Revised & Approved

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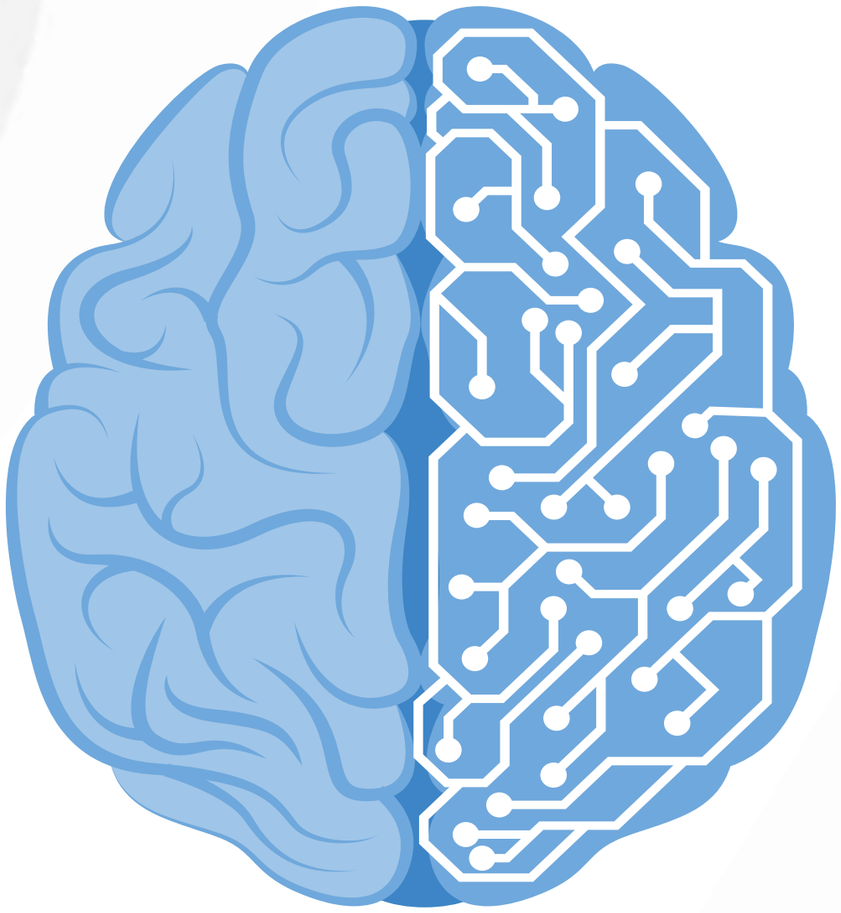
BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY



Alzheimer's Disease

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

Objectives

Click on the objective to go to the related slide

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

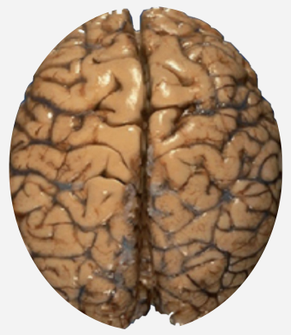
Level 5 (with each lecture you will level up and it will get harder to find the scientist)
Hello my name is Alois Alzheimer, Find me in this lecture!
Then click me for more info about what I discovered.

Click the number between the [ ] to see the related notes.

Objective: 1

Neurodegenerative disease

- Diseases of gray matter characterized principally by the progressive loss of neurons
- The pattern of neuronal loss is selective affecting one or more groups of neurons leaving the others intact
- The diseases arise without any clear inciting event in patients without previous neurological deficits
- A common theme is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation [1]
- The aggregated proteins are generally cytotoxic



Alzheimer disease

1

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

2

- Its principal clinical manifestation is dementia [2]
- 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
- At least 5-10% are familial

Pathogenesis of Alzheimer's

- Still being intensively studied
- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques [3]

- Biochemical markers correlated to degree of dementia include:
  1. Loss of choline acetyltransferase [4]
  2. Synaptophysin immunoreactivity [5]
  3. Amyloid burden [6]

- Loss of synapses best correlates with severity of dementia
- The Aβ peptide forms β-pleated sheets and aggregates [7]
- Resistant to degradation
- Elicits a response from astrocytes and microglia
- Can be directly neurotoxic

Aβ peptide

- Aβ is a critical molecule in the pathogenesis of Alzheimer's disease
- Derived from the processing of APP (amyloid precursor protein) [8]
- APP is a protein of uncertain cellular function
- It is synthesized with a single transmembrane domain and expressed on the cell surface

Click the number between the [ ] to see the related notes.

