L5

Neuropsychiatry Block

Biochemical Aspects of Alzheimer's Disease

Editing File

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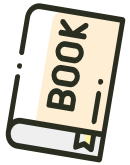
Objectives



1. Define neurodegenerative disorders.
2. Identify the clinical picture and diagnostic criteria of Alzheimer's disease.
3. Understand the different ways of processing of amyloid precursor protein leading to amyloid generation and accumulation.
4. Differentiate between the neuritic plaques, neurofibrillary tangles and tau protein and their role in the pathogenesis of the disease.
5. Understand the genetics of Alzheimer's disease.
6. Discuss ongoing research and therapeutic approach to treat these disorders.

Neurodegenerative Diseases

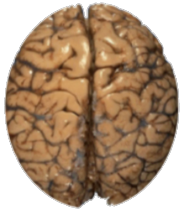
1. Diseases of gray matter are **characterized** principally by the progressive loss of neurons.

2. The pattern of neuronal loss is selective **(not random)** affecting one or more groups of neurons leaving the others intact.

3. The diseases arise without any clear inciting event in patients without previous neurological deficits.

4. A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation.

5. The aggregated proteins are **generally cytotoxic.**



Alzheimer's Disease

1

A degenerative disease with the prominent involvement of the **cerebral cortex**

2

- Its principal clinical manifestation is **dementia**.
- Dementia is the progressive loss of cognitive function independent of the state of attention

3

Patients rarely become symptomatic before 50 yr. of age but the **incidence of disease rises with age**

4

The disease becomes apparent with:

- Gradual impairment of higher intellectual function
- Alterations in mood and behavior
- Progressive disorientation
- Memory loss

5

- In 5-10 yrs, the patient becomes profoundly disabled, mute and immobile
- Most cases are **sporadic**

(no genetic compound)

- At least 5-10% are familial

Attention is fine, but there is a loss of cognitive function.

It's associated with older age.

Pathogenesis of Alzheimer's

- Still being intensively studied
- Strong correlation of number of **neurofibrillary tangles** with degree of **dementia** than neuritic plaques.

-When Alzheimer's starts to develop, **neuritic plaques** will appear, but patients may not show any symptoms. Symptoms start when the **neurofibrillary tangles** appear. -symptom severity is actually Proportionate to the presence of the neurofibrillary tangles.

Important! It might come as **SAQ**.

- **Biochemical markers correlated to degree of dementia include:**
  1. **Loss of choline acetyltransferase** (enzyme required for synthesis of neurotransmitter (Ach))
  2. **Synaptophysin immunoreactivity**. Synaptophysin is a protein present in the synaptic vesicle.
  3. **Amyloid burden.**

- **Loss of synapses** best correlates with severity of **dementia.**
- The **Aß peptide** forms B-pleated sheets and aggregates;
  1- Resistant to degradation.
  2- Elicits a response from astrocytes and microglia.
  3- Can be directly neurotoxic.

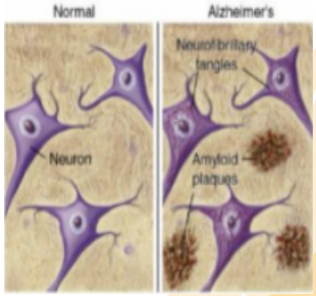
AB peptide :

- **Aß is a critical molecule in the pathogenesis of Alzheimer's disease**
- Derived from the processing of **APP** (amyloid precursor protein)
- APP is a protein of uncertain cellular function
- It is synthesized with a single transmembrane domain and expressed on the cell surface

Diagnosis

1- Combination of clinical assessment (patient history) and radiologic methods.
2- Pathologic examination (microscopic examination) of brain tissue is necessary for definitive diagnosis.
3- **major microscopic abnormalities** include: **Neuritic (senile) Plaques, Neurofibrillary Tangles, and Amyloid Angiopathy.**

Neurofibrillary Tangles (intracellular)	Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus. These filaments mainly contain: **hyperphosphorylated** forms of the **tau protein**. Which is a protein that enhances microtubules assembly. Hyperphosphorylation of Tau protein causes its loss of function, and consequently its aggregation into tangles
Amyloid Angiopathy (Angiopathy is disease of the blood vessels)	- **Amyloid proteins** build up on the walls of the arteries of the brain. - The condition increases the risk of hemorrhagic,stroke and dementia. - An almost invariable accompaniment of Alzheimer's disease but **not specific** for Alzheimer's. (it's also seen in Parkinson's disease)



Diagnosis cont.

