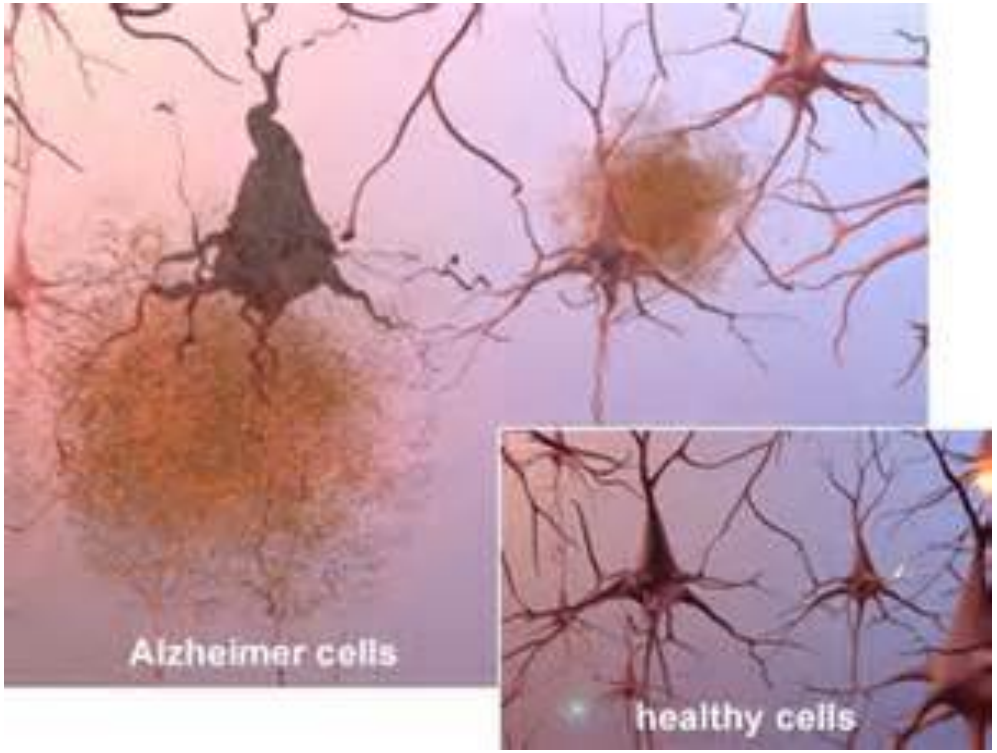
morphology


Normal
Alzheimer's
Neurofibrillary tangles
Neuron
Amyloid plaques

amyloid



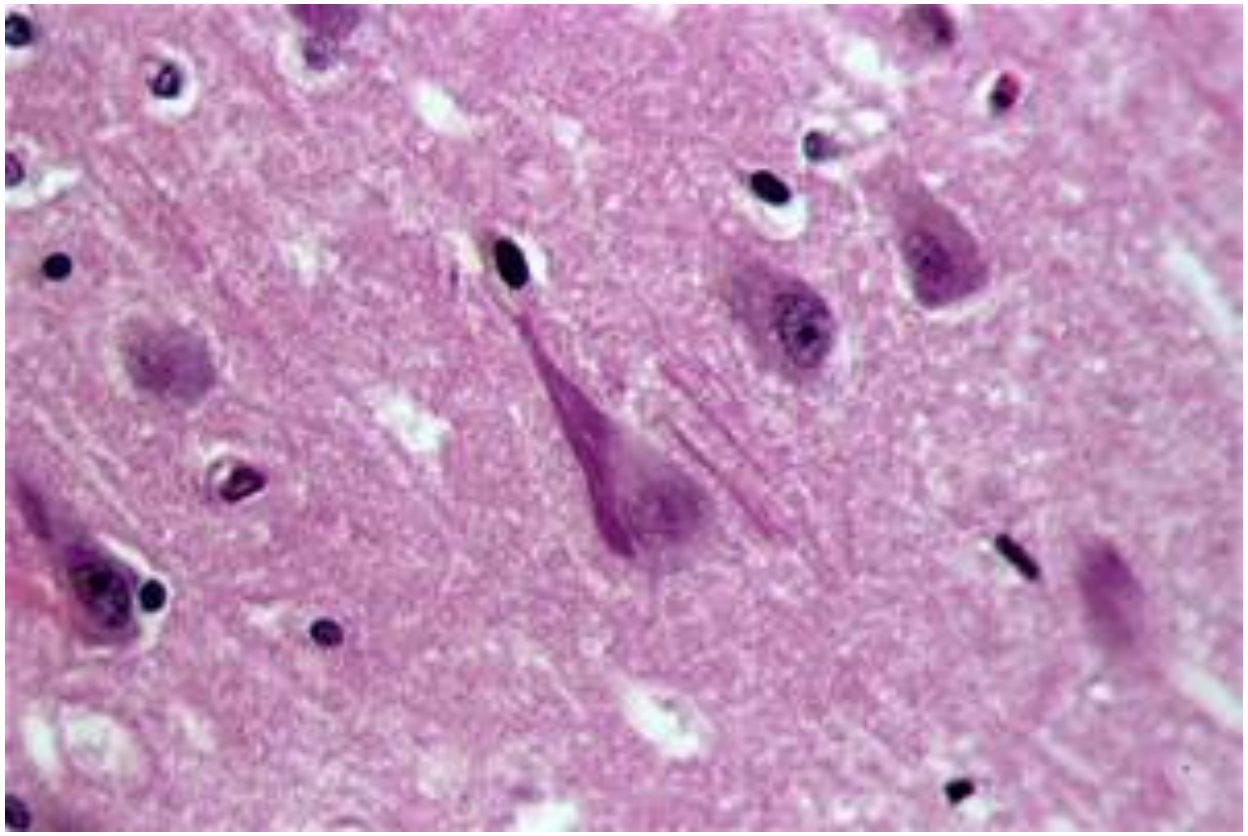
amyloid



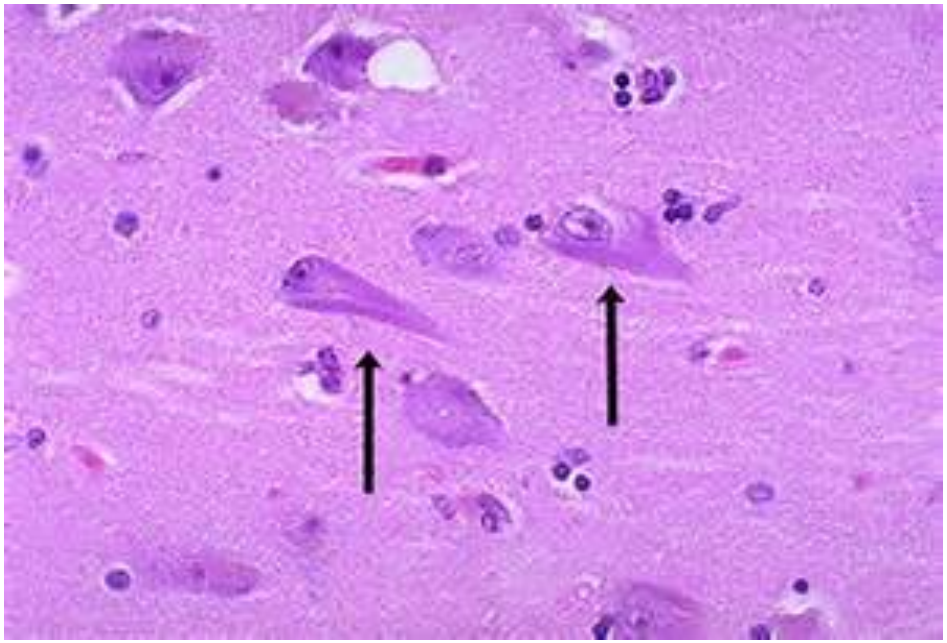
Neurofibrillary tangles

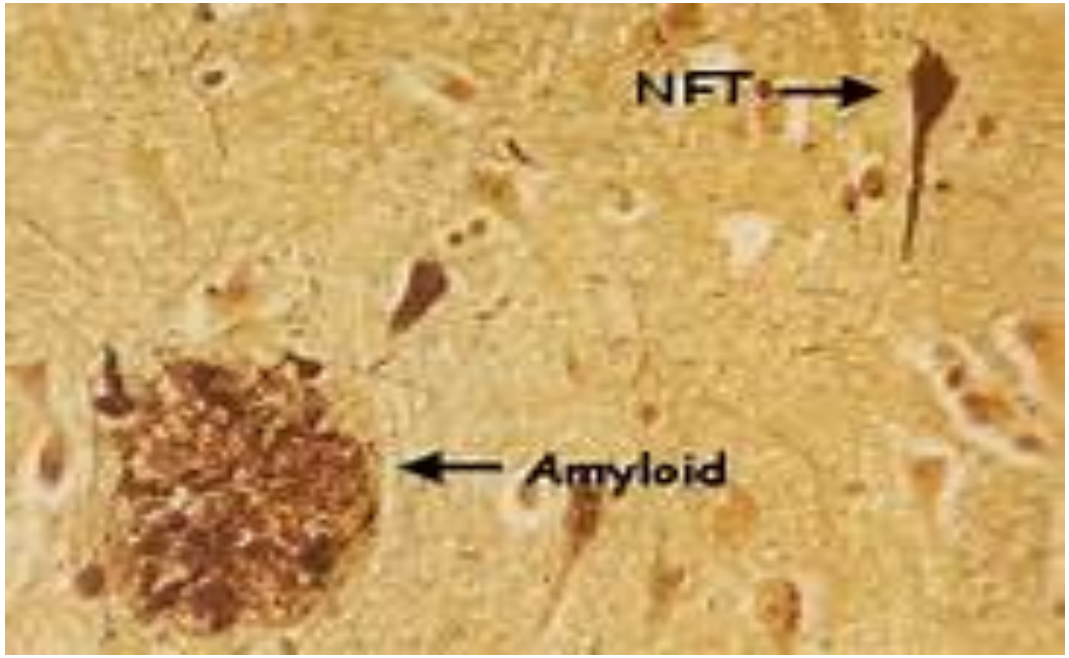
- Bundles of helical filaments seen as basophilic fibrillary structures in the cytoplasm of neurones
- Major component: hyper phosphorylated tau
- Tangles are seen in other degenerative diseases

Neurofibrillary tangles



Neurofibrillary tangles




NFT
Amyloid


Thank
you!