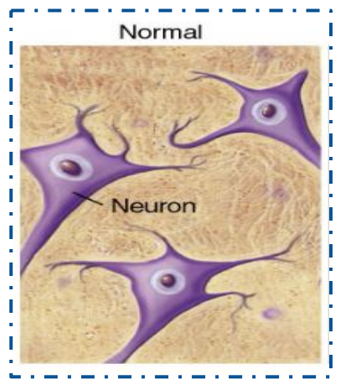
Objective: 2 & 4

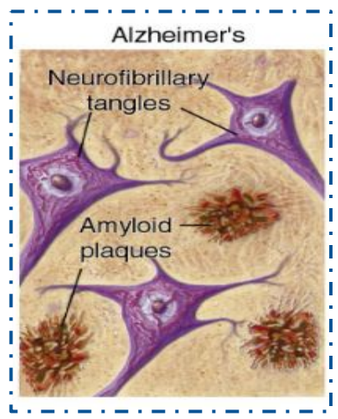
Diagnosis

Recommended video from our team
(6:27 minutes)

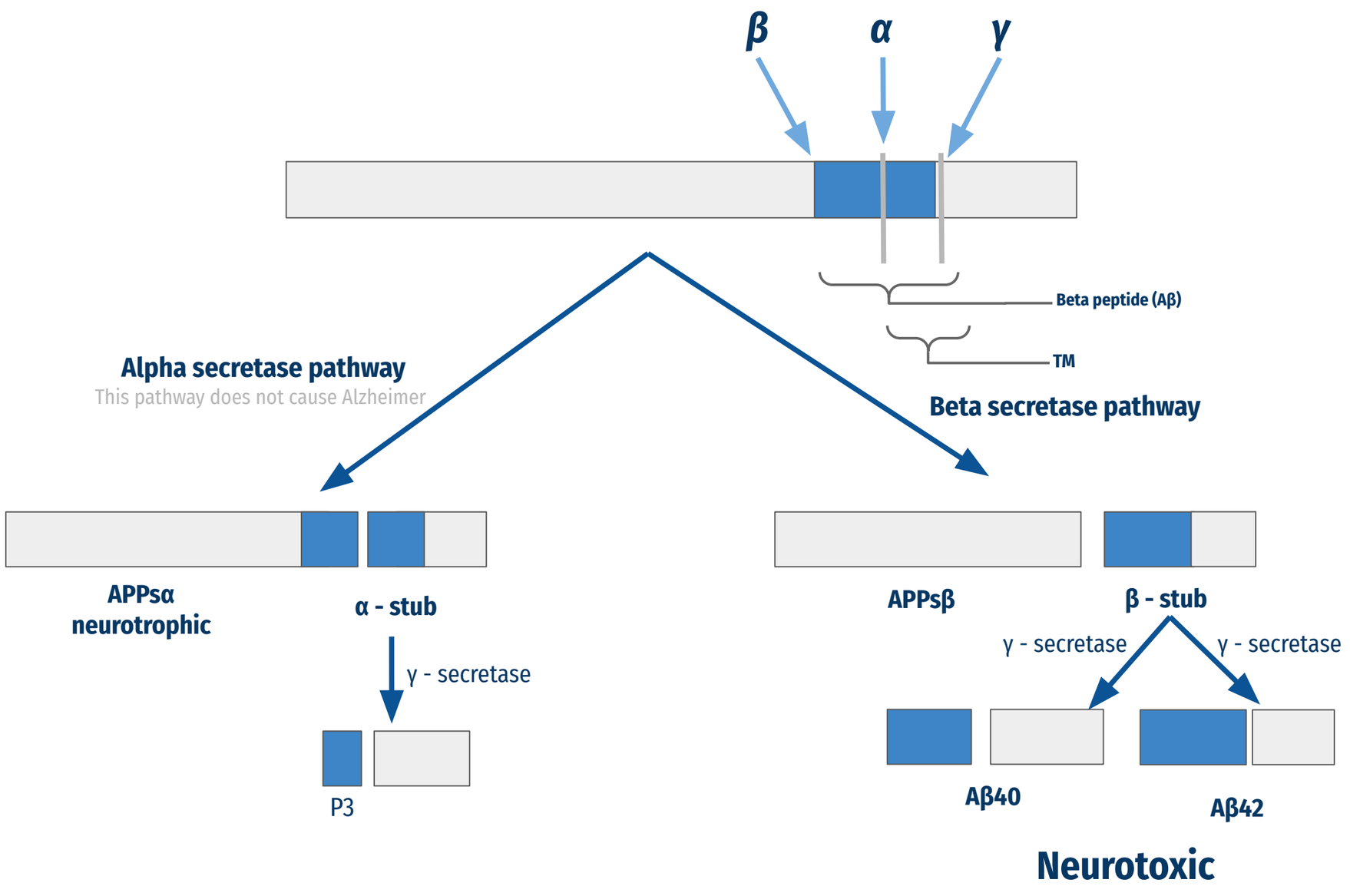
1. Combination of clinical assessment and radiologic methods [9]
2. Pathologic examination of brain tissue is necessary for definitive diagnosis
3. **Major microscopic abnormalities** include: **neuritic (senile) plaques**, **neurofibrillary tangles** and **amyloid angiopathy**

