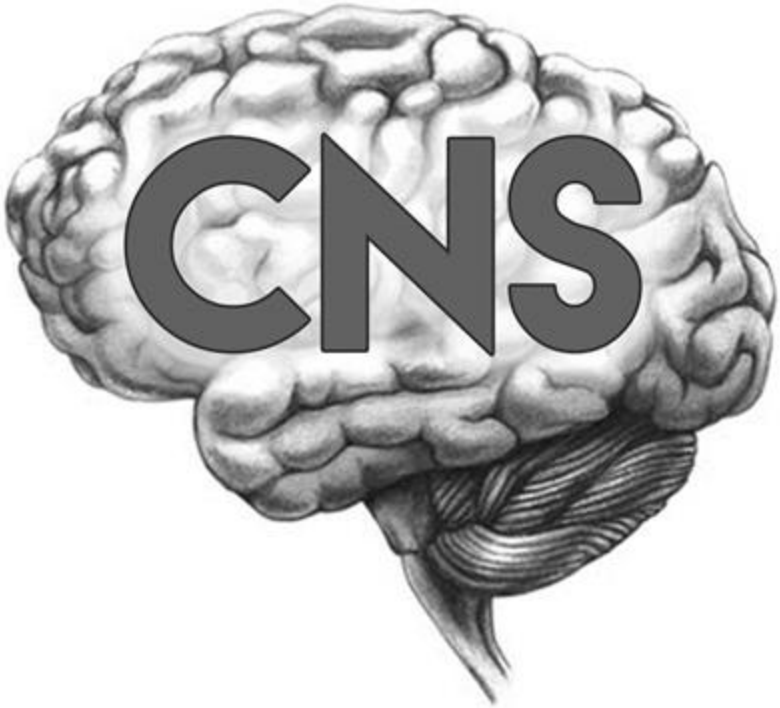


PATHOLOGY

☑ Sheet ○ Slide ○ Handout

Number

6

Subject

Neurodegenerative Diseases

Done By

Deena Younis

Corrected by

Wahib Zehlawi

Doctor

Heyam Awad

Date: 00/00/2016

Price:

In the name of of Allah the Merciful

- This lecture mainly talks about things that you are probably familiar with, so hopefully you'll enjoy these upcoming topics. ☺.
- It is written according to the record of sec.2 and revised according to sec.3. This sheet also includes the beginning of the following lecture.
- All the information in the slides are included so you don't have to go through them.
- SLIDE 17-26 are for your information and interest, they talk about types of memories, if you have time, it's certainly beneficial for you to see them ☺.

Neurodegenerative diseases

- From the word "degenerative" (تدهور، ارتكاس، انتكاس)
- We can say that they are a group of heterogeneous and gradually happening diseases (they're diseases of old age).
- That leads us to the fact that these disease are increasing with time as the population's ages are increasing.
- These diseases cause degeneration of functionally related neurons, i.e., it can happen in the cerebral cortex (e.g., dementia), basal ganglia (e.g., Parkinsonism), or it might affect the cerebellum, causing ataxia. And so on.
- So the signs and symptoms of the patient depend on which site of the brain is affected.

<u>Pathogenesis</u>:

- Most of These diseases are thought to be caused by an accumulation of abnormal proteins, that are <u>toxic</u> and non-functional, other than the fact that the accumulated proteins <u>affect the normal function</u> of the cell as more and more they are shunted into the aggregates rather than performing normal physiologic functions.
- These proteins are normally present in the brain, so the cause of this accumulation is unknown!

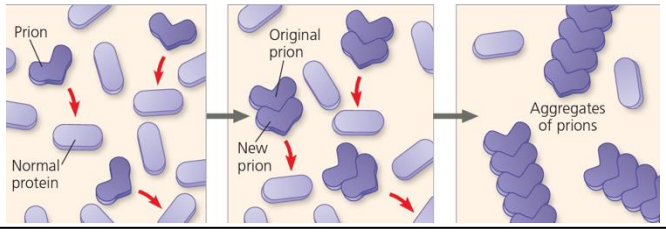
So the abnormally aggregated proteins:

1. Often are directly toxic to the neurons
2. Cause loss of normal function

- Every disease of these neurodegenerative diseases has a certain protein that accumulates. We will discuss them thoroughly.
- Usually these proteins, when they're normal, they're of the Alpha Helix type. And there are enzymes that contribute to their turnover so that they do not accumulate. However, when these proteins become abnormal they switch to the Beta Pleated Sheets type. So the enzymes will not be able to act on them and the proteins will accumulate.

