PATHOLOGY

SHEET NO. 5

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Lecture outline

Introduction

- Classic features of neurodegenerative diseases
- Causes of protein accumulation
- Neurodegenerative diseases classification
- Common features of neurodegenerative diseases

Dementia

- Definition
- symptoms
- complications

Alzheimer disease (AD)

- General overview
- pathogenesis (general pathway of the disease, role of αβ, tau & inflammation, Basis for cognitive impairment)
- Morphology

Frontotemporal Lobar Degeneration (FTLD)

- General overview
- The Difference between AD & FTLD
- Morphology

INTRODUCTION

CLASSIC FEATURES OF NEURODEGENERATIVE DISEASES

- ✓ Progressive (تدريجي) slowly loss of neurons.
- ✓ Typically affects groups of neurons with functional interconnections.
- ✓ Different diseases involve different neural systems, so different symptoms.
- ✓ The histologic hallmark for ALL diseases is the **accumulation of protein aggregates.**
- ✓ Same protein may aggregate in different diseases, but at different distribution.
- ✓ Proteins resist degradation, accumulate within the cells, elicit inflammatory response, and are toxic to neurons, so neurons will die while proteins will stay and spread from one cell to another.

CAUSES OF PROTEIN ACCUMULATION

- ✓ Mutations that alter **protein conformation** as the protein is misfolded and resistant to cleavage.
- ✓ Mutations disrupting the processing and **clearance of proteins**.

- ✓ Subtle **imbalance** between protein synthesis and clearance (genetic or environmental factors)

NEURODEGENERATIVE DISEASES CLASSIFICATION

- ✓ **Involving the cortex:** causes dementia which is a collection of cognitive abnormalities (**memory**, **behaviour** and **language**).
  -**Examples:** Alzheimer disease (AD) / frontotemporal dementia (FTD)/ pick disease (subtype of FTD).
  (This lecture will be about diseases involving cortex only, rest of the diseases will be discussed in the next lecture)
- ✓ **Involving the basal ganglia:** causes movement disorders.
  -Examples:
  - **Parkinson disease:** causes hypokinesia بطء في الحركة
  - **Huntington disease:** causes hyperkinesia زيادة في الحركة
- ✓ **Involving the cerebellum:** causes ataxia (اختلاج في الحركة) because cerebellum is the coordinator of balance (e.g. spinocerebellar ataxia).
- ✓ **Involving the motor system:** causes difficulty swallowing and respiration with muscle weakness (e.g. amyotrophic lateral sclerosis).

COMMON FEATURES OF NEURODEGENERATIVE DISEASES

- ✓ Protein aggregates can seed the development of more aggregates.
- ✓ Protein aggregates can spread from one neuron to another in Prion-like pattern.
- ✓ No evidence of person-to-person transmission.
- ✓ Activation of the innate immune system is a common feature of neurodegenerative diseases.

DEMENTIA

DEFINITION

- ✓ Development of memory impairment and other cognitive (إدراكي) 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, if not: it's called "mild cognitive impairment" (Normal manifestation that affect elderly people and causes subtle decline in cognitive function like a slowed reaction time).

SYMPTOMS

→ Cognitive or Psychological changes

✓ **Cognitive changes, includes:**

- Memory loss, which is usually noticed by someone else.
- Difficulty communicating or finding words.
- Difficulty reasoning or problem-solving (solving math problem for example).
- Difficulty handling complex tasks (Many tasks at the same time).
- Difficulty with planning and organizing.
- Difficulty with coordination and motor functions later (can't wear his boots).
- Confusion and disorientation.

✓ **Psychological changes, includes:**

- Personality changes.
- Depression.
- Anxiety.
- Inappropriate behaviour. يبكي من موقف مضحك أو يغضب من موقف اعتيادي
- Paranoia. جنون العظمة
- Agitation.
- Hallucinations. يتخيل أشياء مش موجودة

COMPLICATIONS

✓ **Inadequate nutrition:** Many people with dementia eventually reduce or stop their intake of nutrients (sometimes they stop eating because of swallowing difficulty, and sometimes they simply forget to eat or drink water).

✓ **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 in lungs by aspiration of food as we mentioned.