Important!
it might come as **SAQ**. (**in red**)

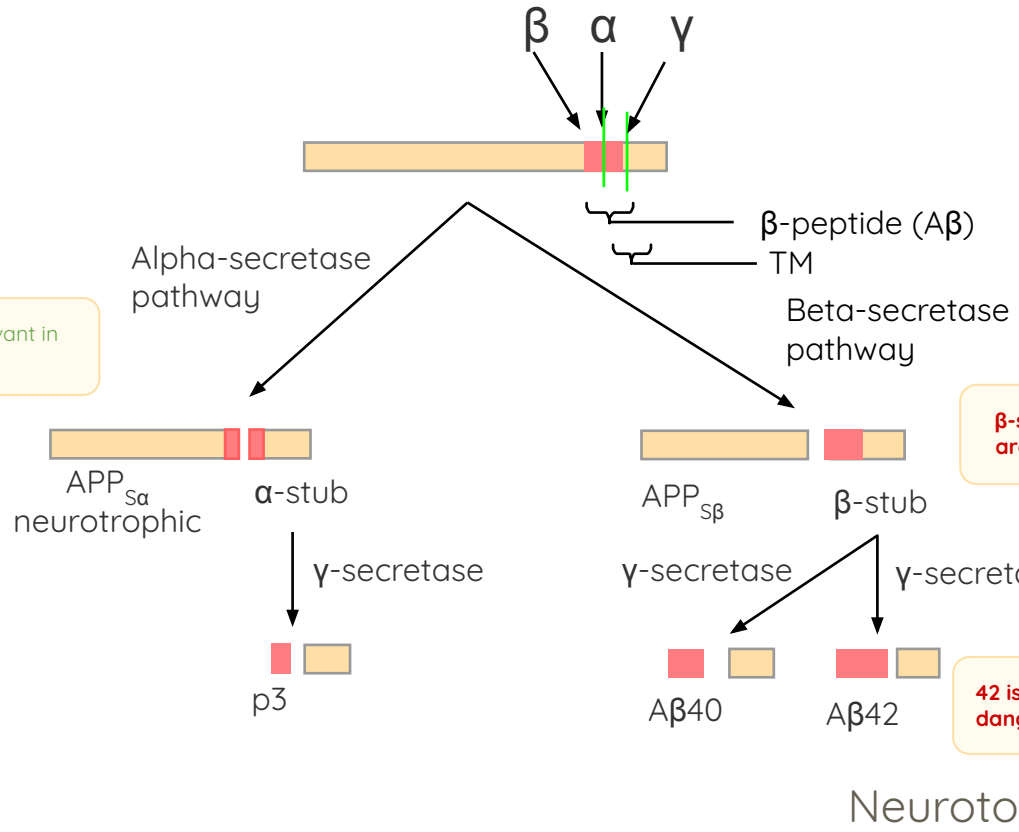
Neuritic plaques
(Senile plaques)
(extracellular)

- Spherical with 20-200 um in diameter.
- Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria.
- The amyloid core contains several abnormal proteins.
- The **dominant component of the plaque core is Aß**, a peptide derived from a larger molecule, **amyloid precursor protein (APP)**.
- The two dominant species of **Aβ**, called **Aß40** and **Aß42** share an N-terminus and differ in length by two amino acids. **Aß42** is more dangerous

-Other less dominant proteins in the plaque:

1. **Components of the complement cascade**
2. **Proinflammatory cytokines**
3. **A1-antichymotrypsin** kind of protease inhibitor
4. **Apolipoproteins** Especially ApoE

Two Different Pathways for APP Processing



To process APP, it either goes through the alpha pathway (cleavage by Alpha secretase) or through β Pathway (cleavage by Beta Secretase), but never together