- Recently, it has become clear that these protein aggregates are capable of behaving like **prions**.

  - If you recall from the microbiology course, we talked about a group of diseases, like mad cow disease, and Creutzfeldt–Jakob disease, and others, that were caused by something we call **prions**.
  - A prion is an infectious agent composed entirely of protein material, which is transmissible to other prion proteins, leading to disease that is similar to viral infection.
  - Meaning that prions (PrP^{sc}) can infect other normal prion proteins (PrP^{c}) as well as get transmitted to other people and infect them.



- So as we said, protein aggregates can act as prions; that is, aggregates derived from one cell are taken up by another, thereby giving rise to more aggregates. (i.e., if one misfolded protein is accumulated inside a certain cell, it can be taken up by its surrounding cells, and interfere with the proteins in them, "like its infecting them" causing more and more aggregates of that protein).
- 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.
- <u>But unlike prions, there's no evidence that these diseases are transmissible to other people</u>.

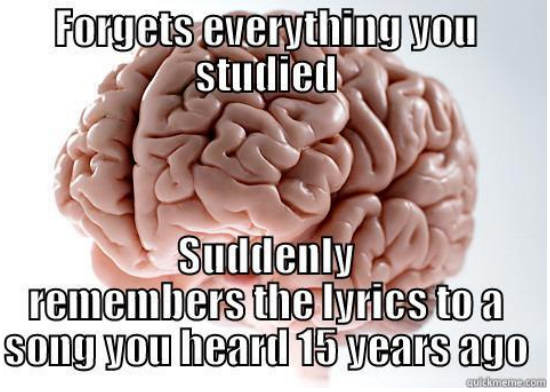
- As mentioned, clinical picture is dictated by the pattern of neuron dysfunctional;
  1. If neurons of the cerebral cortex are affected that will lead to loss of memory, language, insight, and planning. (All of these are components of dementia).
  2. If neurons of basal ganglia are affected this results in movement disorder.
  3. If cerebral neurons are the one affected, this causes ataxia.
  4. And if motor neurons got affected, we will end up with muscle weakness.

Let's start with ***dementia***:

- It's the 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 is a disease of old age.
- Dementia symptoms:

Cognitive Changes	Psychological Changes
Memory loss, which is usually noticed by a spouse or someone else	Personality changes
Difficulty communicating or finding words	Depression
Difficulty reasoning or problem-solving	Anxiety
Difficulty handling complex tasks	Inappropriate behavior
Difficulty with planning and organizing	Paranoia
Difficulty with coordination and motor functions	Agitation
Confusion and disorientation	Hallucinations

- Many of us have some of these symptoms mentioned above. But to diagnose someone with dementia these symptoms most affect their daily life.
- To diagnose a person with dementia, you have to compare the patient with himself before, the way he used to be, which obviously is difficult, as there are no specific criteria for diagnosis.



Causes of dementia:

- Causes of 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 than the disease itself, we have dementia-like (reversible) symptoms that are caused by:
  - fever
  - Infections
  - 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.
  - anoxia
  - 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.

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.

Note: infection is a common cause of death for dementia, regardless of the cause

---

Now, let's talk about ***Alzheimer's disease*** *(AD)*

- It's the most common cause of dementia, characterized by a gradual onset of impaired higher intellectual function, plus altered mood and behavior.
- It progresses to disorientation, memory loss ,aphasia, then, over 5-10 years, the patient becomes disabled, mute and immobile. ☹
- Death due to infections, mainly pneumonia
- Age is the most important risk factor; usually at age 65 and above, in the sporadic cases. However, in the familial cases (5-10%), the disease comes at an earlier age (below the age of 50).