ALZHEIMER DISEASE (AD)

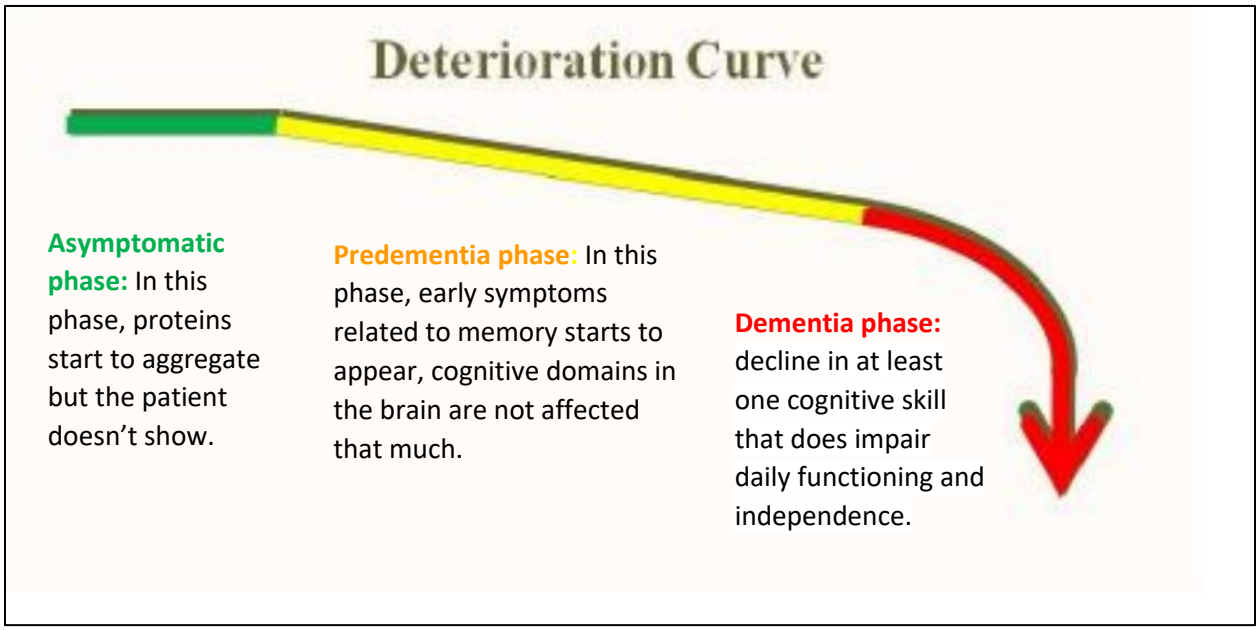
GENERAL OVERVIEW

- ✓ Most common cause of dementia in older adults.
- ✓ Increase incidence with age (47% in those over 84 years).
- ✓ Most cases are sporadic.
- ✓ 5-10% are familial (onset before 50).
- ✓ Gradual onset.
- ✓ Impaired higher intellectual functions as recognition is weak, memory impairment and altered mood and behaviour.
- ✓ Severe cortical dysfunction occurs late in this disease (disorientation ارتباك and aphasia فقدان القدرة على الكلام, profound disability إعاقة شديدة, mute and immobile)
- ✓ Death usually due to infections (pneumonia)

PATHOGENESIS

- ✓ **General pathway of the disease**

  - Remember that this disease occurs because of protein aggregation----> which causes more protein aggregation-----> so the disease manifestations become faster as the disease progress.

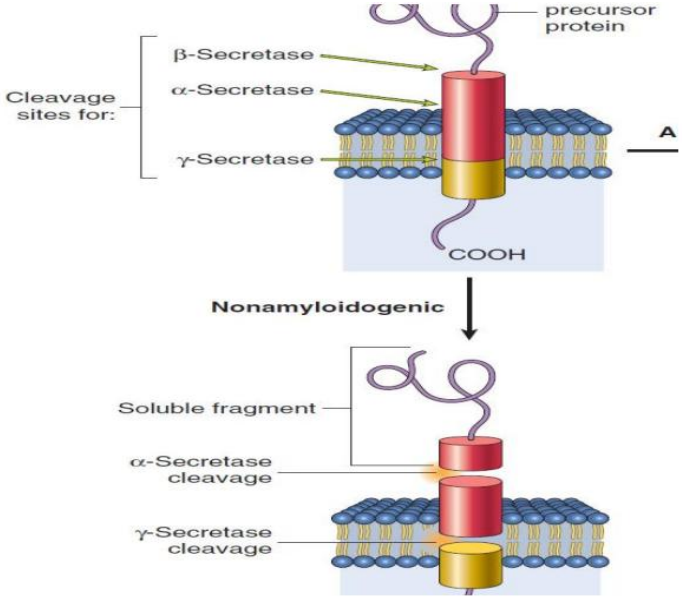


- The most commonly recognised symptom of Alzheimer is an inability to acquire new memories and difficulty in recalling recently observed facts.

