Important Doctors slides

Extra Information **Doctors notes**

Biochemistry

Alzheimer's Disease

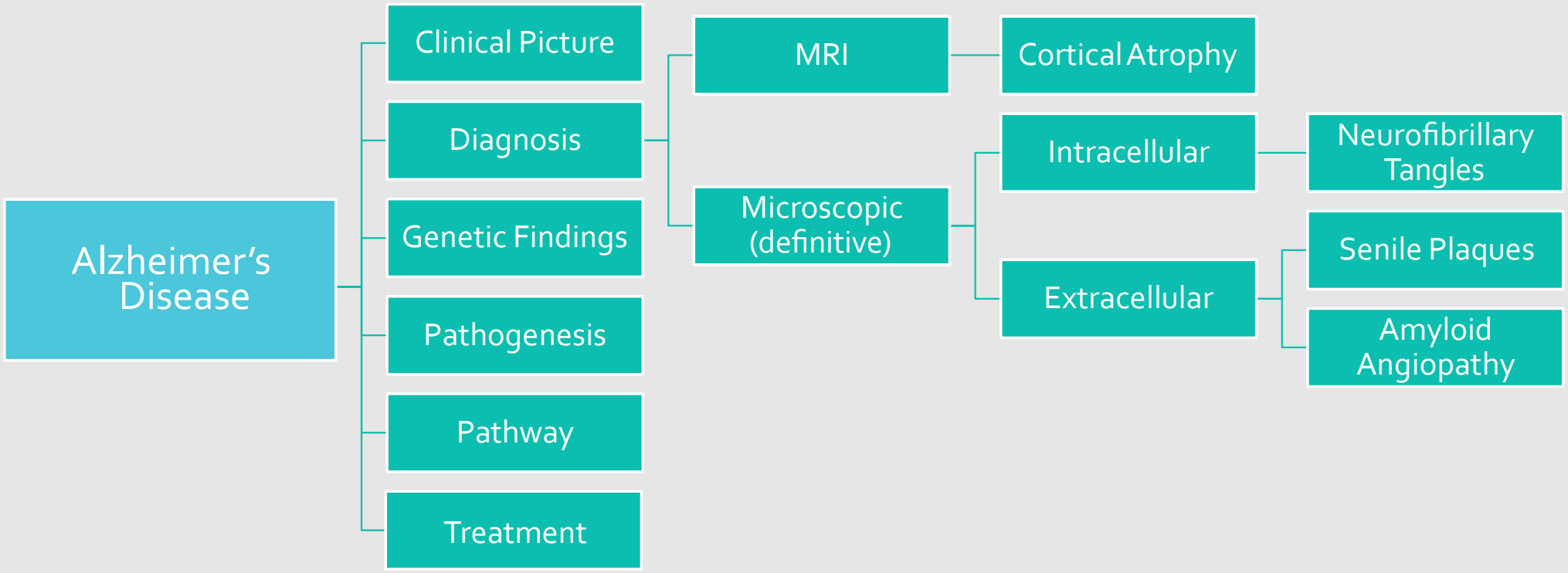
[Editing file]

OBJECTIVES

By the end of this lecture, the students should be able to:

- 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

Mind map


Alzheimer's Disease
Clinical Picture
Diagnosis
Genetic Findings
Pathogenesis
Pathway
Treatment
MRI
Microscopic (definitive)
Cortical Atrophy
Intracellular
Extracellular
Neurofibrillary Tangles
Senile Plaques
Amyloid Angiopathy

Neurodegenerative Diseases

- Diseases of gray matter characterized principally by the progressive loss of neurons .
  (so the neurons keep on dying and lead to symptoms)
- The pattern of neuronal loss is selective affecting one or more groups of neurons leaving the others intact .
  (depending upon what disease it is)
- 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
  ”they can not get cleared from the body because their structure changed and became modified”
- The aggregated proteins are generally cytotoxic

Whenever the protein synthesis happens, proteins are folded and come to the functional states. Sometimes it can produce misfolded proteins normally and they are going to be destructed by Ubiquitin machine.
If the body can not take care of these misfolded proteins it will make clusters (it wont be degraded) which are resistant to cellular machinery and this will lead to the inflammation which will cause the death of neurons.