<u>Pathogenesis</u>:

- There are two types of proteins we are concerned about here:

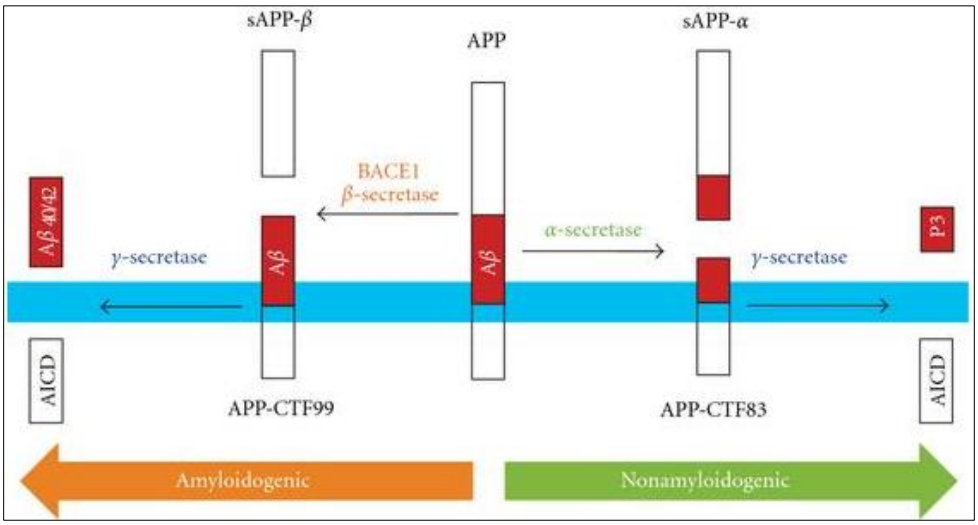
  The **Aβ amyloid**, and the **tau** protein.

- Both are normally present in our brains, however, the overproduction and decreased removal of these proteins will cause them to aggregate, causing neural death and dysfunction. Mark that the Aβ amyloid is made of alpha helices in the normal state, but it is beta-pleated sheets in the abnormal state.

<u>Important</u>: The ***initial*** event in AD is the Aβ accumulation, and that in turn will cause a problem in tau as we will see later on. However, in frontotemporal dementia, tau is the **<u>only</u>** protein responsible, and the amyloid is normal.

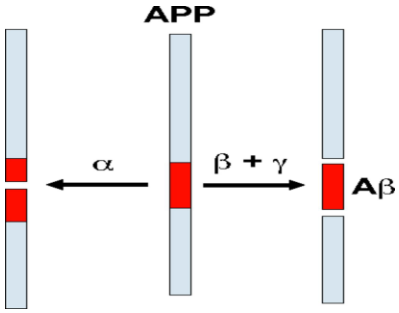
❖ How does the Aβ amyloid deposition occur?

- We start with the Amyloid Precursor Protein (APP). It 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.
- Now we have 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).**
  - If APP endocytosed and cleaved by β-secretase, which cuts at the N-terminal region of the Aβ sequence then Aβ 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 generates Aβ.
- 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.



In summary, we can say that the amyloidic protein occurs when the APP is cleaved by beta and gamma secretase enzymes.

And now to the **tau** protein:

- **Tau** is a microtubule-associated protein, (stabilizer of microtubules) present in axons in association with the microtubular network. In AD, **tau** becomes hyperphosphorylated, and loses the ability to bind to microtubules.
- We can say that what really is the problem here is that the aggregation of beta amyloid alters **neurotransmission** and is toxic to neurons and synapses, plus, large deposits cause neuronal damage and death, cause inflammatory response, and instability of microtubules due to tau inefficiency.
- We said previously that Aβ amyloid in **Alzheimer's** is the initial event to happen. Well yes, that's how **tau** and **Aβ amyloid** are connected; the Aβ amyloid causes hyperphosphorylation of tau protein.
- Speaking of inflammation:

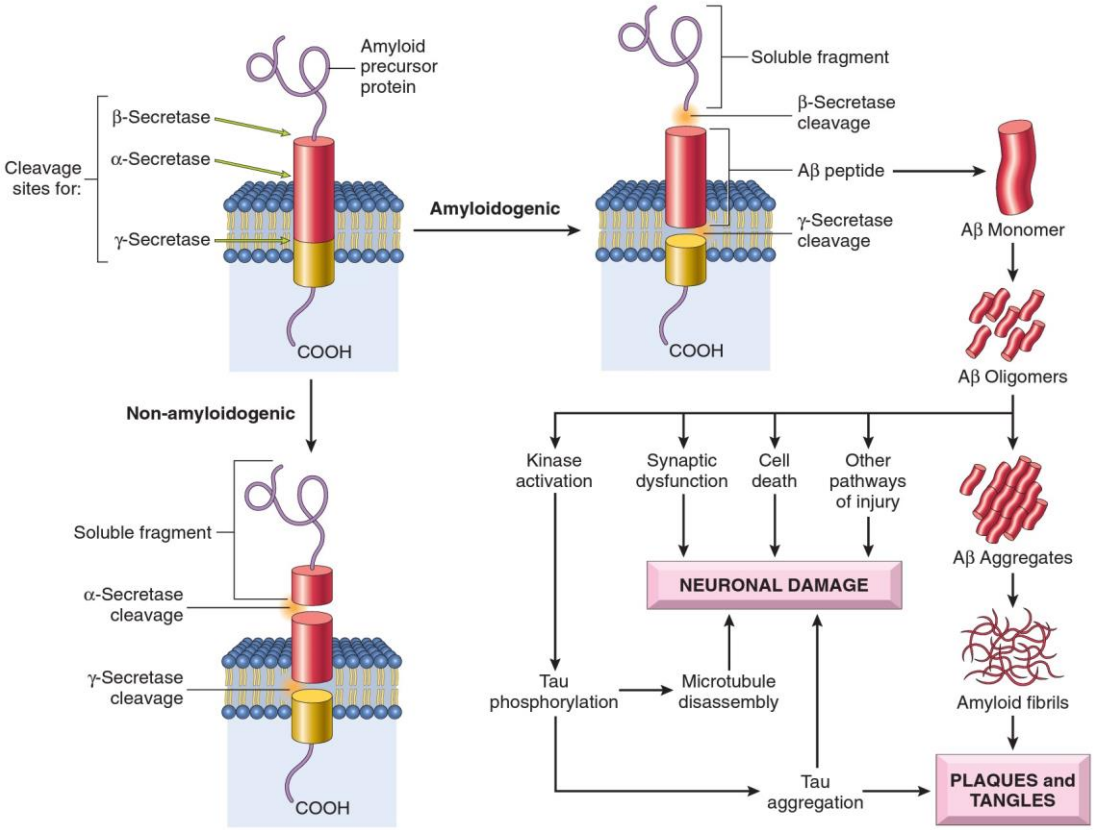
  Both small aggregates and larger deposits of Aβ elicit an inflammatory response from microglia and astrocytes. This response probably assists in the clearance of the aggregated peptides, but may also stimulate the secretion of mediators that cause damage

  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 of AD:
  1. The genetic locus on chromosome 19 that encodes apolipoprotein E (ApoE) has a strong influence on the risk of developing AD.
  2. Since APP gene is present on chromosome 21, trisomy 21 (Down syndrome) have increased risk of Alzheimer.

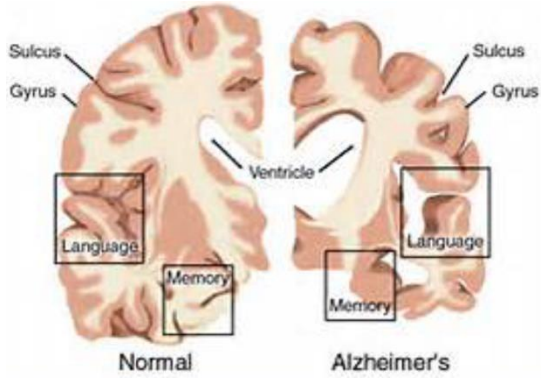
3. Other genetic mutations can also cause Alzheimer like what we said earlier, mutations occurring in APP or secretases.

❖ The following picture, from Robbins, sums up the pathogenies of Alzheimer.



Morphology:

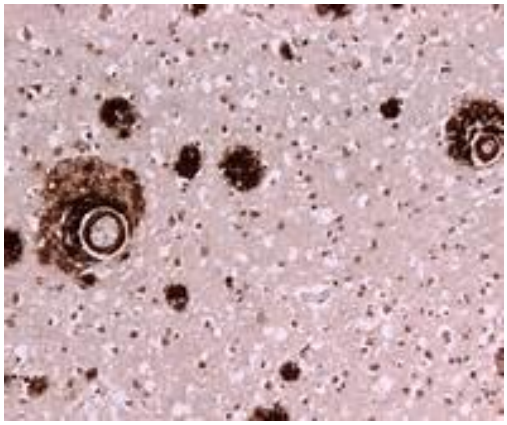
❖ Macroscopically:
- variable degree of cortical atrophy.
- widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes.
- With significant atrophy, there is compensatory ventricular enlargement.