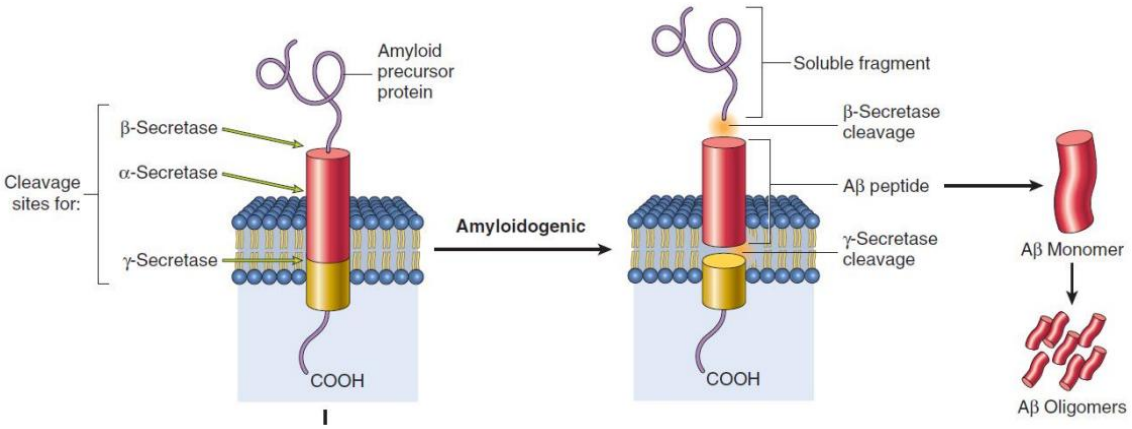
- As the disease advances, symptoms include confusion, irritability and aggression, mood swings, language breakdown, long term memory loss, and ultimately a gradual loss of bodily functions and death.
- The disease occurs by the accumulation of two proteins: **αβ amyloid** and **Tau** in the form of plaques outside the cell and neurofibrillary tangles inside the cell, respectively.
- This leads to neuronal dysfunction, death and inflammation.
- Plaques deposit in the neuropil.
- Tangles develop intracellularly.
- Aβ generation is the critical initiating event for the development of AD.
- Mutations of the gene encoding the precursor protein for Aβ : elevated risk of AD.
- Mutations of Tau gene **do NOT** increase risk of AD.

✓ **Role of αβ amyloid**

- Final role is causing atrophy of the brain.
- αβ amyloid is formed from amyloid precursor protein (APP) which is a transmembrane protein.
- Amyloid precursor protein is formed of many subunits including 3 subunits: α, β & γ.
- Normally, APP can be cleaved by α-secretase and γ-secretase, liberating a non-pathogenic peptide as you can see in the following picture.



- AD results when the (APP) is sequentially cleaved by the enzymes β-amyloid–converting enzyme (BACE) and γ-secretase creating **Aβ amyloid**.