Neuritic plaques (Senile plaques) Plaques = APP Plaques = Aβ	• Spherical with 20-200 µm in diameter • Contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria [10] • The amyloid core contains several abnormal proteins • The **dominant component of the plaque core is Aβ**, a peptide derived from a larger molecule, **amyloid precursor protein (APP)** • The two dominant species of Aβ, **called $A\beta_{40}$ and $A\beta_{42}$** share an N-terminus and differ in length by two amino acids. [11] • Other less abundant proteins in the plaque: 1. Components of the complement cascade 2. Proinflammatory cytokines 3. α1-Antichymotrypsin 4.Apolipoproteins
Neurofibrillary tangles [12] Tangles = Tau protein	Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus. These filaments mainly contain: 1. Hyperphosphorylated forms of the **tau protein** which is a protein that enhances microtubule assembly
Amyloid angiopathy	• Amyloid proteins build up on the walls of the arteries in 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





Two pathways for APP processing [13]



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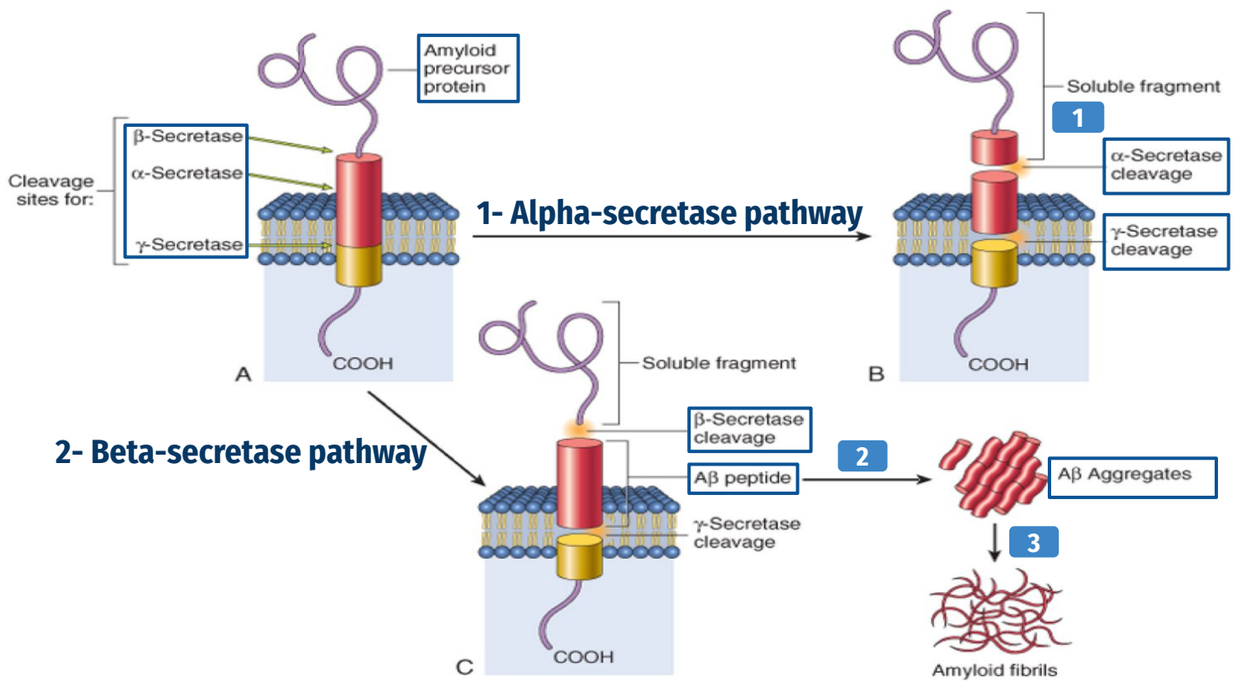
Objective: 3