helpful video

Alzheimer's Disease

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

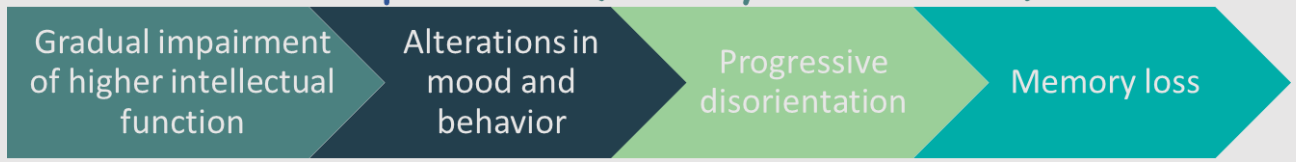
- Its principal clinical manifestation is dementia يكون واعي بس ما فيه إدراك
  - Dementia is the progressive loss of cognitive function independent of the state of attention (the person is still attentive) (dementia is the main characteristic)

- Patients rarely become symptomatic before 50 years of age but the incidence of disease rises with age .

(but dementia at any age is abnormal)

- In **5-10 years**, the patient becomes profoundly disabled, mute and immobile
- Most cases are sporadic " no genetic association "
- At least 5-10% are familial

"Clinical picture (mainly dementia)"



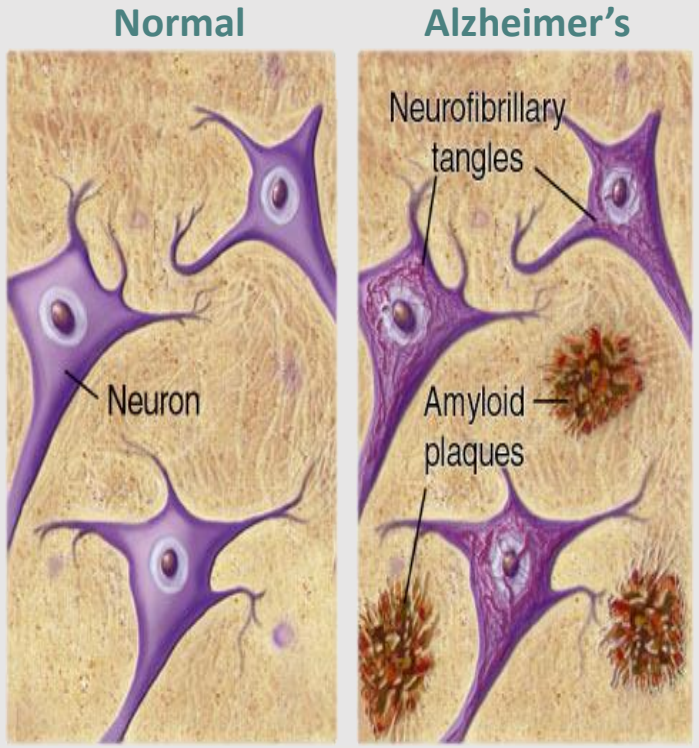
Diagnosis

1. Combination of clinical assessment and radiologic methods "MRI"

2. Pathologic examination of brain tissue is necessary for definitive diagnosis

3. Major microscopic abnormalities include: neuritic plaques (senile plaques) , neurofibrillary tangles and amyloid angiopathy

Microscopic findings : 1. Neuritic Plaques



- Spherical with 20-200 mm 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 Aβ, a peptide derived from a larger molecule, amyloid precursor protein (APP)

"that is cleaved to produce AB –amyloid beta peptide- , this type of protein cannot be degraded by the body so it starts aggregating"

✓ The two dominant species of Aβ, called Aβ40 and Aβ42 share an N-terminus and differ in length by two amino acids.

Other less abundant proteins in the plaque:

1. Components of the complement cascade
2. Pro-inflammatory cytokines .
3. α1-Antichymotrypsin .
4. Apolipoproteins

The brain normally has β amyloid protein which is susceptible to be cleared with normal enzymatic mechanisms but with dysregulation of this protein it becomes resistant to clearance hence it aggregates .

" α1-Antichymotrypsin is a protease inhibitor, proteases are present in cells and they take care of these aggregates. So these plagues produce a1-antichymotrypsin to inhibit theses proteases to aggregate " (when cytokines aggregations are formed they lead to pro-inflammatory and inflammatory processes)

(specifically Apolipoproteins E)
They are extracellular and are more important than neurofibrillary tangles

2. Neurofibrillary Tangles

❖ What is it ?

- Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus

❖ These filaments mainly contain:

- Hyperphosphorylated forms of the tau protein
- A protein that enhances microtubules assembly

(provides support, if it's hyperphosphrylated it cannot bind to microtubules any more, instead, they bind together and form neurofibrillary tangles (intracellular) when the start tangling they form nodes together.)

3. Amyloid Angiopathy

❖ What is it ?