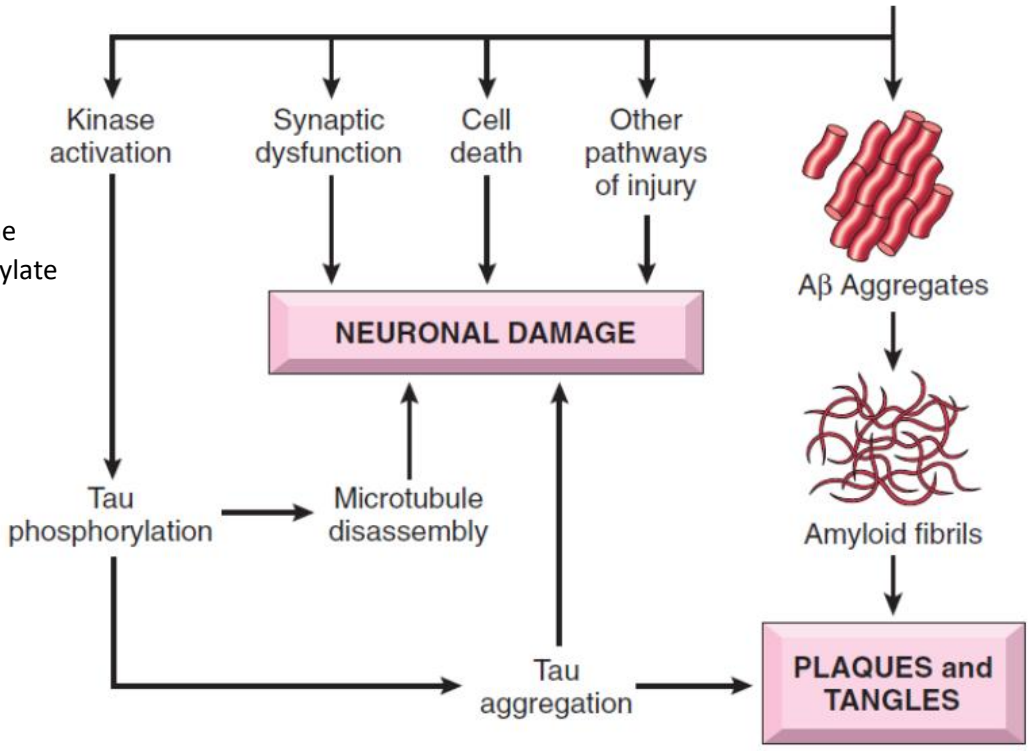
- Mutations in APP or in components of γ-secretase lead to familial AD.
- The APP gene is located on chromosome 21, increased risk in down syndrome.
- Once generated, Aβ is highly prone to aggregation → plaques formation → decreased number of synapses and alter their function → memory disruption.

✓ **Role of tau**

- What is tau?
  - a microtubule-associated protein. Present in axons in association with the microtubular network.

Formation of Aβ amyloid

Kinase: Enzyme that phosphorylate proteins.



- After amyloid formation, a kinase enzyme is activated, Tau is hyper-phospholerated, this will cause:
  → Microtubule disassembly, this will damage the pathway of vesicles as they are carried on microtubules to the synaptic knobs for transmitting of action potential (loss of microtubule stability --> neuronal toxicity and death).
  → Formation of Neurofibrillary tangles.
- Tau aggregates can be passed across synapses from one neuron to the next → spread of lesions.

✓ **Role of inflammation**

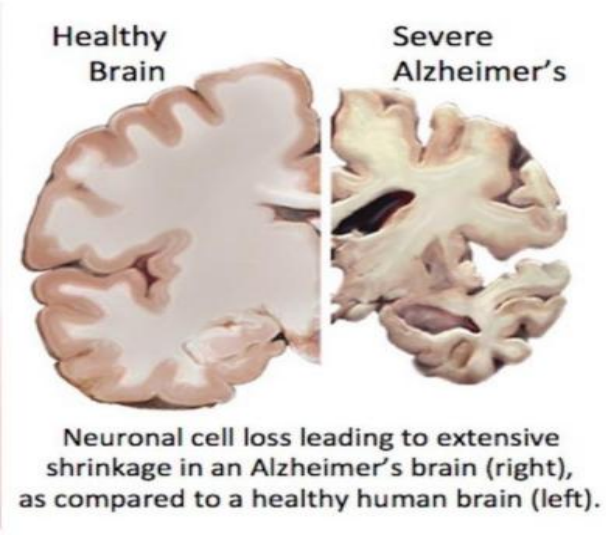
- Innate immune system responds to Aβ and tau.
- Deposits of Aβ start an inflammatory response from microglia and astrocytes. (So we can conclude that if there are more mutations in APP the disease will progress faster, while mutations in tau genes only will not cause the disease because Aβ must be found to start the inflammation).
- Clearance of the aggregated peptide, and secretion of mediators that cause neuronal injury over time.