Mechanism of Amyloid Generation

Recommended video from female's doctor
(4:20 minutes)

There are Two Pathways For APP Processing:



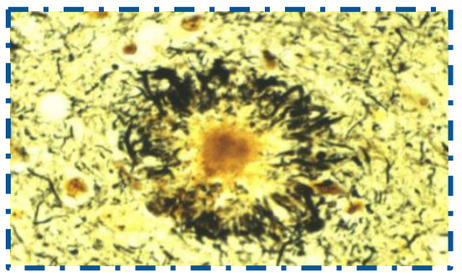
1. When APP is cleaved by **α secretase** , Subsequent (followed) cleavage by **γ secretase does not** yield Aβ (normal).
2. Cleavage by **β-secretase** , followed by **γ-secretase** result in: **Production of Aβ .** Which will lead to AD
3. Aβ can then aggregate and form fibrils.

- The Aβ domain extends from the extracellular side of protein into the transmembrane domain. [14]
- APP has potential cleavage sites for enzymes: **(α, β, and γ-secretases)**

Accumulation of Aβ protein

Accumulation of Aβ protein affects neurons and neuronal function

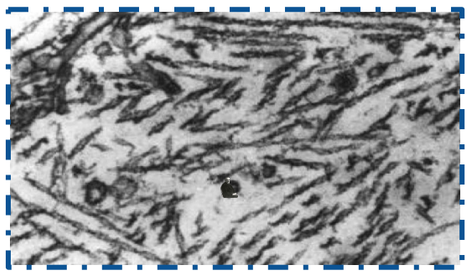
- Small aggregates of Aβ alters **neurotransmission** by sitting between neurons and preventing transmission.
- Aggregates can be toxic to neurons and synaptic endings.
- Larger deposits (plaques) also cause **neuronal death**.
- Elicit a **local inflammatory response** leading to further cell injury.

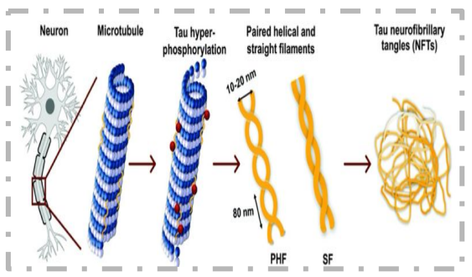


Accumulation of Aβ, plaque formation in extracellular space

The Tau Protein

01. Presence of Aβ causes hyperphosphorylation of tau protein in neurons.
02. This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body).
03. The process results in neuronal dysfunction and cell death. [15]





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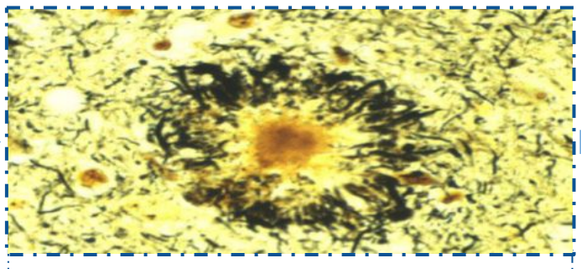
Objective: 5

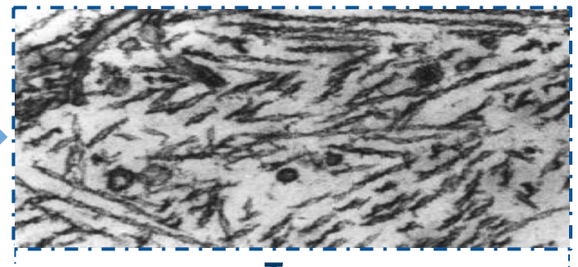
Aβ and Tau may both contribute to the pathogenesis Of the Alzheimer's disease

Factors that elevate Aβ



Aβ

??