- 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 . "also in Parkinson's"

Pathogenesis of Alzheimer's

- Still being intensively studied
- **Strong correlation** of number of neurofibrillary tangles with degree of dementia than neuritic plaques
- Loss of synapses best correlates with severity of dementia

Neuritic plaques "that appears first" can not make the disease symptomatic there must be tangles in order to have symptoms

❖ Include : Biochemical markers correlated to degree of dementia

- Loss of **choline acetyltransferase**
- **Synaptophysin** immunoreactivity
- Amyloid burden

  Burden : overload because of aggregation

Loss of choline acetyltransferase is involved in synthesis in Ach, loss of it correlates with dementia)

Synaptophysin is one of the proteins of synaptic vesicles –p38- so when we have toxicity this leads to loss of synapses, so there is loss of synaptophysin in presynaptic vesicles (loss of immuno-reactivity), the way we test it is with the help of immuno-assay which is adding antibodies to synaptophysin and see if it's positive (synaptophysin immuno-reactive) or negative)

Aβ Peptides

❖ What is it ?

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

❖ Why?

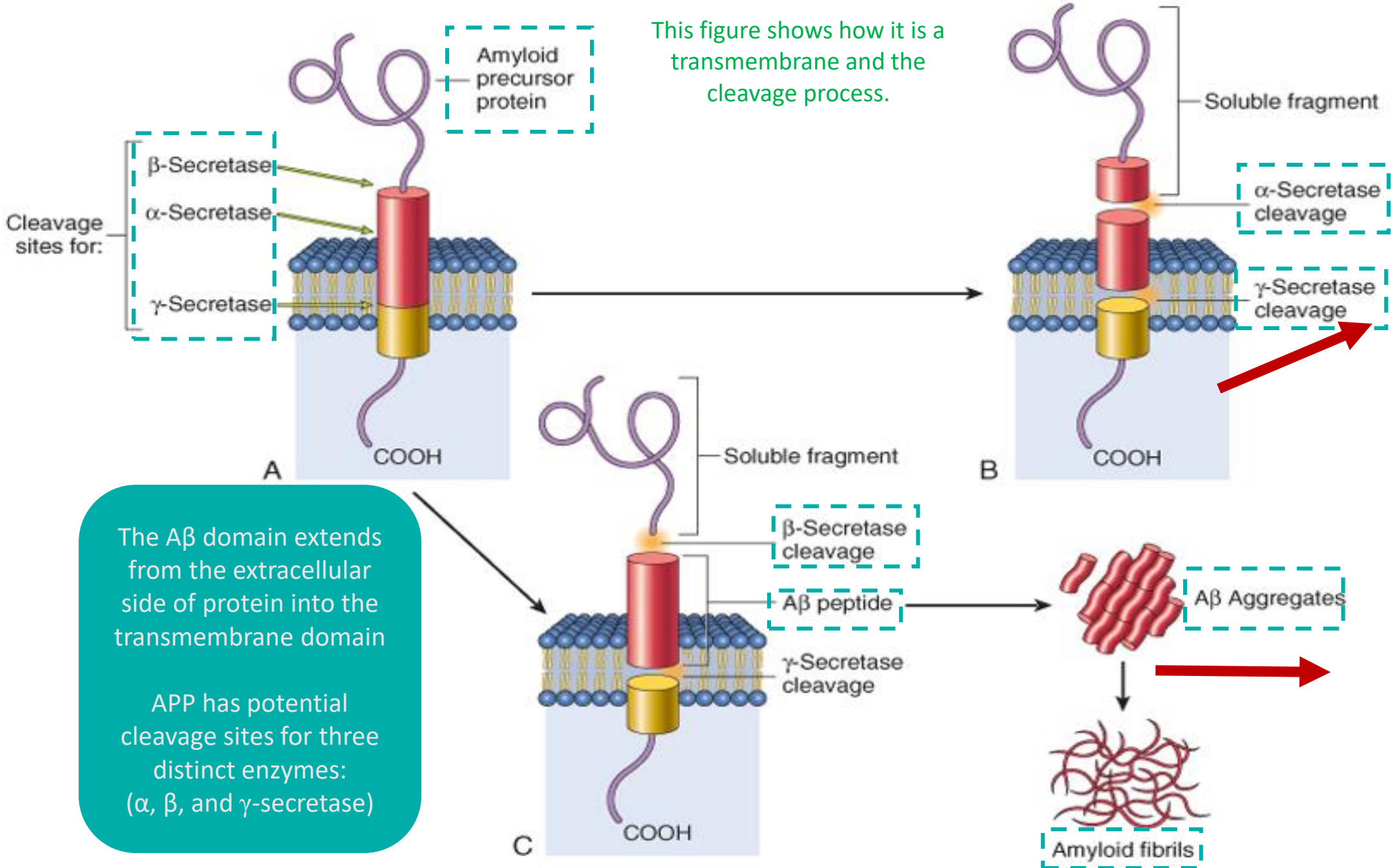
- The Aβ peptide forms β-pleated sheets and aggregates
  (so beta peptides will be in alpha helical structure)
- Resistant to degradation
- Elicits a response from astrocytes and microglia
- Can be directly neurotoxic