Second cleavage is done by γ- secretase

Alpha pathway is not relevant in Alzheimer's

β-secretase and γ-secretase are important in Alzheimer's

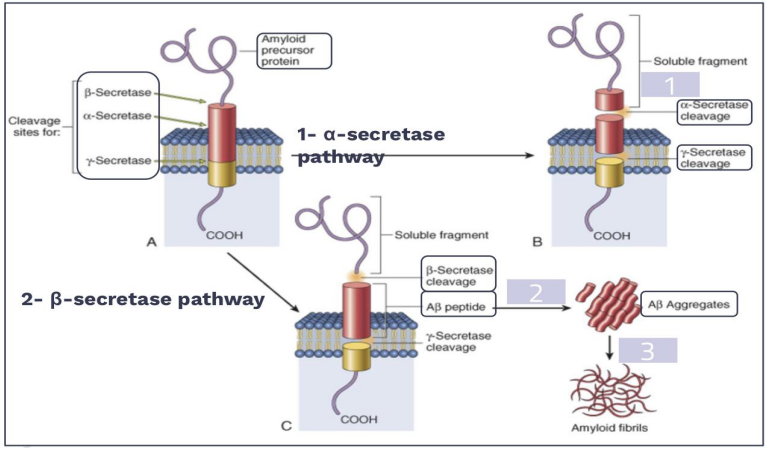
42 is more dangerous

Mechanism of Amyloid Generation

1. When **APP** is cleaved by **α - secretase**, subsequent cleavage by **γ - secretase** **does not** yield **Aβ** .

2. **Cleavage by β-secretase followed by γ - secretase** results in production of **Aβ** leading to Alzheimer's Disease

3. **Aß** can then aggregate and form **fibrils**.



Aß aggregates are oligomers

Oligomers attach and make a bigger plaque

- **APP** has potential cleavage sites for three distinct enzymes **(α, β ,and γ-secretases)** .
- The **Aβ** domain extends from the extracellular side of protein into transmembrane domain.

Accumulation of Aβ protein

Accumulation of Aβ protein affects neurons and neuronal function:

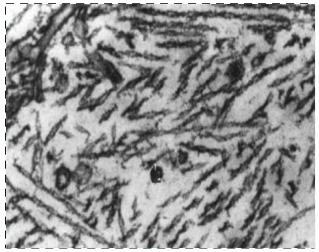
- Small aggregates of Aβ alters **neurotransmission**. By sitting between neurons (synapses) and preventing transmission
- Aggregates can be **toxic** to neurons and synaptic endings.
- Larger deposits (plaques) also cause **neuronal death**.
- Elicit a local **inflammatory** response leading to further cell injury.

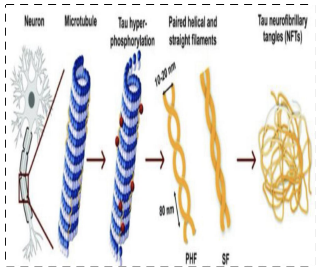
The Tau Protein

1. Presence of Aβ causes **hyper-phosphorylation** of tau protein in neurons.

2. This leads to **redistribution and aggregation of tau protein into tangles in neurons** (from axon into dendrites and cell body).

3. The process results in **neuronal dysfunction** and **cell death**.

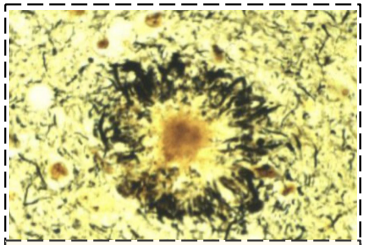




Aβ and Tau may both contribute to the pathogenesis of Alzheimer's Disease

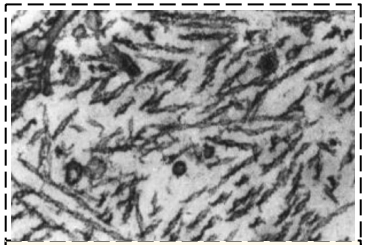
Factors that elevate Aβ

we don't know the factors, but age is one factor



Aβ

??



Tau

Fibril assembly

Filament assembly

Nerve cell mis-function and death?

Nerve cell mis-function and death?

Genetics of Alzheimer's

Important! Male doctor:
It might come as MCQ or mostly SAQ.

- **Mutations in APP** (Amyloid Precursor Protein) gene.
- Mutations in γ-secretase (**presenilin-1 or presenilin-2**) PS-1 PS-2 = component genes of secretase enzyme
- Both lead to early onset of **familial** Alzheimer's disease due to high rate of Aβ accumulation.