Tau

Fibril assembly

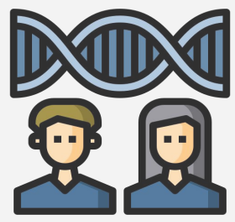
Filament assembly

Nerve cell mis-function and death?

Nerve cell mis-function and death?

Genetics of Alzheimer's

- **Mutations in APP gene.** [16] APP: Amyloid Precursor Protein
- Mutations in γ-secretase (presenilin-1 or presenilin-2). PS-1 , PS-2
- Both lead to early onset of **familial** Alzheimer's disease due to high rate of Aβ accumulation.
- The gene encoding APP is located in **chromosome 21.** [17]
- **Alzheimer's occurs in most patients with Down syndrome (trisomy 21) beyond 45 years of age.**
- Due to **APP gene** dosage effects . APP gene dosage is responsible for increased β-amyloid production ,there is an extra gene of chr 21 in Down syndrome patients which encodes APP hence will lead to 3 copies of APP gene which will increase the risk of AD
- 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

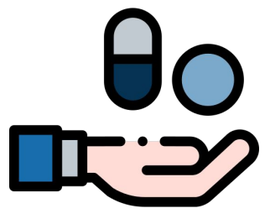
Chromosome	Gene	Consequences
21	**Amyloid Precursor Protein (APP)**	**Early onset FAD[1] Increased Aβ production**
14	Presenilin-1 (PS1)	Early onset FAD Increased Aβ production
1	Presenilin-2 (PS2)	Early onset FAD Increased Aβ production
19	**Apolipoprotein E (ApoE)** [18]	**Increased risk for development of AD Decreased age at onset of AD**

Treatment of Alzheimer Disease

- Currently no effective treatment for AD.
- Epidemiological studies show **NSAIDs** decrease the risk for developing AD, unfortunately Clinical trials of NSAIDs in AD patients are **not very fruitful.**
- **Polyphenols** "antioxidants" such as flavonoids (found in fruit) **reduce proinflammatory responses.**
- **Flavonoid** supplements may be a **new therapeutic approach** for AD. [19]
- Regulating neurotransmitter activity (eg.enhancing cholinergic function improves symptoms).

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"
- Neurotrophic support to remaining cells. [20]
- Prevent the production or accumulation of toxic factors that harm neuron



Continued Research on Alzheimer Disease

1. The small aggregates of Aβ and larger fibrils are directly **neurotoxic**.
2. They can elicit oxidative damage and alterations in calcium homeostasis.
3. How Aβ is correlated to neurodegeneration in AD? How it is linked to tangles and hyperphosphorylation of tau protein?
4. All remain open questions

Doctors' Notes

Click the note to go back to the related slide

[1] After the translation of normal protein they will be folded into their functional shape, How protein folds determine the functionality. If the protein is not folded into an appropriate way "misfolded", it will not perform its function properly. The cell will recognize this misfolded protein by tagging it "add a flag" in a process called " up cutinization then it would be taken care by proteolysis. But when there is a lot of misfolded protein it wouldn't be tagged "wouldn't be recognized for proteolysis, so These proteins start to aggregate and make cluster and cause damage to the cell they are in.

[2] Not all kind of dementia would be Alzheimer. Dementia is a manifestation caused by many different disease. One of them is Alzheimer. So if the patient has a dementia that doesn't mean the patient has Alzheimer.

[3] There is 2 things correlate with dementia: neurofibrillary tangles & loss of synapses. Neuritic plaques are not directly correlate with degree of dementia. They first produce form leading to neurofibrillary tangles and once these tangles are formed, clinical symptoms being present.

[4] Choline acetyltransferase is Responsible for synthesis of Acetylcholine.

[5] Synaptophysin is a protein also called p38 present in the neuronal synapses, since there are loss of synapses when you stain the neurons with synaptophysin there is less staining you will see.

[6] increased levels of A-beta in the blood.

[7] β pleated sheets are wide so that's why Aβ forms aggregates

[8] APP is an essential protein for the growth of the neurons.