✓ **Basis for cognitive impairment**

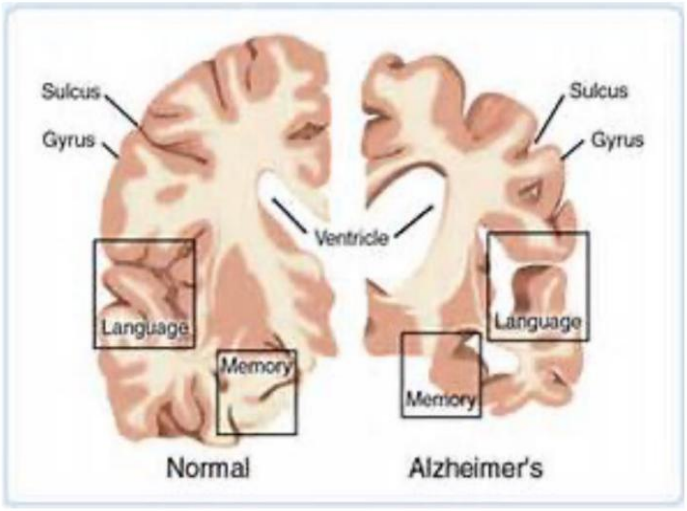
- Deposits of Aβ and tangles appear before cognitive impairment.
- In familial AD, deposition of Aβ and the formation of tangles precede cognitive impairment by as much as 15 to 20 years, it occurs in 50 years old usually.
- Large burden of plaques and tangles is strongly associated with severe cognitive dysfunction.
- The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques.

MORPHOLOGY

- Remember that the diagnosis is done clinically by symptoms and excluding other reasons of the same manifestations.
- Cortical atrophy
- Widening of the cerebral sulci & Compensatory ventricular enlargement (hydrocephalus ex vacuo).
- Most pronounced in the frontal, temporal, and parietal lobes.



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



- **Alzheimer disease neuropathologic changes include 2 things:**

  υ **Neuritic plaques** (an extracellular lesion): central amyloid core surrounded by collections of dilated, tortuous, processes of dystrophic neurites (surrounded by gliosis).

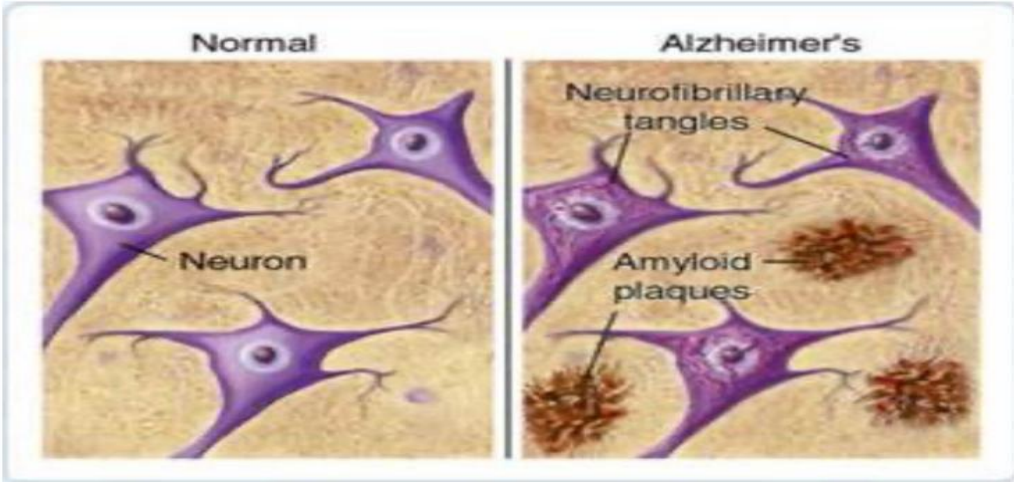
  - Hippocampus and amygdala and neocortex (relative sparing of primary motor and sensory cortices until late).