PS-1 , PS-2 are the component genes of γ-secretase, and mutations on them are associated with familial Alzheimer

By time they reach 45 years old, most individuals who have Down syndrome will develop Alzheimer's

- The gene encoding **APP** is located in **chromosome 21**
- **Alzheimer's occurs in most patients with Down syndrome (trisomy 21) beyond 45 years of age.** Because the gene for APP is present on chromosome 21 .

Important! Male doctor:
Very important note to memorise.

- Due to APP gene dosage effects. APP dosage is responsible for increased β-amyloid production, there is an extra gene for chromosome 21 in Down syndrome patients which encodes APP hence will lead to 3 copies of APP gene which will increase risk of AD. ~439
  - Genes associated with typical, sporadic Alzheimer's disease are being identified.
  - This may provide new clues to pathogenesis of the disease.

Genetics of Alzheimer's

Important!
" It will most likely come as **SAQ**. "

	Chromosome	Gene	Consequences
Familial	**21**	**Amyloid Precursor Protein (APP)**	يقصد به في الثلاثينات مثلاً و ليس في الطفولة **Early onset FAD increased Aβ production**
Familial	14	Presenilin-1 (PS1)	Early onset FAD increased Aβ production
Familial	1	Presenilin-2 (PS2)	Early onset FAD increased Aβ production
Sporadic	**19**	**Apolipoprotein E (ApoE)** Receptor for cholesterol Produced locally in brain by astrocytes (cannot cross BBB)	**-Increased risk for development of AD** **-Decreased age at onset of AD**

Treatment of AD

1. Currently no effective treatment for AD.

2. Regulating neurotransmitter activity (eg.enhancing cholinergic function improves symptoms). By giving acetylcholinesterase inhibitors

3. Epidemiological studies show **NSAIDs** decrease the risk for developing AD, unfortunately Clinical trials of NSAIDs in AD patients are **not very fruitful.**

4. **Polyphenols** "antioxidants" such as flavonoids (found in fruit) **reduce proinflammatory responses.**

5. **Flavonoid** supplements may be a **new therapeutic approach** for AD

6. **Stem cell therapy offers**:
- Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration. "by grafting a certain type of neuron in an affected area"~439
- Neurotrophic support to remaining cells.
-Prevent the production or accumulation of toxic factors that harm neurons.

Treatment of AD

The small aggregates of Aß and larger fibrils are directly neurotoxic

They can elicit oxidative damage and alterations in calcium homeostasis.

How Aß is correlated to neurodegeneration in AD? How it is linked to tangles and hyperphosphorylation of tau protein?

All remain open questions.

Take Home Messages

- Neurodegeneration is the progressive loss of structure or function of neurons, including death of neurons.
- Extracellular deposition of normally soluble proteins in certain tissues in the form of insoluble fibrous aggregates known as amyloid. The deposition of amyloid interferes with normal cellular function, resulting in cell death and eventual organ failure.
- The dominant component of amyloid plaque that accumulates in Alzheimer's disease is amyloid β 42 (Aβ42) peptide.

Summary!