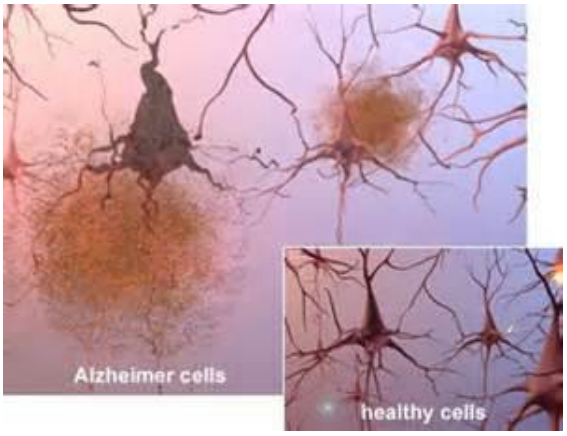


❖ Microscopically:
- We see Aβ amyloid, in the form of **amyloid plaques** (extracellularly). And tau proteins in the form of **neurofibrillary tangles** (intracellularly).

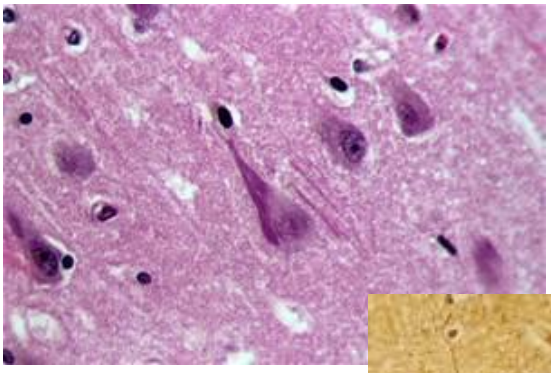
Note: Because these may also be present to a lesser extent in the brains of elderly nondemented persons, so diagnosis needs both clinical and histological findings.

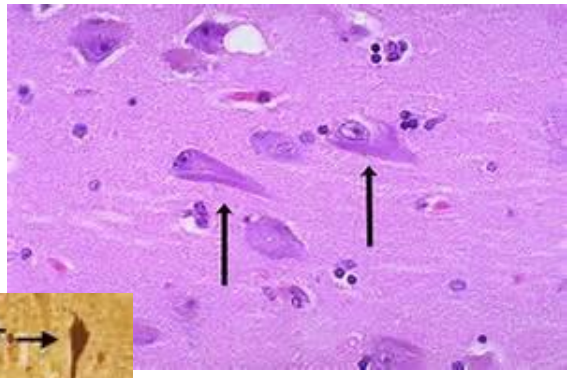
- Plaques are of two types: diffuse or focal.
  - **Focal** (neuritic plaques) are spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites), often around a central amyloid core. And microglial cells and reactive astrocytes are present at their periphery.
  - **Diffuse** plaques lack the surrounding neuritic reaction (only amyloid).
- Amyloid plaques:

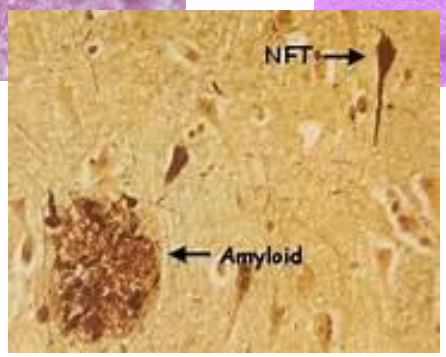




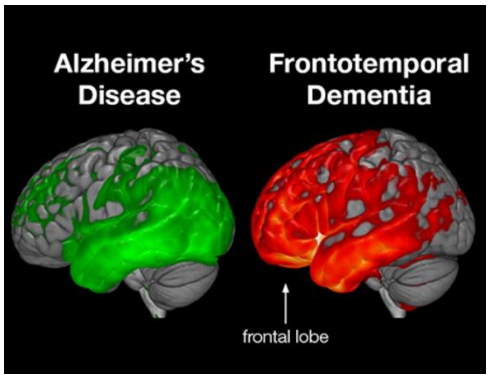
- Neurofibrillary tangles are bundles of helical filaments seen as basophilic fibrillary structures in the cytoplasm of neurons.
  - A major component of paired helical filaments is abnormally hyperphosphorylated tau.
  - Tangles are seen in other degenerative diseases
- Neurofibrillary tangles:







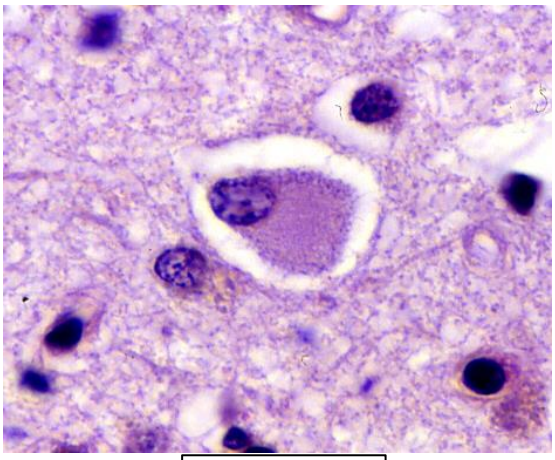
Frontotemporal dementia



- It's another major category of disease that results in dementia. It can be sporadic or familial.
- As the name implies, it first affects the frontal and the temporal lobes (whereas the first part affected in Alzheimer is the limbic system).
- When the frontal lobe bears the greatest burden of disease, behavioral changes often dominate, whereas when the disease begins in the temporal lobe, language problems often are the presenting complaint.
- These symptoms precede memory disturbances, which can assist in their separation from AD on clinical grounds, since in Alzheimer the memory disturbances come first.
- Another important difference is that in frontotemporal dementia, the **tau** is the **only** problem not amyloid, as tau is hyperphosphorylated but the amyloid is normal.

Morphology:

- As we said previously, tau protein accumulates intracellularly. But this accumulation happens in two forms:
  1. It's the same form we discussed in Alzheimer; neurofibrillary tangles.
  2. Accumulates as Pick bodies (smooth and rounded).
- So the tangles and pick bodies are tau accumulations inside the cells
- If pick bodies increase a lot in number, we call that "Pick disease", which is a subtype of the frontotemporal degenerations. So if you have a patient with frontotemporal degeneration and the main finding is smooth rounded inclusion or "pick bodies", this is Pick disease.



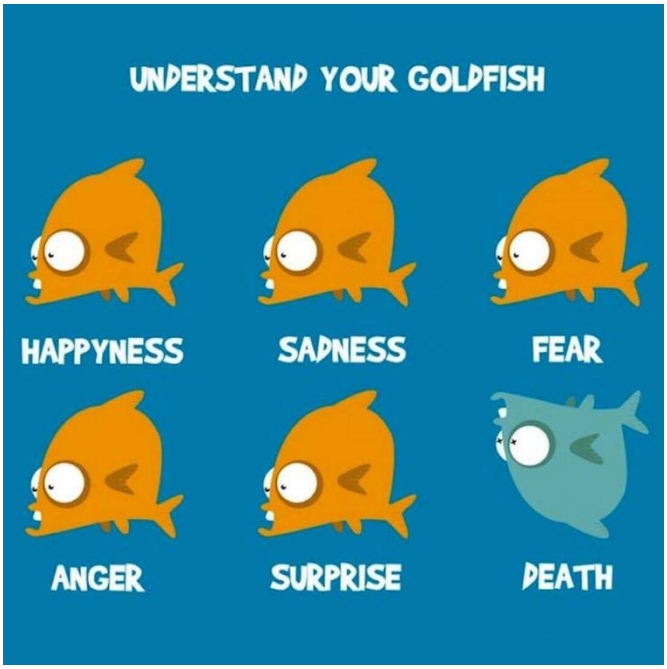
Pick bodies

- There are other causes of dementia which are not neurodegenerative in origin, but are related to **tau** protein;
    - If someone had repetitive mild traumas to the head (like in contact sports), they might cause symptoms similar to dementia with time, making it a subtype of it. It's caused by a **tau** abnormality and accumulation, this subtype is now called chronic traumatic encephalopathy. And its mechanism is not known.

    - Vascular dementia (multi-infarct dementia), as several minor strokes can lead to dementia. So if you have a patient with dementia symptoms, you should think of all of the differential causes.

And by that we have finished the neurodegenerative disorders related to dementia.

The upcoming neurodegenerative disorders are related to the motor tracts.



Sorry for any mistakes, And wish you all best of luck. <3 <3