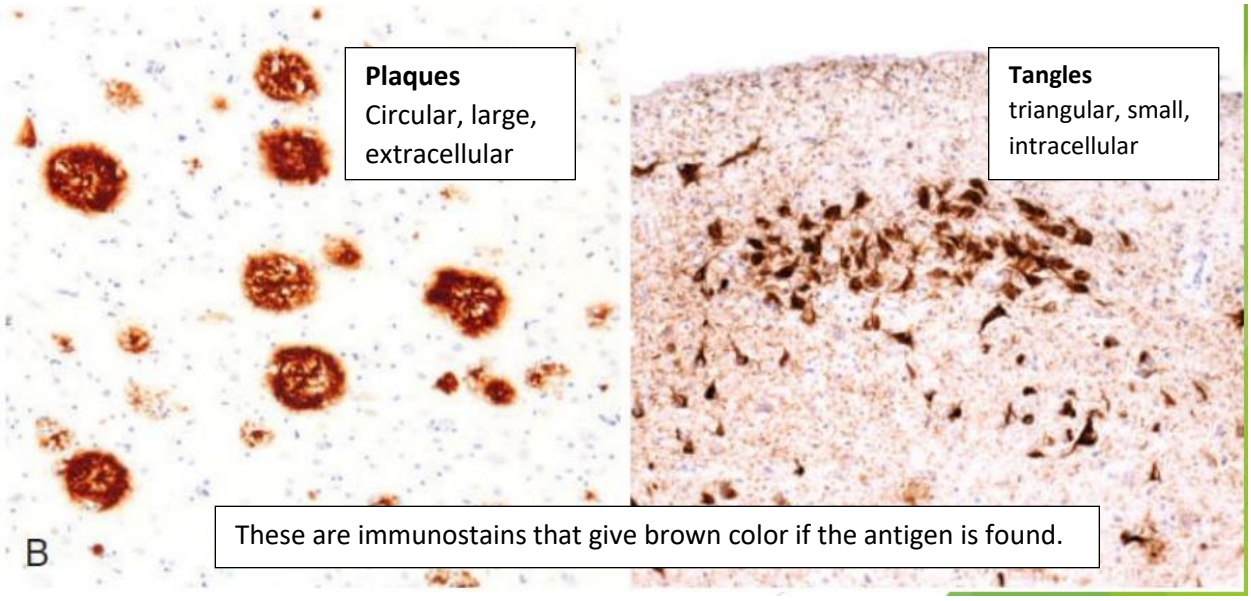
  - The amyloid core contains Aβ

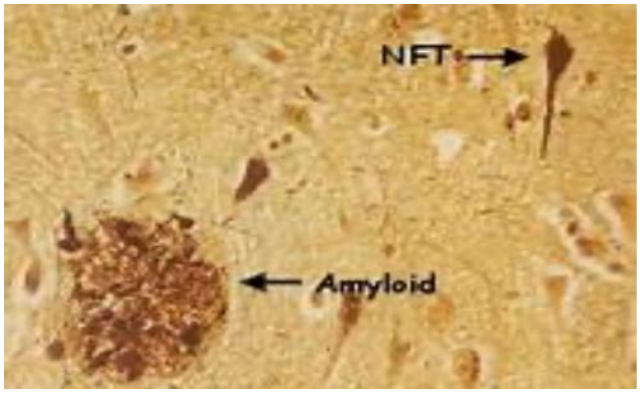
  υ **Neurofibrillary tangles:** basophilic fibrillary structures in the cytoplasm of neurons, displace or encircle the nucleus; persist after neurons die, becoming extracellular.

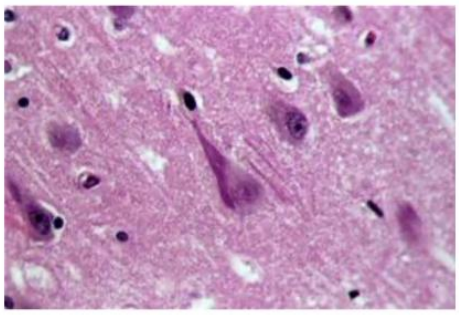
  - found in Cortical neurons, pyramidal cells of hippocampus, the amygdala, the basal forebrain, and the raphe nuclei.

  - Made of Hyperphosphorylated tau.









NEUROFIBRILLARY TANGLES

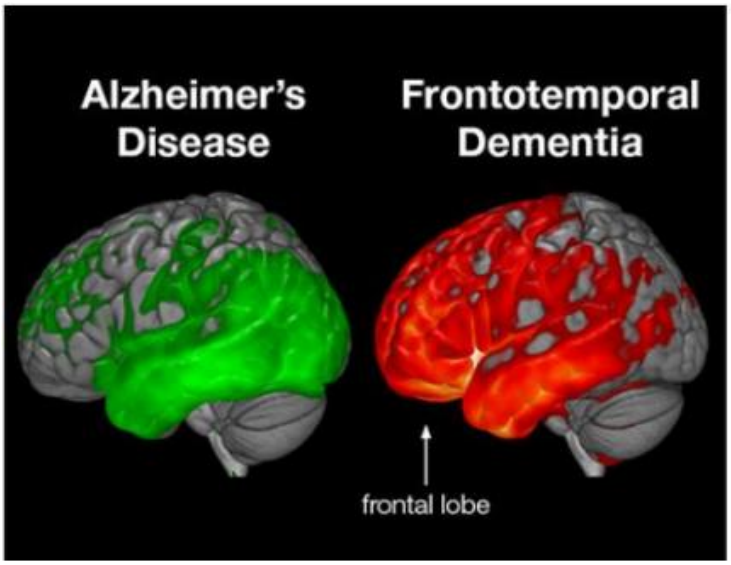
FRONTOTEMPORAL LOBAR DEGENERATION (FTLD)