Aβ is produced inside the cells and have to go out to produce aggregates, and one of the hormones that helps in this movement is insulin, so people with diabetes are at more risk of getting Alzheimer's disease

(astrocytes leads to inflammatory process, and microglia leads to formation of ROS – response to the Ab aggregates is coming mainly from microglia and astrocytes and are found to be accumulated in patients with Alzheimer's disease)

Two Pathways For APP Processing

This figure shows how it is a transmembrane and the cleavage process.



The Aβ domain extends from the extracellular side of protein into the transmembrane domain

APP has potential cleavage sites for three distinct enzymes: (α, β, and γ-secretase)

1

When APP is cleaved by α-secretase subsequent cleavage by γ-secretase doesn't yield Aβ (normal)

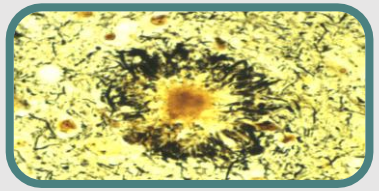
2

cleavage by β-secretase followed by γ-secretase results in production of Aβ

- Aβ can then aggregate and form fibrils

Accumulation of Aβ protein

❖ **Accumulation of Aβ protein affects neurons and neuronal function:**

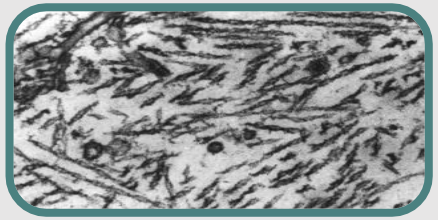


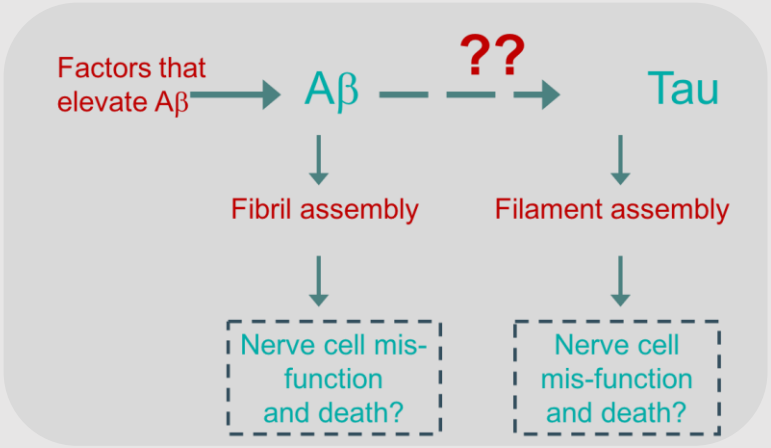
1. Small aggregates of Aβ alters neurotransmission
2. Aggregates can be toxic to neurons and synaptic endings
3. Larger deposits (plaques) also cause neuronal death
4. Elicit a local inflammatory response leading to further cell injury

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

The Tau Protein

- Presence of Aβ causes hyper-phosphorylation of tau protein in neurons
  - (these cannot bind to microtubules so instead they bind together and start forming nodes which makes filaments)
- This leads to redistribution and aggregation of tau protein into tangles in neurons (from axon into dendrites and cell body)
- The process results in neuronal dysfunction and cell death





Genetics of Alzheimer's

- Mutations in APP gene
- Mutations in γ-secretase (presenilin-1 or presenilin-2)
- Both lead to early onset of familial Alzheimer's disease due to high rate of Aβ accumulation

- Alzheimer's occurs in most patients with Down's syndrome (trisomy 21) beyond 45 years of age
- The gene encoding APP is located in chromosome 21
- Due to APP gene dosage effects

- Genes associated with typical, sporadic Alzheimer's disease are being identified

not all are know but they found APO-E gene, which is present in mainly LDL, HDL, they can act as receptor as cholesterol which is abundantly present in myelin sheath (20% of membrane cholesterol is found in the brain, 80% of it is present in myelin sheath