[9] Most of the time the diagnosis of Alzheimer disease is done by Radiological and neurological examinations, but for definitive diagnosis you need to do pathological examinations, the sample is taken by autopsy or biopsy.

[10] Paired helical filaments are formed of tau proteins. These three components make the surrounding of the plaque, the core contained abnormal protein. Most dominant protein present in the core is "A beta" this AB is formed in impropriate form which become insoluble and it starts aggregate and then leads to the formation of necrotic plaque.

[11] AB40 & AB42 are two types of AB peptide and they are coming from the same APP but they differ in number of amino acids, the first type has 40aa, the second has 42aa. When APP is cleaved by an enzyme into two types of A-beta, if APP is cleaved after 40th amino acid, A-beta40 is produced. If it is cleaved after 42aa! A-beta42 is produced. So AB40 & AB42 are sharing the same "N terminal" but they differ in C terminal "c terminal is longer in AB42" Aβ42 has two more amino acids in the C terminus and it's more toxic on neurons.

[12] When AB is formed "toxic peptide" it is go out the neuronal cell and and attaches to other ABs to make oligomers in ECF. Microglia cells phagocyte these oligomers "this is a good thing" the bad thing is that these microglia start to release inflammatory cytokines that enhance Ca entrance to neuronal cells. Increased Ca inside neuronal cells enhance the production of kinases enzymes such as GSK3 "glycogen synthase kinase 3" this enzyme is involved in the phosphorylation of tau protein. So AB oligomers will cause tau protein hyperphosphorylation. When tau protein get phosphorylated, it detaches from microtubule and and aggregate inside the cell to form tangles. The microtubule that get detached from tau protein will breakdown followed by neuronal death.

[13] α secretase pathway yields P3 and its normal, β secretase pathway yields Aβ40 and Aβ42 which are toxic to neurons

[14] membrane proteins has 3 domains 1-extracellular domain 2-intracellular domain 3-transmembrane domain, APP has one transmembrane domain

[15] Tangles will cause progressive motor & behavior impairment leading to the death of the patient.

[16] APP gene and gamma secretes are associated with familial Alzheimer. But ApoE gene "present in 19ch" is considered to be a risk factor of sporadic Alzheimer

[17] APP gene is present in chromosome 21. In Down syndrome, there is an extra copy of APP gene so they have extra production of AB and those patients are more likely to develop Alzheimer's in early ages.

[18] ApoE has many isomers such as ApoE1, ApoE2, ApoE3. ApoE3 isomer is responsible for increasing the risk fo development of AD and early onset of the disease

[19] Flavonoids are present in green tea and green coffee

[20] Neurotrophic support is done by growing neurons in a media outside the body, then this media is taken out without the neurons. This media is called "stem cells conditioned media" and it is added to the affected area of the brain

Take Home Messages

- Neurodegeneration is **progressive** loss of structure and **function of neurons including neuronal death.**

- 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 β42 (Aβ42) peptide**

Click on the picture to **donate** for Saudi Alzheimer's Disease Association

Summary

Alzheimer disease

Pathogenesis

- Strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques.
- Loss of synapses best correlates with severity of dementia.
- The Aβ peptide forms β-pleated sheets and aggregates.
- Resistant to degradation & Can be directly neurotoxic.
- Elicits a response from astrocytes and microglia.