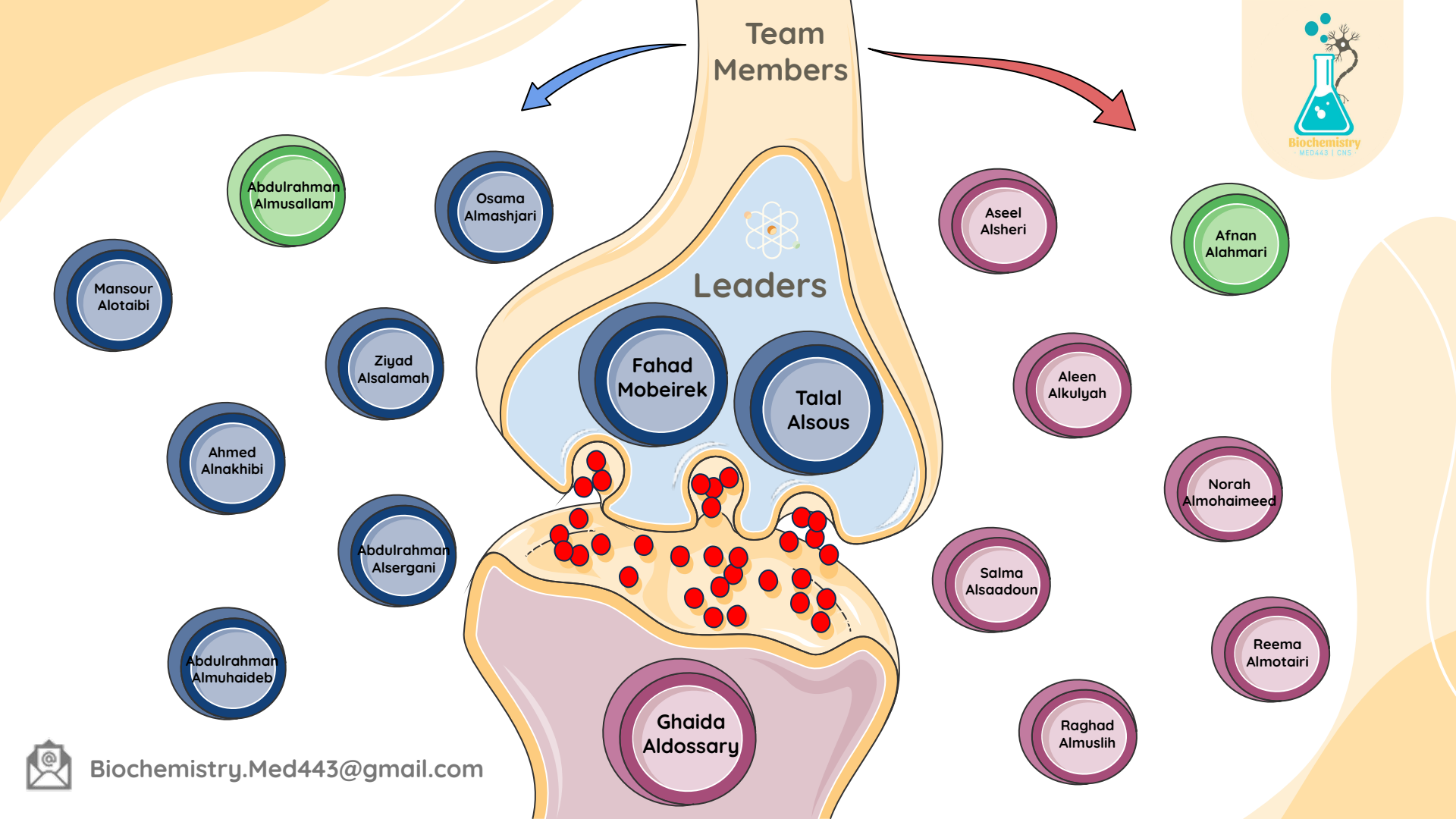
MCQs

Q1: which chromosome associated with amyloid precursor protein?							
A	1	B	14	C	21	D	19
Q2: Which of the following may contribute the pathogenesis of Alzheimer's Disease?							
A	Aß	B	Tau	C	Both	D	None
Q3: Which of the following pathways lead to Aß accumulation ?							
A	a-secretase	B	ß-secretase	C	Both	D	None
Q4: which one of the following is related to protein?							
A	plaques	B	amyloid angiography	C	fibrillary tangles	D	None
Q5: Most condition of alzheimer disease are due to ?							
A	sporadic	B	familial	C	myopathy	D	MS

5) A
4) C
3) B
2) C
1) C

SAQ

Q6: What are the main genes affected in alzheimer ?	
Answer:	amyloid precursor protein (APP) Presenilin-1, Presenilin-2 Apolipoprotein E
Q7: who are the patients most susceptible to Alzheimer's ?	
Answer:	Alzheimer's occurs in most patients with Down syndrome (trisomy 21) beyond 45 years of age.
Q8: what mutation occurs in Alzheimer's disease ?	
Answer:	Mutations in APP (Amyloid Precursor Protein) gene.


Team Members
Leaders
Fahad Mobeirek
Talal Alsous
Ghaida Aldossary
Abdulrahman Almusallam
Osama Almashjari
Mansour Alotaibi
Ziyad Alsalamah
Ahmed Alnakhibi
Abdulrahman Alsergani
Abdulrahman Almuhaideb
Aseel Alsheri
Afnan Alahmari
Aleen Alkulyah
Norah Almohaimeed
Salma Alsaadoun
Reema Almotairi
Raghad Almuslih
Biochemistry
MED443 | CNS
Biochemistry.Med443@gmail.com