- This may provide new clues to pathogenesis of the disease

Chromosome	Gene	Consequences
21 "down syndrome patients are more susceptible"	Amyloid Precursor Protein (APP)	Early onset FAD Increased Aβ production
14	Presenilin-1 (PS1) gamma- secretase	Early onset FAD Increased Aβ production
1	Presenilin-2 (PS2) gamma- secretase	Early onset FAD Increased Aβ production
19	Apolipoprotein E (ApoE) (1,2,3,4 – 2 is protective but 1 and 4 are risk factors)	Increased risk for development of AD Decreased age at onset of AD

Treatment of Alzheimer

- Currently, ***no effective treatment for AD***

- regulating neurotransmitter activity e.g., Enhancing cholinergic function improves AD
- Epidemiological studies showed that treatment with NSAIDs decreases the risk for developing AD. Unfortunately, clinical trials of NSAIDs in AD patients have not been very fruitful.
- Cellular therapies using stem cells offer great promise for the treatment of AD

- Pro-inflammatory responses may be countered through polyphenol(flavonoids present in green tea Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.

❖ **Stem cells offer:**

1. Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration.

2. Neurotrophic support to remaining cells or prevent the production or accumulation of toxic factors that harm neurons (reducing toxicity)

Continued Research on AD

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

summary

Alzheimer's Disease	
▪ prominent involvement of the cerebral cortex , Its principal clinical manifestation is dementia , Most cases are sporadic ➢ **the patient** : ▪ become symptomatic before 50 years of age but the incidence of disease rises with age . ▪ becomes profoundly disabled, mute and immobile In **5-10 years**, At least 5-10% are familial	
Diagnosis	1. Combination of clinical assessment and radiologic methods 2. microscopic abnormalities include: neuritic plaques, neurofibrillary tangles and amyloid angiopathy 3. for definitive diagnosis : Pathologic examination of brain tissue
Treatment of AD	• Currently, **no effective treatment for AD** • regulating neurotransmitter activity • clinical trials of NSAIDs in AD patients have not been very fruitful. • Cellular therapies using **stem cells** offer great promise for the treatment of AD: 1. Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration. 2. Neurotrophic support to remaining cells or prevent the production or accumulation of toxic factors that harm neurons. • Pro-inflammatory responses may be countered through polyphenol(flavonoids). Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.

summary

Alzheimer's 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

- Biochemical markers correlated to degree of dementia include:
  - Loss of choline acetyltransferase , Synaptophysin immunoreactivity, Amyloid burden

Neuritic Plaques	• Spherical with 20-200 mm in diameter. • The dominant component of the plaque core is Aβ, a peptide derived from a larger molecule, 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 **Aβ is a critical molecule in the pathogenesis of Alzheimer's disease** • The two dominant species of Aβ, called Aβ40 and Aβ42 share an N-terminus and differ in length by two amino acids. ▪ Other **less** abundant proteins in the plaque: Components of the complement cascade ,Pro-inflammatory cytokines , α1-Antichymotrypsin, Apolipoproteins
Neurofibrillary Tangles	• It is Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus. Contain: • Hyperphosphorylated forms of the **tau protein ,** A protein that enhances microtubule assembly
Amyloid Angiopathy	• It is 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

Quiz

1) Which ONE of the following is the main component of neuritic plaques ?

a) amyloid precursor protein
b) Tau proteins
c) Aβ peptides
d) All of the above

2) Which ONE of the following biochemical markers is <u>not</u> correlated with the degree of dementia in Alzheimer patients ?

a) Choline acetyltransferase
b) Synaptophysin
c) Amyloid burden
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) Neurofibrillary tangle has a protein that <u>enhances</u> microtubules assembly ?

a) True
b) False

Q : What are the main genes affected in Alzheimer ?

Q : Describe the pathway of Aβ peptides aggregation ?

1- C
2- D
3- D
4- A

Suggestions and recommendations

Biochemistry Team 436

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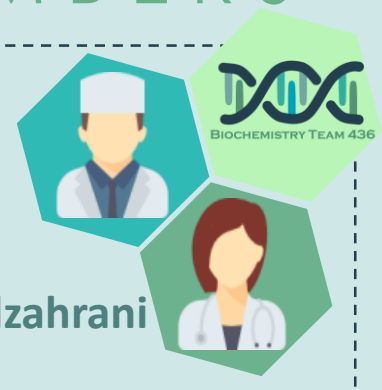

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THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

- Lippincott's Illusrated Reviews Biochemistry 6th E

https://www.youtube.com/watch?v=v5gdH_Hydes

Don’t forget to review the notes

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