Symptoms

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

Diagnosis

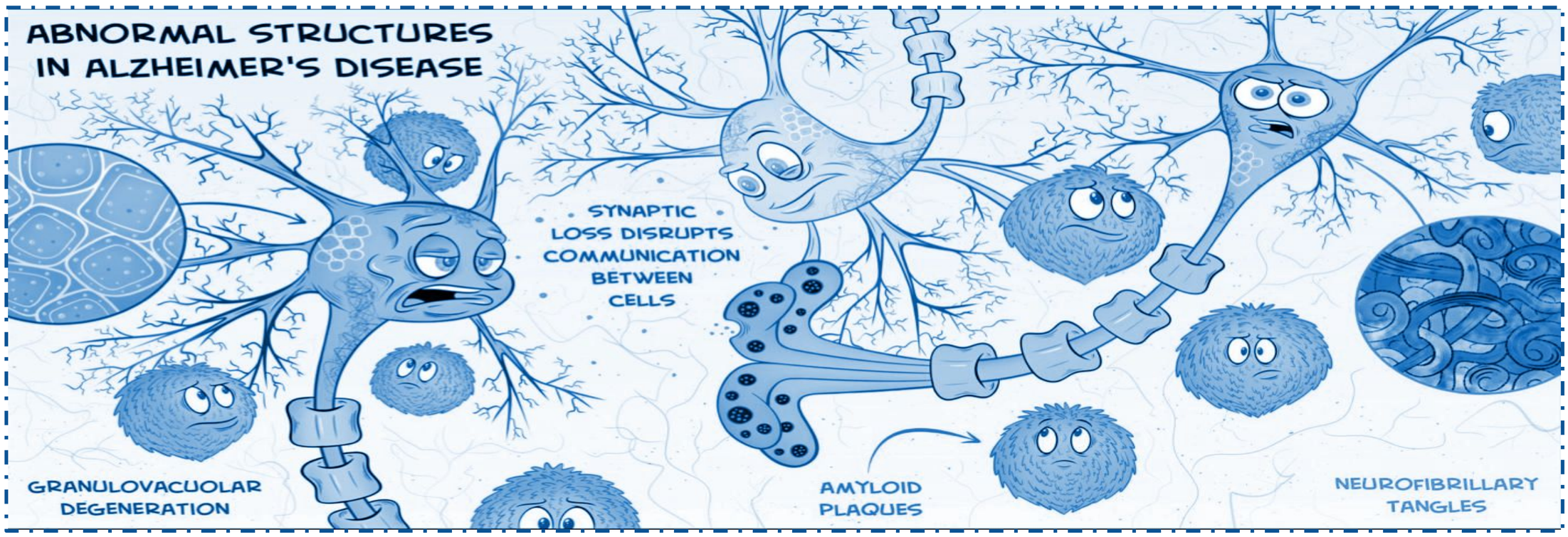
- Combination of clinical assessment and radiologic methods
- Pathologic examination of brain tissue is necessary for definitive diagnosis
- Major microscopic abnormalities

Microscopic findings

- Neuritic Plaques
- Neurofibrillary Tangles
- Amyloid Angiopathy

Alzheimer’s disease

Click on the pictures for more info



MCQs

1-Most of conditions of alzheimer disease are due to:
A- MS
B- Familial
C- Sporadic
D- Myopathy

2-Which ONE of the following biochemical markers is not correlated with the degree of dementia in Alzheimer patients ?
A- Choline acetyltransferase
B- Amyloid burden
C- Synaptophysin
D- Troponin I

3-Alzheimer's Disease is diagnosed with ?
A- Clinical assessment
B- Radiologic methods
C-Pathologic examination of brain tissue
D-All of the above

4-Which ONE of the following is the main component of senile plaques ?
A- amyloid precursor protein
B- Tau proteins
C- Aβ peptides
D- All of the above

5-The gene encoding APP is located in chromosome number?
A- 19
B- 21
C- 4
D- 5

6-Alzheimer disease is a degenerative disease with prominent involvement of the ?
A- Cerebral cortex
B- Thalamus
C- Hypothalamus
D- Epithalumus

Answers key

1- C 2- D 3- D 4- C 5- B 6- A

🧠 SAQs

1- APP has potential cleavage sites for three distinct enzymes, name them:

- α, β, and γ-secretase.

2- What are the neurofibrillary filaments and what are they composed of?

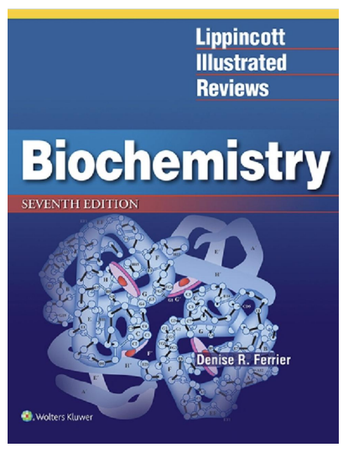
- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus.
- They contain:
  Hyper-phosphorylated forms of the tau protein (a protein that enhances microtubule assembly).

3- What are the major microscopical findings of Alzheimer's?

- Major microscopic abnormalities include: neuritic plaques, neurofibrillary tangles and amyloid angiopathy.

Resources

Click on the book to download the resource



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Special thanks to Fahad AlAjmi for designing our team's logo.