GENERAL OVERVIEW

- ✓ Several disorders starts in temporal & frontal lobes (remember that the frontal lobe is responsible for behaviour, so the behaviour is affected first).
- ✓ Causes Progressive deterioration of language and changes in personality
- ✓ Clinically, causes frontotemporal dementias.
- ✓ Keep in your mind that Behavioural and language problems precede memory disturbances, in contrast to AD. (Later the patient will have all these manifestations)

- ✓ The onset of symptoms occurs at younger ages than for AD.
- ✓ Neuronal inclusions, which may contain tau or TDP43.
- ✓ Pick disease (subtype of FTLD-tau), associated with smooth, round inclusions known as Pick bodies.

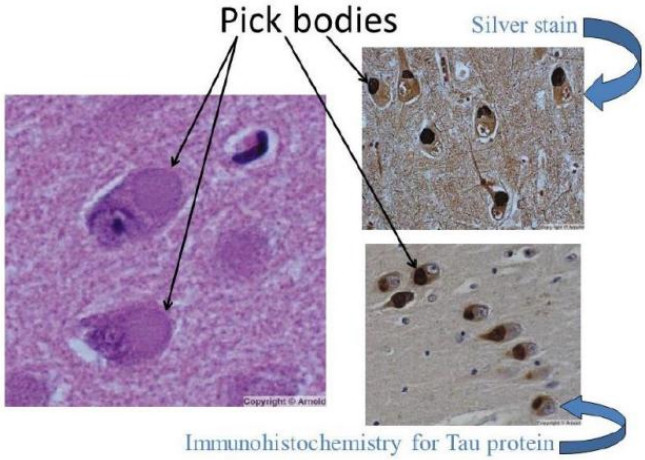
THE DIFFERENCE BETWEEN AD & FTLD



- 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.

MORPHOLOGY

- ✓ Atrophy of frontal and temporal lobes.
- ✓ Neuronal loss and gliosis. In FTLD-tau, the characteristic neurofibrillary tangles, similar to AD
- ✓ Rounded Pick bodies in pick disease (see the next picture).



QUESTIONS

1.Alzheimer's is the most common form of which of these?
A. MalnutritionB. DementiaC. FatigueD. Psychosis
2. How is Alzheimer's diagnosed?
A. Mental-status testsB. Blood testsC. Neurological testsD. All of the above
3. Physiologically, what happens to the brain as Alzheimer's progresses?
A. Tissue swellsB. Fluid collectsC. Many cells dieD. Brain-stem atrophies
4. Which of these is the strongest risk factor for developing the disease?
A. HeredityB. AgeC. Exposure to toxinsD. None of the above
5. Occasionally, other medical conditions may mimic this disease. What are they?
A. Side effects to medicationB. DehydrationC. Poor nutritionD. All of the above
6. Signs of Alzheimer's include which of these symptoms?
A. Loss of memoryB. Increase in irritabilityC. RestlessnessD. All of the above

7. Which age group has the highest rate of Alzheimer's cases reported?
A. 85 and olderB. 74 to 84C. 65 to 74D. 55 to 65
8. Because no drugs cure this condition, emphasis is put on delaying the onset of severe symptoms. Which of these strategies helps?
A. ExerciseB. HobbiesC. Good nutritionD. All of the above
9. The average time from the onset of symptoms to death is how long?
A. 20 yearsB. 8 yearsC. 6 yearsD. 4 years
10. If you care for a relative with Alzheimer's, which of these measures will help stabilize the patient mentally?
A. Move to a small apartmentB. Correct "bad" behavior gentlyC. Establish a regular routineD. Repaint or buy new furniture

ANSWERS

1	2	3	4	5	6	7	8	9	10
b	d	c	b	d	d	a	d	b	c

- Note: sometimes we give AD patients b12.

الحكمة في ابتلاء الكبراء بالذنوب؛ لينقلوا منها إلى درجة المحبوب المفروح به؛ فإن الله يحب التوابين، ويحب المتطهرين، والله أشد فرحًا بتوبة عبده من فاقد الضالة التي عليها طعامه وشرابه إذا وجدها بعد الفقدان.

- ابن تيمية رحمه الله